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REVIEW

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Folic acid supplementation in European women of reproductive age and during pregnancy with excessive weight: a systematic review

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Abstract

Objective Neural tube defects (NTDs), well-known consequences of folate deficiency, are the second most common cause of serious birth defects, affecting approximately one in a thousand pregnancies in Europe. Maternal folate deficiency before conception and during early pregnancy has been suggested as the most important preventable risk factor for NTDs; thus women should be supplemented before conception with 0.4 mg of folic acid (FA) until the first trimester of gestation. Findings have described a positive association between elevated Body Mass Index (BMI) and birth defect risk; data on plasma folate levels in pregnant women with obesity have shown values lower than recommended because of a state of chronic low-grade inflammation, resulting in increased metabolic demands. Nowadays, disparities exist regarding the recommended dose of FA in women at risk, including women of childbearing age with excessive weight. Therefore, this systematic review aimed to investigate if European childbearing age/pregnant women with overweight/obesity are supplemented according to the current country-specific FA recommendations and whether the dosage of 5 mg recommended for pregnant women with obesity is effective in preventing NTDs.

Methods The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed. An electronic database search of manuscripts was carried out in Web of Sciences, PubMed and Medline. The quality of the included studies was assessed by using the Quality Assessment for Diverse Studies statement.

Results Out of 1718 records identified, 8 manuscripts met all the inclusion criteria. Overall, the results showed that pregnant women with obesity adherent to FA recommendations ranged between 4% and 9.5%. Furthermore, the majority (61%) started the supplementation after conception, highlighting that European pregnant women are not particularly adherent to recommendations during the period of greatest need.

Conclusions The scarce adherence to the current guidelines shows an urgent need to standardize the recommendations across European countries. Particularly, women of childbearing age with excess weight should be monitored

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assessing serum folate, RBC folate, and homocysteine levels developing tailored supplementation protocols, to counteract the occurrence of NTDs.

Keywords Neural tube defects, Folic acid, Childbearing age, Pregnancy, Women with excessive weight, Supplementation

Plain English Summary

- Neural tube defects (NTDs) are severe congenital abnormalities connected to maternal folate deficiency. Current international guidelines recommend a daily supplementation of 0.4 mg of folic acid (FA) starting before conception and during the first trimester of pregnancy, to prevent NTDs.
- Women with excessive weight need higher folic acid doses due to their altered metabolic demands. Women with obesity encounter a greater risk of NTDs, as they often have lower plasma folate levels. This deficiency may result from chronic low-grade inflammation and increased nutrient requirements. For these vulnerable women, a higher dose of 5 mg of FA is recommended by the World Health Organization guidelines.
- However, only 4–9.5% of pregnant women with obesity adhere to FA supplementation recommendations, taking FA supplementation after conception, and missing the critical preconception period necessary for effective NTDs prevention.
- There is an urgent need to standardize FA supplementation recommendations across European countries and to monitor the folate status of women with excess weight. This will help develop personalized supplementation strategies aimed at effectively reducing the risk of NTDs.

Introduction

Neural tube defects (NTDs), are the second most common cause of serious congenital disorders and affect 0.2 –10 per 1000 established pregnancies worldwide, including about 1 in 1000 pregnancies in Europe [1, 2]. NTDs result from a failure of the neural tube to close properly within 4 weeks following conception. There are different types of NTDs, among which spina bifida, anencephaly, and encephalocele, are the most prevalent forms, while iniencephaly and craniorachischisis, are considered rare. The clinical characteristics and outcomes differ depending on the type of NTD [3]. In recent decades, maternal folate deficiency before conception and during early pregnancy has been suggested as the most preventable risk factor for NTDs. As reported by the World Health Organization (WHO), Red Blood Cell (RBC) folate concentrations should be above 400 ng/mL (906 nmol/L) in women of reproductive age to achieve the greatest reduction in NTDs [4]. Thus, women should i) supplement with 0.4 mg of folic acid (FA) before conception until the first trimester of pregnancy, ii) regularly include foods naturally rich in folate into their diet (e.g. leafy green vegetables such as spinach, asparagus, beets, broccoli, and artichokes), iii) consume fortified foods [5–7]. Indeed, mandatory fortification of staple foods, such as wheat flour, maize flour, and rice with folic acid, has become an important public health strategy for the primary prevention of NTDs. This safe and cost-effective initiative is currently implemented in nearly 60 countries worldwide and has successfully prevented a substantial number of NTD cases [3].

Data reveal that folate deficiency (defined as < 7 nmol/L) [8] is rare (0–5%) in developed countries; however, insufficient levels of folate (defined as < 25.5 nmol/L) [8] are more common (40–50%), suggesting a higher risk of NTDs even though folate storage may be adequate [9]. To date, despite the WHO's recommendation to start FA supplementation during childbearing age, many women begin later, often during the first trimester of pregnancy, which reduces its protective effect [10]. In this regard, existing literature reports a notable prevalence of unplanned pregnancies, potentially leading to delays in supplementation [11, 12].

