SYSTEMATIC REVIEW

The impact of micronutrient supplementation on the outcome of In Vitro Fertilization: A comprehensive systematic review of current studies

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ABSTRACT

Objective: In vitro fertilization is the most common form of assisted reproductive and fertility technology. However, it is important to note the success rates of IVF generally decrease as a person gets older. Identifying modifiable factors affecting human fertility, including diet, is significant for clinical and community wellness. This systematic review investigates the role of micronutrients supplementation in fertility and its potential impact on in vitro fertilization (IVF) outcomes.

Materials and Methods: A systematic search in multiple databases using specific keywords related to in vitro fertilization, micronutrient supplementation, and outcome measures.

Results: Out of 1462 retrieved studies, 8 were included in the systematic review. These studies covered a range of micronutrients and their effects on different IVF outcomes. Findings indicated potential benefits of vitamin D3 supplementation. Vitamin D3 supplementation was associated with a significant improvement in implantation rates ($p < 0.05$) in two studies, while no significant effect was observed in clinical pregnancy rates in other micronutrients. The systematic review highlights the diverse effects of various micronutrient supplements on IVF outcomes. While some supplements showed potential benefits, others did not significantly improve pregnancy rates. Further research with larger cohorts is necessary to establish conclusive evidence. Keywords: micronutrient supplements, IVF outcomes, pregnancy rates.

Conclusion: In conclusion, this systematic review sheds light on the impact of micronutrients on IVF outcomes. Some studies suggested potential benefits of vitamin D3 supplementation >20 ng/ml, further research is needed to provide more definitive conclusions. Understanding the function of micronutrients in fertility could have significant implications for IVF treatment and female infertility management.

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Highlights:

1. Potential benefits of vitamin D3 supplementation >20 ng/ml, along with myo-inositol, folic acid, and melatonin, on implantation rates.
2. Subsequent studies revealed no substantial enhancement in pregnancy rates when specific supplements were used.
3. Further research is needed to provide more definitive conclusions.

INTRODUCTION

In-vitro fertilization (IVF) is the predominant method of assisted reproductive and fertility technology and is employed to assist patients experiencing difficulties in achieving conception. As per the Society for Reproductive Technology (SART), 55.6% of successful births through in vitro fertilization (IVF) happen in women who are younger than 35 years old. Additionally, 41.4% of initial embryo transfers lead to live births. The birth rate following embryo transfer is approximately 47%. For women between the ages of 38 and 40, the success rate is 26.8%, which represents a notable decline compared to the age range of 35 to 37. Women over the age of 42 have a success rate of only 3.9%. As a woman ages, both the number and quality of her eggs typically decrease. This may result in suboptimal embryo quality, thereby diminishing the probability of a successful uterine implantation. Recent scientific discussions have sparked an interest in the role of micronutrients in fertility.[1]

The correlation between maintaining a nutritious diet and fertility has been consistently and recently proven.[1,2] Micronutrients refer to crucial micro-nutrients that are necessary in small amounts as essential components of the diet. There is a scarcity of research conducted on humans, resulting in limited knowledge regarding the impact of micronutrient levels on female fertility. Nevertheless, micronutrients fulfill significant functions at different stages of the reproductive process. For example, the quality, maturation, fertilization, and implantation of oocytes rely on appropriate levels of folate. While these micronutrients do not contribute to the energy supply, they are important for both anabolic and catabolic processes. Micronutrients must be acquired from external sources.[3] A prospective study found that women who followed the dietary recommendations in the Netherlands had a higher probability of achieving pregnancy when undergoing in-vitro fertilization procedure or intracytoplasmic sperm injection.[4]

Assessing the influence of micronutrient deficiency on female infertility is difficult because it involves various crucial cofactors, such as salpingitis and sexually transmitted diseases, which can lead to infertility. Moreover, in a recent evaluation, specific scientists have emphasized the potential impact of micronutrients on female reproductive ability, yet have not been able to offer precise overall suggestions.[1] This highlights the imperative need for additional investigation on this topic. In order to assess the influence of potential micronutrient supplementation on female infertility, we performed a comprehensive analysis to examine the consequences of micronutrient supplementation on the results of in vitro fertilization.

