Research Article
ISSN : 3048-104X

Volume 01, Issue No.08 . 2024

The Indonesian Journal of General Medicine

Neural Tube Defects Prevention with Folic Acid Supplementation and Fortification: A Comprehensive Systematic Review

[1]Henni Purnasari, [2]Mutia Juliana

[1] Immanuel College of Health Science, Bandung, Indonesia
[2] Faculty of Midwifery, General Achmad Yani University, Bandung, Indonesia

Correspondence : mutia9d15@gmail.com

Article History :
Received date : 2023/12/27
Revised date : 2024/02/17
Accepted date : 2024/03/18
Published date : 2024/06/20

Copyright: *© 2024 by the authors. Submitted for possible open access publication under the terms and conditions of the Creative Commons Attribution (BY NC) license (https://creativecommons.org/licenses/by-nc/4.0/).*

ISSN 3048-104X

ABSTRACT

Background: Neural tube defects (NTDs), affecting 1–2 per 1000 live births globally, leading to significant health and economic burdens. Folate supplementation and food fortification are crucial for prevention. The aim of this systematic review is to comprehensively evaluate the role of folate fortification and supplementation in reducing the incidence of NTDs. **Methods:** The review adhered to PRISMA 2020 standards and analyzed full-text English literature from 2014 to 2024. It excluded editorials, review papers from the same journal, and submissions lacking a DOI. Literature sources included PubMed, SagePub, SpringerLink, and Google Scholar. **Result:** A total of 500 articles were retrieved from online databases (PubMed, SagePub, SpringerLink and Google Scholar). After three rounds of screening, five articles directly relevant to the systematic review were selected for full-text reading and analysis. **Conclusion**: Folic acid supplementation and fortification are effective in lowering global NTD rates, despite disparities in implementation and outcomes, especially in low-resource areas.

Keyword: folate supplementation, folate fortification, neural tube defects

INTRODUCTION

Neural tube defects (NTDs) represent the most prevalent category of neurological developmental anomalies, affecting approximately 1–2 per 1000 live births globally. These defects, which include conditions such as spina bifida and anencephaly, arise from the failure of the neural tube to fuse properly during embryonic development. The incidence of NTDs is particularly alarming, with an estimated 300,000 to 400,000 new cases each year worldwide. The high prevalence and significant health implications of NTDs underscore the urgent need for effective prevention strategies.[1,2]

The management of NTDs typically involves a combination of prenatal and postnatal surgical interventions. Prenatal myelomeningocele repair, encephalocele repair, and Chiari decompression are common neurosurgical procedures aimed at mitigating the impact of these defects. Long-term management often includes addressing associated conditions such as hydrocephalus and tethered cord syndrome, requiring a multidisciplinary approach to care. Despite advancements in medical and surgical techniques that have increased survival rates, a substantial proportion of children with NTDs remain functionally dependent, facing challenges in mobility, bowel and bladder function, and overall quality of life.[3,4]

The economic burden of NTDs is considerable, encompassing direct medical costs, direct non-medical costs, and indirect costs, including caregiver time. The comprehensive care required for individuals with NTDs, along with the associated treatments and supportive equipment, contribute to the high financial impact on families and healthcare systems. Moreover, in many low- to middle-income countries (LMICs), the lack of access to prenatal screening, ultrasound, and intrauterine prenatal repair exacerbates the challenges in managing these conditions effectively. This highlights the need for accessible and cost-effective prevention strategies, particularly in resource-limited settings.[5,6]

Primary prevention of NTDs through public health initiatives has shown promise, especially in reducing the incidence of folate-sensitive NTDs. Folate, a B-vitamin essential for cell growth and reproduction, plays a crucial role in preventing these defects. Research indicates that adequate folate intake before conception and during early pregnancy can prevent approximately half of all NTD cases. Consequently, public health recommendations advocate for women of childbearing age to consume 400 µg of folate daily. This preventive measure has been supported by various public health interventions aimed at increasing folate consumption among the population.[7,8]