Concurrently, the rising incidence of overweight and obesity among adolescents, particularly during the childbearing years, become one of the most significant challenges in obstetric care, due to its potential implications for maternal and fetal health [13]. Notably, in Europe, the prevalence of pre-pregnancy overweight and obesity ranges between 26.8% and 54.0% [14]. Research has indicated markedly decreased plasma folate levels in pregnant women with obesity, showing much lower values than those recommended, exposing them to higher risks of developing NTDs [15, 16]. Specifically, the literature indicates that during the first trimester, women with excessive weight exhibit lower serum folate levels when compared to those of normal weight ($\beta = -2.3$, $p < 0.01$),

showing an association with a higher likelihood of folate deficiency (OR = 2.0, p < 0.01) [17].

Findings from a recent meta-analysis registered a positive association between women with excessive pre-gravid Body Mass Index (BMI) and congenital abnormalities such as spina bifida and other NTDs when compared to those with normal pre-gravid BMI [18].

Women with obesity may have a lower folate level caused by a state of chronic low-grade inflammation, which results in an increased metabolic requirement [19]. This phenomenon could be explained by what is commonly defined as the "obesity paradox" [20]. According to this theory, individuals with excessive weight exhibit higher activity of the enzyme cytochrome P450 (CYP) 2E1, which can use FA as a substrate [21]. Indeed, women with overweight or obesity have been found to have higher levels of plasma folate oxidation products (specifically, 5-methyltetrahydrofolate oxidation product; MeFox) compared to those without obesity [19]. Overall, current global guidelines agree that women with a history of NTDs should take a higher dose of folic acid (5 mg) [5]. Although the same dosage is also recommended for women of childbearing age who are planning for pregnancy and pregnant women with obesity, the supporting scientific evidence remains limited [22, 23]. Therefore, further research and systematic reviews are essential to enable clinicians to provide an appropriate dosage.

Furthermore, because NTDs and obesity continue to have a significant health and economic impact at the European level, it is crucial to identify women at risk, to develop tailored recommendations and specific guidelines for FA supplementation and NTDs prevention. Considering the substantial evidence highlighting the benefits of folate fortification, this strategy should be considered alongside supplementation to achieve equitable primary prevention of NTDs globally.

Based on these considerations, the main research question of the present systematic review aimed at investigating if European childbearing age/pregnant women with overweight/obesity are supplemented according to the current country-specific FA recommendations.

Additionally, the authors will examine whether the dosage of 5 mg recommended for pregnant women with obesity is effective in preventing NTDs. The potential role of folate food fortification, when addressed in the studies included, will also be discussed.

Methods

The present systematic review has been registered in the PROSPERO International prospective register of systematic reviews (www.crd.york.ac.uk/PROSPERO; register no. CRD42024469780), and has been reported following the *Preferred Reporting Items for Systematic Reviews and Meta-Analyses* (PRISMA) guidelines [24].

Search strategy

A systematic literature review was initially performed in October 2023, then repeated in December 2023, and finally in February 2024. PubMed (http://www.ncbi.nlm.nih.gov/pubmed), and Web of Science have been searched, without time range restriction. A literature search was performed using structured search strings considering the following combined search terms for pregnancy and childbearing age, weight status, and FA supplementation. Therefore, "pregnan*" OR "gestation*" OR "preconception" OR "peri-conception" OR "prepregnancy" OR "pre-pregnancy" OR "childbearing" combined to "obes*" OR "overweight" OR "body mass index" OR "BMI", as well as "folic acid" OR "folin*" OR "vitamin B9" OR "folat*". A search sample has been added in the Additional File section (Additional file 1): "Query used for the search in the different databases".

Types of studies

Studies referred to humans were considered. Clinical Study, Clinical Trial, Clinical Trial, Phase IV, Clinical Trial Protocol, Clinical Trial, Phase I, Clinical Trial, Phase II, Clinical Trial, Phase III, Comparative Study, Controlled Clinical Trial, Multicenter Study, Observational Study, Randomized Controlled Trial in English language investigating both childbearing/pregnant women with overweight/obesity related to FA supplementation and completed in European countries were included. Research articles have considered referring to European women of childbearing age/European pregnant women with overweight and obesity as one of the populations at greater risk of giving birth to newborns with NTDs.

Types of participants

Eligible participants were women of childbearing age or pregnant (age range ≥ 18 years) with overweight or obesity defined by the WHO (overweight, 25.0–29.9; grade 1 obesity, 30.0–34.9; grade 2 obesity, 35.0–39.9; and grade 3 obesity, ≥ 40.0.) [25].