MATERIALS AND METHODS

Research protocol and registration

Prior to writing this review, we submitted a protocol that was officially registered in the International PROSPERO on February 7th, 2024 (CRD4202 4507137).

Eligibility criteria

The strengths of this review encompass the assessment of an extensive range of international literature, conducted in accordance with a peer-reviewed protocol. This approach involved a stringent critical evaluation of dietary assessment methodologies and overall study quality, ensuring the inclusion of only reliable research. The inclusion standards for the study were based on the following criteria: the study had to be an original research study; the topic had to be suitable, specifically focusing on micronutrient supplementation in in vitro fertilization patients; the study had to include one control group and one exposure group; and a transparent extraction and statistical analysis method had to be used. The exclusion criteria was studies focusing on male infertility or lacking a control group to ensure that the results specifically reflect the impact of micronutrients on female fertility. We also excluded the studies with absence of a complete text version and the study of languages other than English. This approach was intended to minimize confounding factors and enhance the specificity of the findings

Search strategy

This study employed the PRISMA guidelines. We performed a comprehensive literature search using the latest editions of PubMed, ScienceDirect, Scopus, Embase, and the Cochrane Library up to May 20th 2024. The search included articles published in the last 10 years, focusing on studies examining micronutrient supplementation and IVF outcomes. The systematic search covered articles published between January 2014 and December 2023 to ensure the relevance and novelty of the findings.

Data extraction and study selection

In this review, four researchers independently reviewed the title and abstract of the studies and excluded those that were not relevant. The studies that were ultimately obtained were examined for any duplicate entries and

then systematically assessed based on the predetermined criteria for inclusion and exclusion. The researchers evaluated the subject characteristics (patients undergoing in vitro fertilization), the intervention used in the study (supplementation with micronutrients), the outcome of the study (in vitro fertilization outcomes), and any other pertinent information. This systematic review was analyzed using Microsoft Excel software.

Risk of bias assessment

The quality of the included studies was assessed using the Cochrane Risk of Bias Tool for Randomized Controlled Trials (RCTs) and the Newcastle-Ottawa Scale for observational studies. Two independent reviewers evaluated each study for potential biases in selection, performance, detection, and attrition. Discrepancies were resolved through discussion or by consulting a third reviewer. Furthermore, sensitivity analyses were conducted to determine the impact of excluding studies with a high risk of bias.

RESULTS AND DISCUSSION

A combined total of 1462 studies were obtained by searching the databases PubMed/Medline (n = 64), Science Direct (n = 681), Scopus (697), Embase (13), and Cochrane Library (n = 7) using the specified keywords. Following the evaluation of abstracts and titles, a total of 1450 studies were eliminated. The studies were then compared for duplicates, and no studies were excluded. Out of the remaining 10 studies, they were evaluated based on the inclusion and exclusion criteria, and two of them were excluded. After the final screening, 8 studies were found to fulfill the inclusion and exclusion criteria. The flowchart illustrating the process of study selection is presented in Figure 1.

This systematic review obtained the results of 8 studies that met the inclusion criteria. The search results can be observed in Table 1.