One of the most notable public health measures is the fortification of food products with folate. For instance, the 1998 mandate by the US Food and Drug Administration (FDA) for cereal grain enrichment led to a 20% reduction in the national incidence of spina bifida. This example illustrates the significant impact that policy-driven folate fortification can have on reducing NTD rates. However, the implementation and type of

© The Indonesian Journal of General Medicine

fortification and supplementation policies vary widely across different countries, reflecting a lack of uniformity in public health approaches to NTD prevention.[9,10]

Given the substantial evidence supporting the effectiveness of folate fortification and supplementation, it is crucial to systematically review the various policies and their outcomes. This systematic review aims to evaluate folate fortification and supplementation effectiveness in reducing the incidence of NTDs.

METHODS

Protocol

The author carefully followed the rules laid out in the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020. This was done to make sure the study met all its standards. The selection of this methodological approach was specifically aimed at ensuring the precision and reliability of the conclusions drawn from the investigation.

Criteria for Eligibility

This systematic review was done to evaluate folate fortification and supplementation effectiveness in reducing the incidence of NTDs based on literatures of the last 10 years. This study meticulously analyzed data on literatures to provide insights and enhance patient treatment strategies. The primary objective of this paper is to highlight the collective significance of the identified key points.

Inclusion criteria for this study entail: 1) Papers must be in English, and 2) Papers must have been published between 2014 and 2024. Exclusion criteria comprise: 1) Editorials; 2) Submissions without a DOI; 3) Previously published review articles; and 4) Duplicate entries in journals.

Search Strategy

The keywords used for this research are folate supplementation, folate fortification, neural tube defects. The Boolean MeSH keywords inputted on databases for this research are: (("folic acid"[MeSH Terms] OR ("folic"[All Fields] AND "acid"[All Fields]) OR "folic acid"[All Fields] OR "folate"[All Fields] OR "folates"[All Fields]) AND ("supplemental"[All Fields] OR "supplementating"[All Fields] OR "supplementation"[All Fields] OR "supplementation s"[All Fields] OR "supplementations"[All Fields] OR "supplemention"[All Fields])) OR (("folic acid"[MeSH Terms] OR ("folic"[All Fields] AND "acid"[All Fields]) OR "folic acid"[All Fields] OR "folate"[All Fields] OR "folates"[All Fields]) AND ("fortification"[All Fields] OR "fortifications"[All Fields]))) AND ("neural tube defects"[MeSH Terms] OR ("neural"[All Fields] AND "tube"[All Fields] AND "defects"[All Fields]) OR "neural tube defects"[All Fields]).

Data retrieval

The authors assessed the studies by reviewing their abstracts and titles to determine their eligibility, selecting relevant ones based on their adherence to the inclusion criteria, which aligned with the article's objectives. A consistent trend observed across multiple studies led to a conclusive result. The chosen submissions had to meet the

eligibility criteria of being in English and a full-text.

This systematic review exclusively incorporated literature that met all predefined inclusion criteria and directly pertained to the investigated topic. Studies failing to meet these criteria were systematically excluded, and their findings were not considered. Subsequent analysis examined various details uncovered during the research process, including titles, authors, publication dates, locations, study methodologies, and parameters.

Quality Assessment and Data Synthesis

Each author independently evaluated the research presented in the title and abstract of the publication to determine which ones merited further exploration. The subsequent stage involved assessing all articles that met the predefined criteria for inclusion in the review. Decisions on including articles in the review were based on the findings uncovered during this evaluation process. This criterion aimed to streamline the paper selection process for further assessment, facilitating a comprehensive discussion of previous investigations and the factors that made them suitable for inclusion in the review.