Outcome

The present systematic review aimed to explore if women of childbearing age/pregnant women with overweight/obesity across European countries supplement with FA according to the recommendations. Since childbearing age/pregnant women with obesity require a higher dosage of FA, the secondary objective of our systematic review was to determine whether the current recommended dosage is adequate to achieve blood folate levels within the reference range. Finally, the

authors evaluated whether the higher FA dose (5 mg) recommended for pregnant women with obesity, is effective in preventing NTDs in the offspring.

Inclusion and exclusion criteria

The inclusion criteria for exposed women were: aged ≥ 18 years; not diagnosed with type 2 Diabetes Mellitus (T2DM) and diseases related to malabsorption (*e.g.* celiac disease; Inflammatory Bowel Disease (IBD); bariatric surgery); no alcohol abuse; no enzyme defects related to folate metabolism (MTHFR mutation).

The exclusion criteria were as follows: aged < 18 years; diagnosed with T2DM and diseases related to malabsorption (e.g. celiac disease; IBD; bariatric surgery); alcohol abuse; defects of enzymes related to folate metabolism.

Study selection, data collection, and extraction

The flowchart of the study selection process is presented in Fig. 1, according to the PRISMA guidelines [24]. Three coauthors (FL, FS, and IB) determined whether the studies met the criteria previously established by undertaking the initial duplicates, title screening, and abstract review independently. In brief, after applying the search filters, the studies were equally divided among the three coauthors for the data extraction. A fourth co-author (DEM) randomly checked a sample of about 20% of the studies. Before the inclusion in the manuscript, each full-text article selected for retrieval has been reviewed independently by the three coauthors, checking the eligibility. Any difference in the selection process has been determined by discussion. Whenever there is no full consensus, a fourth co-author has been consulted. The three co-authors independently extracted relevant information from all the included studies on an Office Excel datasheet, as follows: *i)* authors and publication year; *ii)* type of the study; *iv)* country; *v)* sample size; *vi)* characteristics of participants (*e.g.* age, childbearing age or pregnant, demographic and socioeconomic characteristics, BMI expressed as Kg/m^2; *vii)* outcome assessment (FA supplementation evaluation—expressed as Y/N – related to BMI; FA supplementation dosage—expressed as mg/die—related to BMI; blood folate levels – expressed as ng/mL – related to BMI); *viii)* timing of supplementation (preconceptionally/during the first trimester); *ix)* protocol of supplementation (type of supplementation e.g. exclusively FA, multi-vitamins supplementation, formulation of supplement, frequency of supplementation); *x)* summary of findings; *xi)* European country-specific FA policy fortification. Whenever there was no consensus, a fourth co-author was consulted.

Data synthesis

Data extracted from this systematic research are presented as a summary of findings and the quality assessment of the eligible studies are shown in Tables 1 and 2.

Moreover, the extracted data are summarized according to the following columns: *i)* authors; *ii)* type of the study; *iv)* country; *vi)* characteristics of participants (*e.g.* age, childbearing age or pregnancy, demographic and socioeconomic characteristics, BMI expressed as Kg/m^2; *vii)* outcome assessment (FA supplementation evaluation—expressed as Y/N – related to BMI; FA supplementation dosage—expressed as mg/die—related to BMI; blood folate levels – expressed as ng/mL – related to BMI), *viii)* timing of supplementation (preconceptionally/during the first trimester); *ix)* protocol of supplementation (type of supplementation e.g. (exclusively FA, multi-vitamins supplementation, formulation of supplement, frequency of supplementation); *xi)* European country-specific FA policy fortification.

The blood folate levels have been taken into account about the FA-supplemented dosage, considering different classes of BMI (normal weight: 18.5 ≤ BMI < 24.99 kg/m^2; overweight: 25.00 ≤ BMI < 29.99 kg/m^2; obesity: BMI ≥ 30.00 kg/m^2) and countries.

In general, all continuous variables are reported/converted into means and SDs. Data regarding frequencies will be presented as percentages and the absolute number.

Study quality assessment

Regarding the quality assessment of the human-included studies, three co-authors (FL, FS, IB) independently assessed the quality of each study that met inclusion criteria. Following a discussion, the final score was determined; any differences were discussed with a fourth reviewer (DEM).

The authors adopted the criteria for quality appraisal from the *Quality Assessment for Diverse Studies (QuADS)* [26]. QuADS consists of 16 quality criteria, with 14 applying to qualitative studies, 14 to quantitative studies, and all 16 to any mixed methods study. Each criterion is rated on a scale from 0 to 3. The scores have been converted into percentages. No specific score was set as a cut-off for determining whether a study is of high or low quality. For instance, the authors then discuss the quality assessment considering the studies included.

Results

Overview of the studies

Searches from PubMed and Web of Science (WoS) returned 1718 records: 759 were excluded based on the applied filters (language, species, study design) (Fig. 1).