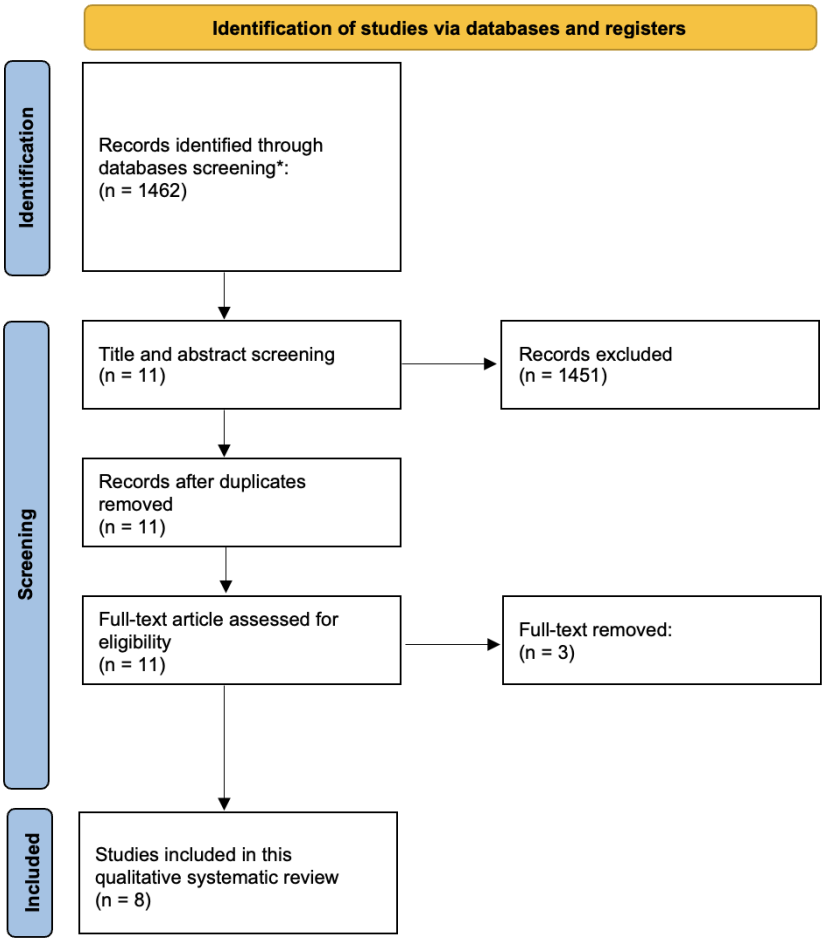

Figure 1. Article search and selection flowchart

Table 1. Search results[5-13]

Author and Year	Research design	Study population	Results
Espinola MSB et al, 2021	RCT	Population: Infertile women undergoing in vitro fertilization procedure Intervention: Oral vitamin D3, folic acid, myo-inositol, and melatonin Comparison: Oral myo-inositol, folic acid, and alpha-lactalbumin Outcome: Implantation rate	The research discovered that the addition of vitamin D supplementation, along with folic acid, myo-inositol, and melatonin, resulted in higher levels of vitamin D3 and showed a positive relationship with success rate of implantation in invitro fertilization (IVF). Larger cohorts of patients need to confirm these findings.
Somigliana E et al, 2021	RCT	Population: Women aged 18-39 years with low level of vitamin D undergoing IVF procedure Intervention: Single dose oral 600,000 IU of vitamin D3 Comparison: Placebo group Outcome: Rate of clinical pregnancy per cycle	The study concluded that administering oral vitamin D3 supplements didn't enhance the clinical pregnancy rate in women with preserved ovarian reserve, normal weight, and low levels of vitamin D who were undergoing invitro fertilization.
Makieva S et al, 2021	RCT	Population: Women with Vitamin D deficiency undergoing IVF Intervention: Oral vitamin D Comparison: Placebo group Outcome: Gene expression in granulosa cells and hormone levels in follicular fluid	The study found vitamin D resulted in a transcriptomic signature in luteinized granulosa cells. However, it did not alter hormone levels in follicular fluid.
Murto T et al, 2014	Case control	Population: Woman with unexplained infertility Intervention: Folic acid supplementation Comparison: None mentioned Outcome: IVF pregnancy outcome	The study found that woman with unexplained infertility had a higher consumption of folic acid supplements and a greater overall intake of folic acid compared to fertile women in the control group. Women who had infertility without a known cause had higher levels of folate in their blood and lower levels of homocysteine. Nevertheless, there was no correlation found between the supplementation of folic acid and the status of folate, and the outcome of pregnancy in women with unexplained infertility.
Lu X et al, 2018	RCT	Population: Patients with endometriosis undergoing IVF-ET Intervention: Vitamin C supplementation Comparison: VitC non-treatment group Outcome: IVF-ET outcomes	The study revealed that individuals with endometriosis exhibited diminished levels of vitamin C, superoxide dismutase (SOD), and total antioxidant capacity (TAC) in comparison to control group. Following a 2-month vitamin C treatment, there was a notable increase in serum vitamin C levels, while oxidative stress markers remained unchanged. The study concluded that oral vitamin C supplementation improved vitamin C levels but didn't affect the markers of oxidative stress in patients with endometriosis. A total of 245 patients with endometriosis and 132 patients without endometriosis underwent successful in vitro fertilization and embryo transfer (IVF-ET) and were followed up.
Polzikov M et al, 2022	RCT	Population: Normogonadotropic women undergoing fresh in vitro fertilization cycles Intervention: Serum level of total magnesium, folate, and calcium before ovarian stimulation Comparison: None mentioned Outcome: IVF cycle outcomes	Women with elevated folate levels in their bloodstream exhibited a reduced quantity of retrieved eggs and diminished probabilities of attaining a clinical pregnancy and live birth, in contrast to women with lower folate levels. Women with an elevated Ca/Mg ratio exhibited greater odds ratios for biochemical pregnancy, clinical pregnancy, and live birth in comparison to women with a lower Ca/Mg ratio. The study indicated that increased levels of folate in the blood and a higher ratio of calcium to magnesium were linked to poorer outcomes in in vitro fertilization (IVF) procedures among women with normal levels of gonadotropins.