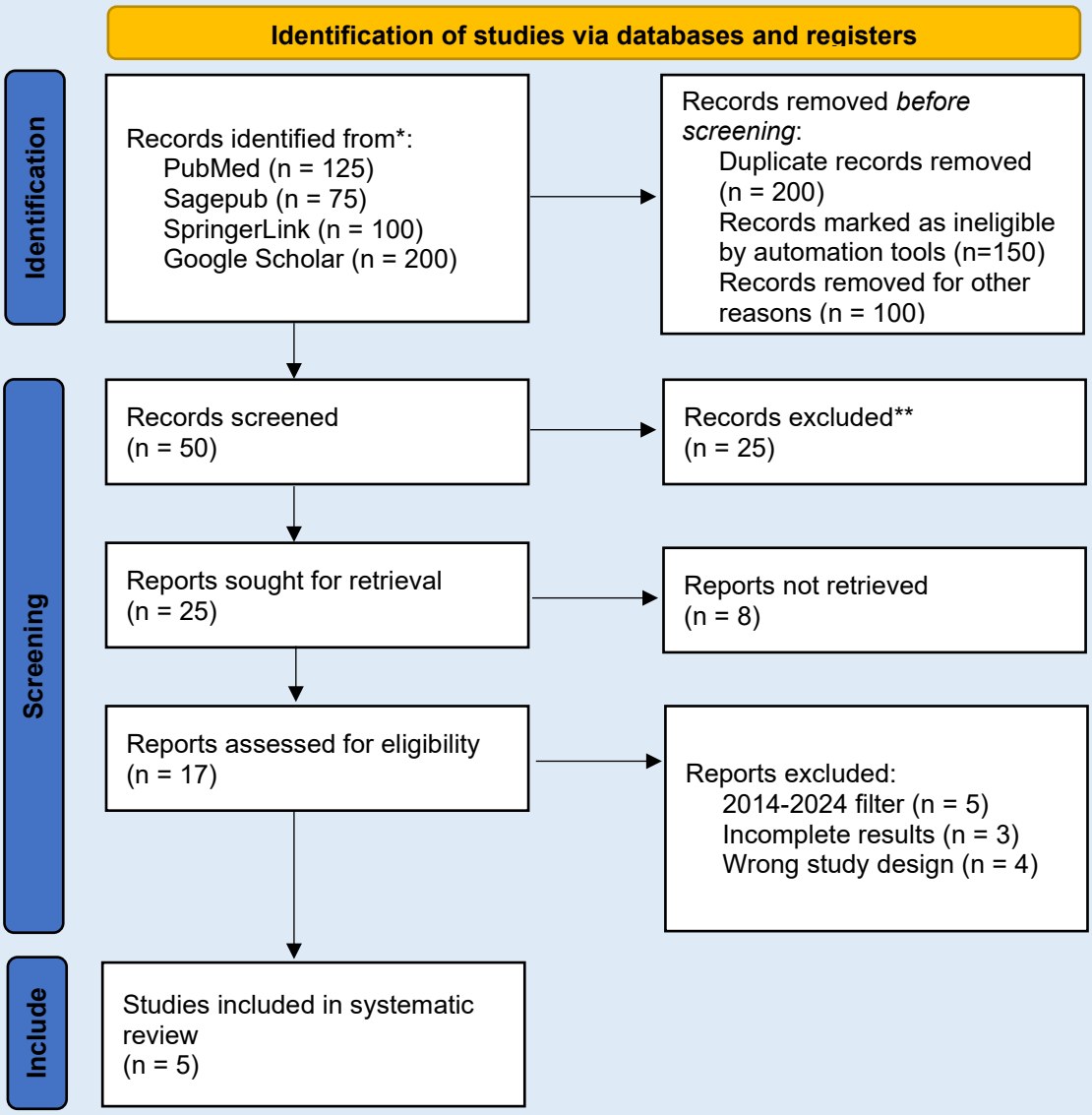


Figure 1. Article search flow chart

© The Indonesian Journal of General Medicine

RESULT

The initial number of articles retrieved from online databases (PubMed, SagePub, SpringerLink, and Google Scholar) is 500 articles. After conducting three levels of screening, five articles that directly relate to the current systematic review have been chosen for further assessment through full-text reading and analysis. Table 1 presents the selected literature included in this analysis.