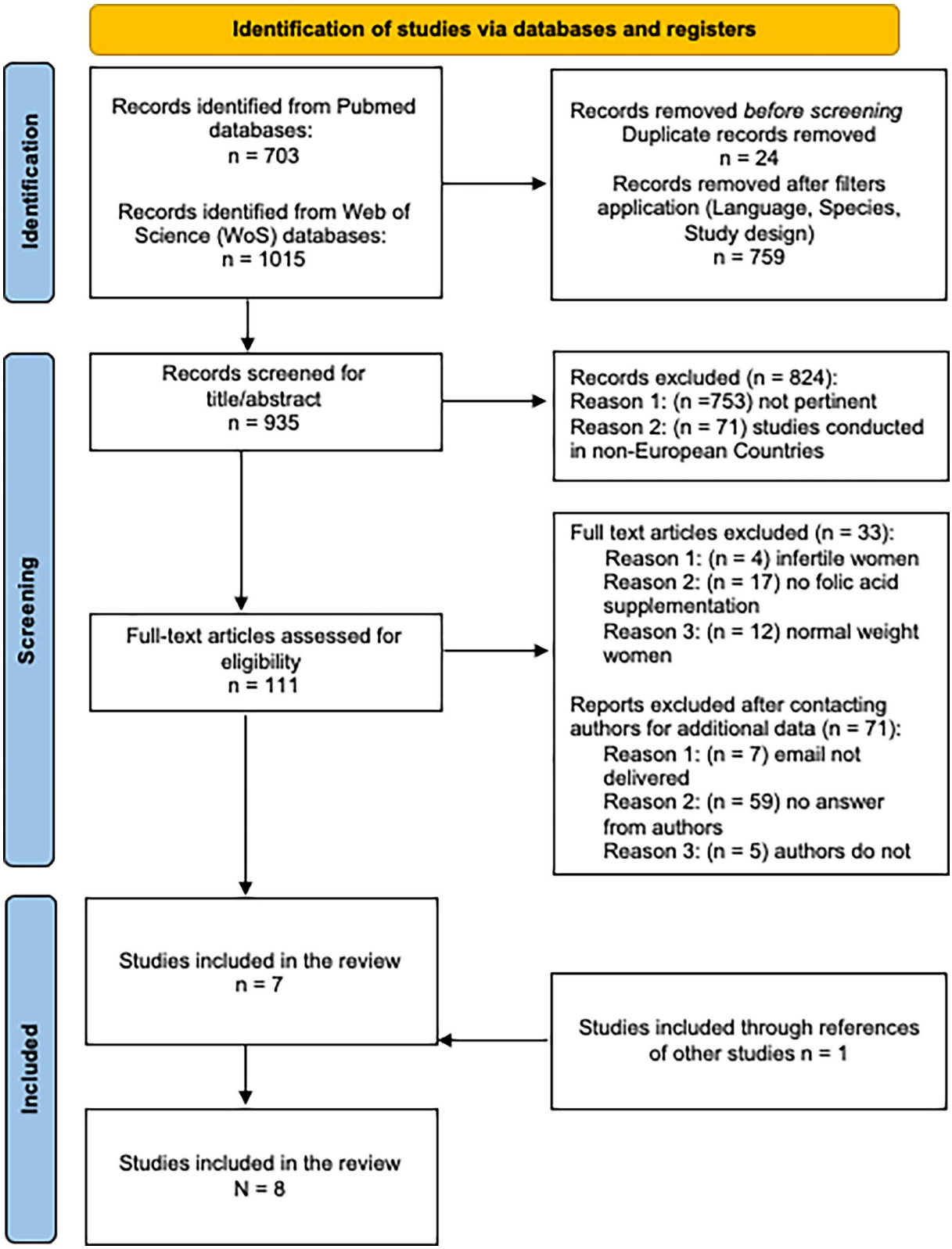

Fig. 1 Flowchart of the study selection process, based on the PRISMA guidelines

Table 1 Description of the studies selected according to the inclusion and exclusion criteria and included in the systematic review