Nouri K et al, 2017	RCT	Population: Women undergoing IVF/ICSI Intervention: PROfertil® female (micronutrient supplementation) Comparison: Folic acid supplementation Outcome: Embryo quality, clinical pregnancy rate	The study utilized a multinutrient supplementation called PROfertil ®, which consisted of selenium, folic acid, catechins, glycyrrhizin, vitamin E, damiana, diosgenin, and omega-3-fatty acids. The findings indicated that women who received multinutrient supplementation exhibited a greater proportion of high-quality embryos (embryos with a minimum of 6 cells and a fragmentation rate below 20%) in comparison to those who received folic acid supplementation. The clinical pregnancy rate was excluded. The study concluded that the provision of micronutrient supplementation had a beneficial effect on the quality of embryos in in vitro fertilization (IVF) procedures.
Youssef MAFM et al, 2015	RCT	Population: Women with unexplained infertility undergoing in vitro fertilization or ICSI Intervention: Oral antioxidants supplementation (multivitamins and minerals) Comparison: No antioxidant supplementation Outcome: The quantity of mature metaphase II (MII) oocytes and the rate of successful pregnancies.	The study revealed that the addition of oral multivitamins and minerals supplementation didn't have a significant impact on the quantity of mature metaphase II oocytes or the success rate of clinical pregnancies who were undergoing ICSI/IVF treatment. There were no notable disparities between the group that received antioxidant supplementation and the control group in terms of age, BMI, number of metaphase II oocytes, and rate of clinical pregnancy.

The systematic review analyzed eight relevant research studies that investigated the impact of different micronutrient supplements on the outcomes of in vitro fertilization (IVF). These studies covered a wide variety of micronutrients and their effects on various aspects of IVF treatment. It emphasizes the lack of published studies that investigate the effects of micronutrient supplementation on clinical outcomes in couples undergoing IVF treatment and subsequent follow-up. Although the eight studies that fulfilled the inclusion criteria showed significant differences in clinical outcomes and varied in their research methods, conducting a meta-analysis was not feasible.

Prior research has primarily focused on investigating the effects of antioxidants, such as vitamins A, B, C, D, E, and coenzyme Q10, as dietary micronutrient supplements in assisted reproductive techniques. Research has demonstrated that antioxidants can decrease the amount of reactive oxygen species in males, safeguarding semen from oxidative harm and enhancing sperm characteristics like motility.[13,14] However, there is limited clinical evidence regarding the impact of antioxidants on female infertility.

Espinola et al. (2021) investigated the effects of vitamin D3 supplementation, along with myo-inositol, folic acid, and melatonin, on the implantation rate of embryos in women who are experiencing infertility and undergoing in vitro fertilization (IVF) treatment. This demonstrated a statistically significant improvement in implantation rates with vitamin D3 supplementation ($p < 0.05$). However, the small sample size ($n = 23$) limits the generalizability of the findings. The study revealed a clear correlation between vitamin D3 levels and the rate of successful attachment of an implanted embryo to the uterus, suggesting potential benefits for in vitro fertilization (IVF) outcomes. However, it is imperative to have larger cohorts of participants to validate and establish the veracity of these findings.[5] In contrast, Somigliana et al. (2021) reported no significant difference in clinical pregnancy rates, indicating the potential role of other factors such as baseline vitamin D status, dosage, and timing of supplementation. Somigliana et al. (2021) conducted a retrospective cohort study on women undergoing in vitro fertilization (IVF) with deficient levels of vitamin D. Women with normal body weight, preserved ovarian reserve, and low level of vitamin D did not experience any improvement in the clinical pregnancy rate after receiving a single oral dose of 600,000 IU of vitamin D3 supplementation.[6] Makieva et al. (2021) examined the effects of administering Vitamin D orally to women with Vitamin D deficiency who were undergoing in vitro fertilization (IVF). The study discovered that vitamin D supplementation induced a distinct gene expression pattern in luteinized granulosa cells, but had no impact on hormone levels in the fluid surrounding the ovarian follicles.[7]