Table 1. The literature included in this study

No	Author	Origin	Method	Sample	Result
1.	Santos, et al.[11] (2016)	Brazil	Retrospective study	18,120,587 samples	Between 2001 and 2014, there were 8,554 neural tube defects (NTDs) reported for 17,925,729 live births and 2,673 NTDs reported for 194,858 stillbirths. The overall prevalence of NTDs decreased from 0.79 per 1000 live births pre-fortification to 0.55 per 1000 live births post-fortification, with a prevalence ratio (PR) of 1.43 (95% confidence interval, CI: 1.38–1.50). For stillbirths, the prevalence decreased from 17.74 per 1000 stillbirths pre-fortification to 11.70 per 1000 stillbirths post-fortification. Among live births, the prevalence fell from 0.57 per 1000 to 0.44 per 1000 in the same period.
2.	Poletta, et al.[12] (2018)	South America	Cross-sectional study	2,597 samples	In Chile and Argentina, the prevalence of neural tube defects (NTDs), particularly anencephaly and cervico-thoracic spina bifida, showed a greater reduction in females than in males after folic acid fortification (FAF). This resulted in a shift in the sex ratio of infants with NTDs. The study suggests possible mechanisms behind this differential reduction, which could help in understanding the overall pathogenesis of NTDs and specifically those that are susceptible to folic acid's protective effects.
3.	Grosse, et al.[13] (2016)	USA	Retrospective study	767 samples	The fortification mandate in the U.S. is estimated to have reduced the annual number of live-born spina bifida cases by 767, with a lower-bound estimate of 614 cases. The mean direct lifetime cost per

					infant with spina bifida is estimated at $791,900, or $577,000 excluding caregiving costs. With the best estimate of avoided cases, fortification is projected to reduce the present value of total direct costs for each year's birth cohort by $603 million, exceeding the cost of fortification. A conservative lower-bound estimate of cost savings, using higher fortification cost assumptions, is $299 million.
4.	Kancherla, et al.[14] (2018)	Multicenter	Retrospective study	230,000 samples	In 2017, 59 countries implemented mandatory folic acid fortification of wheat and/or maize flour, preventing approximately 50,270 out of 280,500 folic acid-preventable spina bifida and anencephaly (FAP SBA) births, achieving only 18% global prevention. Many countries in Africa and Asia, where the number of FAP SBA-affected births is high, do not have mandatory fortification.
5.	Arth, et al.[15] (2016)	Multicenter	Retrospective study	268,700 samples	In 2015, mandatory folic acid fortification of wheat and maize flour in 58 countries prevented 13.2% (35,500 out of 268,700) of global folic acid-preventable spina bifida and anencephaly (FAP SBA) cases. However, most countries in Europe, Africa, and Asia were not implementing this fortification. Despite 25 years of knowledge that folic acid prevents these defects, only a small fraction of FAP SBA cases are being prevented globally. Many countries continue to experience significantly higher rates of FAP SBA. Mandatory folic acid fortification offers a proven, rapid method for governments to reduce FAP SBA-related disability and mortality and to support health-related Sustainable Development Goals.

In this systematic review, a total of 18,622,651 samples were analyzed across diverse populations and geographic regions. The summarized studies encompass a diverse global distribution, including Brazil, South America (Chile and Argentina), the USA, and multiple global regions. They highlight reductions in neural tube defects (NTDs) post-fortification of folic acid, with varying impacts and implementation levels across different continents.

DISCUSSION

Folic acid supplementation and fortification have demonstrated significant impacts on reducing the prevalence of neural tube defects (NTDs) globally. The studies reviewed provide valuable insights into the effectiveness of these interventions across different regions and populations. Santos et al. (2016) observed a substantial decrease in NTD prevalence in Brazil following mandatory fortification of wheat and maize flour. Their findings underscore the effectiveness of national fortification programs in large, diverse populations, where the prevalence of NTDs decreased notably post-fortification. This supports the notion that population-wide strategies can effectively reduce NTD rates, benefiting both live births and stillbirths.[11,16]