Authors	Study Design	Country	Sample Size	Study Participants	Aim of the Study	FA supplementation evaluation Y/N	Dietary folate intake Y/N	FA dosage (mg)	FA supplementation protocol	FA supplementation related to BMI	FA timing of supplementation	FA Recommendation	Folate Blood Level (if available)	Fortification Policy
Cawley et al. [28]	Prospective Cohort Study	Ireland	n = 587	Pregnant women in the 1rst trimester: - BMI < 18.5 kg/m2: 1.9% (n = 11) - 18.5 < BMI < 25 kg/m2: 50.7% (n = 296) - 25 < BMI < 30 kg/m2: n = 171 (29,3%) - BMI > 30 kg/m2: n = 106 (18,1%)	To analyse folic acid supplementation among women seeking antenatal care at a large maternity hospital in Ireland	Y	N	- 0,4 mg of FA; - 5 mg as high-dose	na	- 0.4 mg FA (n = 549) - 5 mg (2 of them with obesity) (n = 15)	-Preconceptionally; - > 12 weeks preconceptionally; - Post conception	- 12 weeks of 400 mg folic acid (FA) supplementation is needed to reach the target RCF level of 906 nmols[38]; - International guidelines suggest that women with obesity should take high-dose (5 mg) FA around the time of conception to lower their risk of neural tube defects (NTDs)[38]	na	Northern Ireland: Mandatory fortification of wheat flour [35]. The NCFAFF recommends the mandatory fortification with FA of most white, brown and wholemeal breads on sale in Ireland [36]
Linell et al. [29]	Prospective Cohort Study	Ireland	n = 328	Pregnant women at ≤ 18 weeks' gestation: - BMI < 18.5 kg/m2: 1,2% (n = 4) - 18.5 < BMI < 25 kg/m2: 41,2% (n = 135) - 25 < BMI < 30 kg/m2: 33,8% (n = 111) - BMI > 30 kg/m2: 23,8% (n = 78)	To assess the use of folic acid supplementation among pregnant women, based on their obesity status	Y	N	- 0,4 mg of FA; - 5 mg as high-dose	na	- 0.4 mg FA; n = 216 (65,9%) - 5 mg; n = 22 (6,7%) out of the 78 women with obesity	- 30.2% (n = 99) commenced FA < 12 weeks prior to conception; - 30.5% (n = 100) commenced FA > 12 weeks prior to conception; - 61% (n = 199) commenced FA when found out they were pregnant	-Women of childbearing age should take 400 µg of folic acid daily, alongside dietary sources, for at least 12 weeks before conception - Women with obesity are recommended a higher dose of 5 mg of folic acid to reduce the risk of neural tube defects (NTDs) - The 5 mg dosage of FA should be taken before conception and continued through the first trimester of pregnancy[39]	na	Northern Ireland: Mandatory fortification of wheat flour [35]. The NCFAFF recommends the mandatory fortification with FA of most white, brown and wholemeal breads on sale in Ireland [36]

Table 1 (continued)

Authors	Study Design	Country	Sample Size	Study Participants	Aim of the Study	FA supplementation evaluation Y/N	Dietary folate intake Y/N	FA dosage (mg)	FA supplementation protocol	FA supplementation related to BMI	FA timing of supplementation	FA Recommendation	Folate Blood Level (if available)	Fortification Policy
Malvasi A. et al. [30]	Prospective, randomized, double-blind, placebo controlled clinical trial, pilot study	Italy, Greece, Russia	n = 48	- Uniparous healthy pregnant women between 13 and 24th week of pregnancy - 25 < BMI < 30 kg/m2	To assess biochemical parameters during the second trimester of pregnancy in women who received Inositol supplementation	N (preconception not mentioned)	N	- 0,4 mg of FA	Formulation of Supplement (MDFN)—Daily	- n = 24 (treated group): 0,4 mg - n = 24 (control group): NA	Between 13 and 24th week of pregnancy	na	na	No official food fortification policy [35]
Mohd-Shukri N. et al. [31]	Prospective case–control study	UK	n = 241	- BMI > 40 kg/m2: n = 148 - BMI < 25 kg/m2: n = 93	To compare dietary habits and physical activity levels during pregnancy between women with very severe obesity and those of normal weight	Y	Y	- 0,4 mg of FA; - 5 mg as high-dose	na	BMI < 25 kg/m2: - 0.4 mg FA; n = 84 -5 mg of FA; n = 2 BMI > 40 kg/m2: - 0.4 mg FA; n = 129 (96%) -5 mg of FA; n = 5 (4%)	- Early pregnancy (16 weeks of gestation); - Late pregnancy (28 weeks of gestation)	na	Early pregnancy measurements (16 weeks), (mcg/mL)(SD) - Women with BMI > 40 kg/m2, (n = 25): 7.9 mcg/mL (4.2) - Women with BMI < 25 kg/m2, (n = 25): 15.0 mcg/mL (2.7) Late pregnancy (28 weeks), (mcg/mL)(SD) - Women with BMI > 40 kg/m2, (n = 25): 3.9 mcg/mL (2.8) - Women with BMI < 25 kg/m2, (n = 25): 10.6 mcg/mL (5.7)	Mandatory fortification of wheat flour [35] New legislation (effective November 2024) mandates FA fortification of non-whole-meal wheat flour by late 2026 [37]

Table 1 (continued)