Murto et al. (2014) conducted a case-control study that specifically investigated the impact of folic acid supplementation on women with unexplained infertility. The study found that women with unexplained infertility had a greater consumption of folic acid supplements and showed increased levels of folate in

their blood plasma. Nevertheless, there was no evident association between the administration of folic acid and the results of pregnancy.[8] Lu et al. (2018) conducted a retrospective cohort study on individuals diagnosed with endometriosis who were undergoing in vitro fertilization and embryo transfer (IVF-ET) and receiving vitamin C supplementation. The follicular fluid's microenvironment significantly affects multiple parameters of in vitro fertilization (IVF) outcomes, such as oocyte quality, fertilization rate, and the production of high-grade embryos. It is essential to maintain a precise balance between the amount of reactive oxygen species (ROS) and the capacity of antioxidants in the follicular fluid in order to achieve high-quality oocytes and embryos during in vitro fertilization (IVF) treatment. The study showed that the administration of vitamin C increased vitamin C levels, but it did not affect oxidative stress markers in individuals diagnosed with endometriosis.[9] Polzikov et al. (2022) investigated the relationship between serum folate, total magnesium (Mg), and calcium (Ca) levels before ovarian stimulation and the results of IVF cycles in normogonadotropic women. The study found a link between elevated levels of folate in the bloodstream and a greater calcium to magnesium ratio, as well as adverse outcomes in in vitro fertilization (IVF).[10] Nouri et al. (2017) conducted a study comparing the effects of multinutrient supplementation (PROfertil® female) and folic acid supplementation in women undergoing IVF/ICSI. The study found that women who were given multinutrient supplementation had a higher occurrence of high-quality embryos.[11] In their study, Youssef et al. (2015) provided women with unexplained infertility who were undergoing ICSI/IVF with oral antioxidant supplementation, which included multivitamins and minerals. Nevertheless, they did not detect any substantial improvements in pregnancy rates.[12]

The most promising micronutrient supplementation for improving in vitro fertilization outcomes is vitamin D. According to a study by Hasan et al. (2023), it was shown that the level of 25(OH)D in the mother's blood before conception can be used to predict the outcome of in vitro fertilization (IVF) treatment during pregnancy. A preconception serum level of 25(OH)D greater than 50 nmol/L is linked to a higher probability of achieving a successful pregnancy outcome after undergoing IVF treatment. According to the current guidelines from the Institute of Medicine, our study found that 19% of women had a vitamin D deficiency (less than 30 nmol/L) and 69% had a vitamin D insufficiency (between 30-50 nmol/L).[15] Maternal serum 25(OH)D is likely responsible for controlling the expression and release of hCG, as well as promoting the production of estrogen and progesterone in trophoblasts. These processes ultimately support the successful implantation and maintenance of a healthy pregnancy. Nevertheless, there is disagreement among researchers regarding the specific function of maternal 25(OH)D in enhancing pregnancy outcomes. Some studies have found no correlation between the level of maternal serum 25(OH)D and the fertilization rate or indicators of embryo quality.[16] Evaluating the impact of vitamin D supplementation and addressing vitamin D deficiency/insufficiency before IVF treatment is crucial for understanding its effects on pregnancy outcomes.

Despite the growing number of studies in recent years investigating the impact of micronutrient supplementation on in vitro fertilization (IVF), the inconsistencies and the absence of supportive studies specifically focused on female IVF prevent definitive conclusions regarding the use of micronutrients in clinical practice. Furthermore, there is a lack of information regarding which specific group would derive greater benefits from supplementation. Although there may be certain advantages to taking micronutrient supplements, the existing evidence is inadequate to support this assertion. Hence, it is imperative to conduct extensive clinical trials that focus on the administration of micronutrient supplementation, either individually or in conjunction with other treatments, to assess their potential impact on the clinical outcomes of couples undergoing IVF therapy.