Poletta et al. (2018) contributed insights from South America, specifically Chile and Argentina, where they noted differential reductions in NTDs between genders post-fortification. This suggests that while overall prevalence decreases, there may be nuanced effects on specific subgroups, potentially influenced by biological factors or varying fortification levels between regions. Such observations highlight the importance of considering demographic and regional factors when implementing and assessing fortification policies.[12]

The study by Grosse et al. (2016) focused on the economic implications of fortification in the USA, estimating substantial cost savings associated with preventing spina bifida cases. This economic perspective underscores the broader benefits of fortification beyond health outcomes, demonstrating that investments in preventive measures can yield significant societal returns.[13,17]

Global perspectives provided by Kancherla et al. (2018) and Arth et al. (2016) reveal disparities in fortification practices and outcomes worldwide. Kancherla et al. highlighted the widespread adoption of fortification in some regions but noted significant gaps in others, particularly in Africa and Asia, where implementation remains limited despite high prevalence rates of folic acid-preventable NTDs. Arth et al. echoed these disparities, emphasizing the urgent need for broader global adoption of fortification strategies to maximize public health benefits and reduce disparities in NTD prevalence globally.[14,15]

Despite the overall success observed in many regions, challenges remain in optimizing fortification strategies universally. Variations in fortification levels and compliance suggest that achieving optimal effectiveness requires careful monitoring and adjustment of fortification programs based on regional and population-specific needs. This adaptive approach is crucial for sustaining reductions in NTD prevalence over the long term.[18]

Furthermore, the varying impacts on different types of NTDs, such as anencephaly and spina bifida, as highlighted by Poletta et al. (2018), indicate the need for continued research into the mechanisms underlying folic acid's protective effects. Understanding these mechanisms can inform targeted interventions and improve outcomes for populations disproportionately affected by specific types of NTDs.[12,19]

The economic analysis by Grosse et al. (2016) underscores the cost-effectiveness of fortification programs, suggesting that while initial implementation costs may be incurred, the long-term economic benefits outweigh these costs significantly. This economic argument strengthens the case for policy makers to prioritize and sustain fortification initiatives as a cost-effective public health intervention.[13,20]

CONCLUSION

The systematic review confirms folic acid's effectiveness in lowering global NTD rates, despite disparities in implementation and outcomes, especially in low-resource areas. Future research should optimize fortification strategies, close implementation gaps, and deepen understanding of folic acid's biological mechanisms for broader health gains.

REFERENCES

1. van Gool JD, Hirche H, Lax H, De Schaepdrijver L. Folic acid and primary prevention of neural tube defects: A review. Reprod Toxicol. 2018 Sep;80:73–84.
2. Kancherla V, Wagh K, Priyadarshini P, Pachón H, Oakley GP. A global update on the status of prevention of folic acid-preventable spina bifida and anencephaly in year 2020: 30-Year anniversary of gaining knowledge about folic acid's prevention potential for neural tube defects. Birth Defects Res. 2022 Dec 1;114(20):1392–403.
3. De-Regil LM, Peña-Rosas JP, Fernández-Gaxiola AC, Rayco-Solon P. Effects and safety of periconceptional oral folate supplementation for preventing birth defects. Cochrane Database Syst Rev. 2015 Dec 14;2015(12):CD007950.
4. Keats EC, Haider BA, Tam E, Bhutta ZA. Multiple-micronutrient supplementation for women during pregnancy. Cochrane Database Syst Rev. 2019 Mar 14;3(3):CD004905.
5. Crider KS, Qi YP, Devine O, Tinker SC, Berry RJ. Modeling the impact of folic acid fortification and supplementation on red blood cell folate concentrations and predicted neural tube defect risk in the United States: have we reached optimal prevention? Am J Clin Nutr. 2018 Jun 1;107(6):1027–34.
6. Tinker SC, Hamner HC, Qi YP, Crider KS. U.S. women of childbearing age who are at possible increased risk of a neural tube defect-affected pregnancy due to suboptimal red blood cell folate concentrations, National Health and Nutrition Examination Survey 2007 to 2012. Birth Defects Res A Clin Mol Teratol. 2015 Jun;103(6):517–26.
7. Centeno Tablante E, Pachón H, Guetterman HM, Finkelstein JL. Fortification of wheat and maize flour with folic acid for population health outcomes. Cochrane Database Syst Rev. 2019 Jul 1;7(7):CD012150.