Authors	Study Design	Country	Sample Size	Study Participants	Aim of the Study	FA supplementation evaluation Y/N	Dietary folate intake Y/N	FA dosage (mg)	FA supplementation protocol	FA supplementation related to BMI	FA timing of supplementation	FA Recommendation	Folate Blood Level (if available)	Fortification Policy
Redfern K. et al. [32]	Prospective observational study	UK	n = 66	Pregnant women with obesity: a BMI ≥ 30 kg/m2 and < 40 kg/m2, at 12 and 14 weeks of gestation	To examine the intake of key micronutrients (iodine, vitamin D, folate) among pregnant women with obesity in the UK, considering relevant demographic characteristics	Y	Y	- 0,4 mg of FA; - 5 mg as high-dose	- Within pregnancy multivitamin; - FA	5 mg of FA, n = 17 (26%) - n = 5 women supplement 5 mg of FA (2/5 with GDM) - n = 12 women supplement 5 mg + 0,4 mg (6/12 with GDM) 0.4 mg FA, n = 24 (36%)	1st trimester	- Women should supplement with 400 µg of folic acid daily from pre-conception until 12 weeks of gestation [40]; - The RCOG, advises that women with obesity who are planning to become pregnant or are already pregnant should take a higher dose of 5 mg of folic acid daily until the end of the first trimester [40]	na	Mandatory fortification of wheat flour [35] New legislation (effective November 2024) mandates FA fortification of non-whole-meal wheat flour by late 2026 [37]
Santamaria A. et al. [33]	Randomized Controlled Trial	Italy	n = 220	- 25 < BMI < 30 kg/m2	To assess whether myo-inositol supplementation can reduce the rate of gestational diabetes mellitus (GDM) in overweight women	N (preconception not mentioned)	N	0,4 mg of FA	- Treated group received: 2 g myo-inositol + 0.2 mg of FA twice a day, - Placebo group received: 0.2 mg of FA twice a day	n = 220 supplemented with 0.2 mg of FA twice a day	12th–13th week of gestation	na	na	No official food fortification policy [35]
Vitale S. et al. [34]	Randomized and Open-Label, placebo Controlled clinical Trial	Italy	n = 223	- 25 < BMI < 30 kg/m2	To examine the effects of myo-inositol supplementation on GDM rates and body water distribution in women with overweight	N (preconception not mentioned)	N	0,4 mg of FA	- Treated group received: 2 g myo-inositol + 0.2 mg of FA twice a day, - Placebo group received: 0.2 mg of FA twice a day	n = 223 supplemented with 0.2 mg of FA twice a day	12th–13th week of gestation The treatment lasted until 3 weeks after delivery	na	na	No official food fortification policy [35]

Table 1 (continued)

Authors	Study Design	Country	Sample Size	Study Participants	Aim of the Study	FA supplementation evaluation Y/N	Dietary folate intake Y/N	FA dosage (mg)	FA supplementation protocol	FA supplementation related to BMI	FA timing of supplementation	FA Recommendation	Folate Blood Level (if available)	Fortification Policy
O'Malley E. et al. [27]	Prospective observational study	Ireland	n = 496	- 18.5 < BMI < 25 kg/m2: n = 269 - BMI > 30 kg/m2: n = 97	To investigate the association between maternal BMI in early pregnancy and serum and RBC folate and plasma vitamin B12 levels	Y	Y	- 0.4 mg of FA; - 5 mg as high-dose	na	Higher dose of FA (5 mg): - BMI > 30 kg/m2: 9.5% (n = 8); - 18.5 < BMI < 25 kg/m2: 7.1% (n = 19) 0.4 mg of FA: - BMI > 30 kg/m2: 90.4% (n = 76);	Women were asked about their FA supplementation - at enrollment (first visit: 12,1 weeks) - pre-pregnancy (retrospectively)	The RCOG [39], RANZCOG[41] and Irish guideline[42] recommendations for obese women advise a dose of 5 mg daily	There was no statistical difference in the mean values of RBC folate between BMI categories: - BMI < 25.0 kg/m2: 139.8 nmol/L (SD 413.5) - BMI > 30 kg/m2: 1184.0 nmol/L (SD 476.7) (p = 0.18)	Northern Ireland: Mandatory fortification of wheat flour [35]. The NCFAFF recommends the mandatory fortification with FA of most white, brown and wholemeal breads on sale in Ireland [36]

Data are presented as percentage and absolute number of pregnant women with overweight or obesity that are supplemented with normal (0.4 mg) or higher (5 mg) of folic acid. Authors also reported the normal weight and underweight status data other than folate blood level (mcg/mL) (if applicable)

FA: Folic Acid; RCF: Red Cell Folate; GDM: Gestational Diabetes Mellitus; RCOG: Royal College of Obstetricians and Gynaecologists; RANZCOG: Royal Australian and New Zealand College of Obstetricians and Gynecologists; BMI: Body Mass Index; na: not applicable; NCFAFF: National Committee for Folic Acid Food Fortification