Modifying one's diet and lifestyle has been the primary method used to achieve natural conception in cases of unexplained infertility.[17] Although quitting smoking[18] and controlling obesity[19] have a significant positive impact on natural conception, the use of micronutrient supplementation has been a subject of debate. Supplementing with vitamins and anti-oxidants enhances the quality of semen, while women tend to exhibit diverse results. Nevertheless, according to our findings, we suggest that micro-nutrients may have positive effects on both males and females.[20]

Given the potential benefits of vitamin D3 supplementation observed in some studies, clinicians should consider assessing and optimizing vitamin D status in women undergoing IVF, particularly those with known deficiencies. However, the current evidence is insufficient to recommend routine micronutrient supplementation for all IVF patients. Personalized supplementation strategies, based on individual nutritional status and reproductive history, should be explored in future research. Future research should focus on large-scale, multicenter RCTs with standardized micronutrient supplementation protocols and homogenous patient populations. Studies should aim to elucidate the optimal dosage, duration, and combination of micronutrient supplements to improve IVF outcomes. Additionally,

investigating the potential mechanisms by which micro-nutrients influence reproductive processes could provide valuable insights into their role in fertility treatment. Subgroup analyses based on factors such as age, BMI, baseline micro-nutrient status, and infertility etiology could provide more nuanced insights into which patient populations are most likely to benefit from specific micronutrient supplementation. Such analyses would help tailor individualized supplementation strategies in clinical practice.

Strength and limitations

The primary strength of the review lies in its comprehensive search strategy and methodical approaches employed to identify relevant data. To include articles that met the review's eligibility or inclusion criteria, we utilized the PRISMA checklist. Eight studies fulfilled the criteria for providing relevant information on the impact of micronutrients supplementation on in vitro fertilization (IVF) outcomes. This study includes its utilization of research sources with a high level of evidence-based practices, notably RCTs, as the most common source of study. As RCTs are considered the most appropriate study design for intervention research, they are included in various micronutrients in IVF outcomes, as reviewed in this systematic review. Additionally, the study benefits from only using recent research, with a limit of including only primary studies conducted within the last 10 years, thus maintaining credibility. Furthermore, the study adheres to the PRISMA checklist, providing a methodo-logical guide for systematic review writing.

Limitations might be the fact that a high level of heterogeneity was observed among studies. This could be due to the differences in research methods used, micronutrient supplementation given, and outcomes studied in each study. Moreover, other associated factors such as supplementation doses, history of infertility, and comorbidities were not clearly reported in several studies. While this systematic review included only eight studies, the limited sample size necessitates cautious interpretation of the findings. To strengthen the conclusions, future research should include a more detailed meta-analysis involving larger cohorts of patients. This study lies in the diverse range of included research types, making it unable to differentiate between various studies on the same micronutrients with the same IVF assessment outcomes, thus precluding meta-analysis. The high heterogeneity observed among the included studies, primarily due to varying research methods, micronutrient supplementation protocols, and outcome measures, hampers the ability to derive definitive conclusions. The variability in micronutrient supplementation protocols (e.g., dosage, duration, and combination of supplements) across the included studies poses a significant limitation. Furthermore, differences in patient populations, such as baseline micronutrient status and underlying causes of infertility, may have influenced the outcomes. The lack of standardized outcome measures for IVF success, including live birth rates and embryo quality, further complicates the interpretation of the results. Therefore, further randomized controlled trials with standardized supplementation protocols and homogeneous patient populations are essential to establish stronger evidence on the effects of micronutrient supplementation on IVF outcomes. However, this weakness does not diminish the usefulness of the information that can be derived from this systematic review.

CONCLUSION

In conclusion, this systematic review examined eight studies on micronutrient supplementation's impact on in vitro fertilization (IVF) outcomes. Some studies suggested potential benefits of vitamin D3 supplementation >20 ng/ml, while others found no significant improvement in pregnancy rates with certain supplements. Further research with larger cohorts is needed to establish conclusive evidence in this area.

DISCLOSURES

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Conflict of interest

The authors declare there are no conflicts of interest.

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Author contribution

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