8. Turner MJ. Neural Tube Defects and Folic Acid Food Fortification in Europe. Am J Public Health. 2018 May;108(5):601–2.
9. Kancherla V, Botto LD, Rowe LA, Shlobin NA, Caceres A, Arynchyna-Smith A, et al. Preventing birth defects, saving lives, and promoting health equity: an urgent call to action for universal mandatory food fortification with folic acid. Lancet Glob Health. 2022 Jul;10(7):e1053–7.
10. Atta CAM, Fiest KM, Frolkis AD, Jette N, Pringsheim T, St Germaine-Smith C, et al. Global Birth Prevalence of Spina Bifida by Folic Acid Fortification Status: A Systematic Review and Meta-Analysis. Am J Public Health. 2016 Jan;106(1):e24-34.
11. Santos LMP, Lecca RCR, Cortez-Escalante JJ, Sanchez MN, Rodrigues HG. Prevention of neural tube defects by the fortification of flour with folic acid: a population-based retrospective study in Brazil. Bull World Health Organ. 2016 Jan 1;94(1):22–9.
12. Poletta FA, Rittler M, Saleme C, Campaña H, Gili JA, Pawluk MS, et al. Neural tube defects: Sex ratio changes after fortification with folic acid. PLOS ONE. 2018 Mar 14;13(3):e0193127.
13. Grosse SD, Berry RJ, Mick Tilford J, Kucik JE, Waitzman NJ. Retrospective Assessment of Cost Savings From Prevention: Folic Acid Fortification and Spina Bifida in the U.S. Am J Prev Med. 2016 May;50(5 Suppl 1):S74–80.
14. Kancherla V, Wagh K, Johnson Q, Oakley GP. A 2017 global update on folic acid-preventable spina bifida and anencephaly. Birth Defects Res. 2018 Aug 15;110(14):1139–47.
15. Arth A, Kancherla V, Pachón H, Zimmerman S, Johnson Q, Oakley GP. A 2015 global update on folic acid-preventable spina bifida and anencephaly. Birth Defects Res A Clin Mol Teratol. 2016 Jul;106(7):520–9.
16. Jalal CS, De-Regil LM, Pike V, Mithra P. Fortification of condiments and seasonings with iron for preventing anaemia and improving health. Cochrane Database Syst Rev. 2023 Sep 1;9(9):CD009604.
17. Wagh K, Kancherla V, Dorsey A, Pachón H, Oakley GP. A global update on the status of prevention of folic acid-preventable spina bifida and anencephaly in year 2022. Birth Defects Res. 2024 May;116(5):e2343.
18. Quinn M, Halsey J, Sherliker P, Pan H, Chen Z, Bennett DA, et al. Global heterogeneity in folic acid fortification policies and implications for prevention of neural tube defects and stroke: a systematic review. eClinicalMedicine [Internet]. 2024 Jan 1 [cited 2024 Jun 20];67. Available from: https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370(23)00543-6/fulltext

19. Viswanathan M, Urrutia RP, Hudson KN, Middleton JC, Kahwati LC. Folic Acid Supplementation to Prevent Neural Tube Defects: Updated Evidence Report and Systematic Review for the US Preventive Services Task Force. JAMA. 2023 Aug 1;330(5):460–6.
20. Wilson RD, Genetics Committee, Wilson RD, Audibert F, Brock JA, Carroll J, et al. Pre-conception Folic Acid and Multivitamin Supplementation for the Primary and Secondary Prevention of Neural Tube Defects and Other Folic Acid-Sensitive Congenital Anomalies. J Obstet Gynaecol Can. 2015 Jun;37(6):534–52.