Table 2 Quality assessment

Items	Cawley et al. [28]	Linell et al. [29]	Malvasi et al. [30]	Nor Moh-d-Shukri et al. [31]	Redfern K et al. [32]	Santamaria et al. [33]	Vitale S et al. [34]	O'Malley et al. [27]
1. Theoretical or conceptual underpinning to the research	3	2	3	2	3	3	2	3
2. Statement of research aim/s	3	3	3	2	3	3	3	3
3. Clear description of research setting and target population	3	3	3	2	3	3	1	2
4. The study design is appropriate to address the stated research aim/s	3	3	2	3	3	3	2	3
5. Appropriate sampling to address the research aim/s	3	3	1	2	2	2	0	2
6. Rationale for choice of data collection tool/s	2	3	2	2	2	2	2	3
7. The format and content of data collection tool is appropriate to address the stated research aim/s	3	2	2	3	3	2	2	3
8. Description of data collection procedure	2	2	3	3	3	3	2	3
9. Recruitment data provided	3	2	3	2	3	2	2	3
10. Justification for analytic method selected	2	3	2	2	2	2	2	2
11. The method of analysis was appropriate to answer the research aim/s	2	3	2	2	2	3	3	3
12. Evidence that the research stakeholders have been considered in research design or conduct	2	1	3	2	2	2	2	2
13. Strengths and limitations critically discussed	3	1	3	1	3	3	3	3
Total score (sum and % of 13 items' score)	34 (80,90%)	31 (73,80%)	32 (76,20%)	28 (66,60%)	34 (80,90%)	33 (78,50%)	26 (66,66%)	35 (83,30%)

The study quality for the eligible studies is presented. A value of between 0 and 3 was assigned to each item

Duplicates (n = 24) were removed. Thus, 824 studies were excluded as their titles/abstracts were not relevant, and 111 studies were assessed for eligibility and full-text screening. Of these, 33 studies were excluded since they did not meet the inclusion criteria, and 71 studies were excluded after contacting the corresponding authors to obtain the datasets and extrapolate the required additional data. Moreover, one other study was selected during the full-text screening since it reported outcomes of relevant interest [27]. In total, 8 studies [27–34] were included in this systematic review. Overall, the studies were conducted in Ireland, Italy, the United Kingdom, Greece, and Russia. Data extracted from this systematic research, including those related to food fortification policies [35–37], are summarized in Table 1.

Overview of the study quality

The assessment of the study's quality for the eligible studies in this systematic review is presented in Table 2. Out of the total studies, the majority (n = 6) [27–30, 32, 33] achieved a total score higher than 70%; the others (n = 2) scored slightly lower, with a percentage above 66% [31, 34].

Characteristics of studies included in the systematic review

The 8 included studies in this systematic review [27–34] are summarized below. All the studies take into account pregnant women with excessive weight and consider FA supplementation in the preconception period and/or during pregnancy. Considering BMI, the studies focused on women with both overweight and/or obesity based on WHO classification (BMI ≥ 25.0 kg/m^2: overweight; BMI ≥ 30.0 kg/m^2: obesity) [43]. As far as studies included in this review, three of them involved women who were taking FA supplements preconceptionally [28, 29], while the rest focused on FA supplementation starting from the 1st trimester [27, 30–34]. Briefly, Cawley and colleagues [28] conducted a prospective cohort study to assess the impact of FA supplementation in n = 587 pregnant women. Questionnaires were used to gather information on FA supplementation during either pre- and periconceptional periods, including details on dosage and specific brand names of the supplements. The authors stratified the population according to BMI, reporting 29.3% (n = 171) women with overweight and 18.1% (n = 106) with obesity. Approximately 75% of the participants did not meet FA supplementation recommendations, which increased the risk of having low Red Cell Folate (RCF) levels. Specifically, only 5.7% (n = 6) of women with obesity were taking the recommended higher dosage of FA (5 mg). Similarly, in their prospective cohort study, Linell et al. [29], stated that out of n = 78 women with a BMI ≥ 30.0 kg/m^2, only 6.7% were supplemented with the recommended higher dosage of FA (p = < 0,001). Furthermore, data revealed that 61% (n = 199) of women started FA supplementation upon becoming aware of their pregnancy, which increased the risk of NTDs in the offspring. These findings are consistent with the results of a case–control study conducted by Mohd-Shukri et al. [31] which examined the role of dietary habits and physical activity in a sample of pregnant women with severe obesity (BMI > 40 kg/m^2) compared to the control group. Notably, only 31% of the former started taking FA supplementations before conception. The study also encompassed the assessment of serum folate levels at 16 weeks (early pregnancy) and 28 weeks (late pregnancy) of gestation in a subset of both groups (n = 25). Results revealed that at the 28th week, women with severe obesity exhibited an average serum folate level of 3.9 ng/mL (± 2.8 SD), while the control group registered 10.6 ng/mL (± 5.7 SD) (p < 0.0001). In this context, the authors highlighted that pregnant woman with obesity exhibited significantly lower circulating folate levels compared to the control group, with early pregnancy (16 weeks) levels averaging 7.9 ng/mL (± 4.2 SD) in women with obesity, versus 15.0 ng/mL (± 2.7 SD) in the control group. Noteworthy, 96% of women with obesity supplemented with 0.4 mg of FA, and did not adhere to the recommendations. While 2% (n = 5) of them did not supplement either before or during pregnancy. Focusing on pregnant women with obesity, Redfern et al.[32], in a cohort of English women, recorded differences in the FA dosage. Out of the 66 recruited women, 26% (n = 17) took 5 mg of FA during the first trimester; n = 12 of these added an extra dose of 0.4 mg. The remaining 36% did not adhere to the recommendations and only supplemented with 0.4 mg. Out of 24 women who were not taking FA by the end of the first trimester, only one achieved the Recommended Nutritional Intake (RNI) of 300 ug of folate through diet. Notably, the study did not assess serum folate levels. In contrast, the prospective-observational study by O'Malley et al. [27], aimed to analyze the association between maternal BMI in early pregnancy and serum folate levels, considering both dietary intake and FA supplementation protocol. Among the 84 women with obesity who were aware of the supplemented dosage of FA, only 9,5% (n = 8) reported taking 5.0 mg, as recommended. These data were consistent with serum folate levels being lower in women with BMI > 30 kg/m^2 compared to the control group (9.23 ng/mL vs 10.44 ng/mL, P = 0.02). However, no significant difference was observed in the mean RCF between the two groups.

Two randomized controlled trials (RCT) were included in this systematic review [30, 33]. Their objective was to evaluate the effectiveness of a supplement containing Myo-inositol (4 g/day) and FA (0.4 mg/day) in preventing

gestational diabetes compared to the placebo group, which received only 0.4 mg of FA per day. Both studies involved overweight pregnant women who started the supplementation protocol at 12–13 weeks of gestation. Overall, the studies demonstrated that the group of women undergoing treatment with Myo-inositol and FA exhibited improved lipid (cholesterol, $p=0.0001$; LDL, $p=0.0001$; HDL, $p=0.047$; TG, $p=0.0001$) and glycemic profiles (glycemia, $p=0.019$) compared with the control group [30]. Furthermore, a reduction in the incidence of GDM was recognised within the same group (11.6% versus 27.4%, respectively, $p=0.004$) [33].

Discussion

Although a decline in the prevalence of NTDs was observed between 2001 and 2015, the prevailing data remains alarming, counting two cases per 1000 births, amounting to an estimated 214.000–322.000 affected pregnancies worldwide annually [3]. Furthermore, while historically NTDs were predominant in low-income countries, nowadays their occurrence increased in high-middle-income countries, notably in Europe. From 1998 to 2017, an estimated 95.213 NTD-affected pregnancies were recorded among 104 million births across 28 countries in the European Union, reflecting a prevalence rate of 0.92 per 1.000 births [44].

Studies reported an association between maternal high BMI (≥ 30 kg/m^2) and the severity of NTDs, identifying this population as more vulnerable [45]. Indeed, women with excessive weight exhibit lower folate levels due to several factors, such as chronic low-grade inflammation, poor-quality diet adherence, and non-compliance to supplementation recommendations [46]. Moreover, reduced intake of FA is often attributed to unplanned pregnancies and ineffective contraceptive methods [47]. For these reasons, scientific literature related to FA supplementation in women of childbearing age with excessive weight has been systematically reviewed. Studies conducted in European countries were evaluated to assess FA supplementation practices. Although this review primarily focuses on FA supplementation, the contribution of folate fortification in staple foods as an additional preventive strategy for NTDs is also recognized and discussed, due to its demonstrated effectiveness in reducing folate deficiency at the population level.

As shown in Table 2, most of the studies included were of good quality showing a percentage higher than 66% according to the QUADs criteria.

Overall, most of the studies analyzed in this review reported a high number of women non-compliant with the FA recommendations during the periconceptional period [27–29, 31, 32, 34]. In particular, the study conducted by Cawley and colleagues exhibits that only 5.7% ($n=6$) of pregnant women with obesity were taking the recommended higher dosage (5 mg) of FA supplementation [28]. These data were in line with the results by Linell et al., showing that only 6.7% of women with obesity were supplemented with the recommended higher dose, emphasizing the low adherence to FA recommendations in this vulnerable group [29, 48]. Mohd-Shukri and colleagues [31] also reported lower folate levels in women with obesity, emphasizing the need for improved supplementation practices. These results might be due to inadequate adherence to the FA protocol and chronic low-grade inflammatory state, typical of obesity [49]. Regarding diet, a poor-quality and unbalanced dietary pattern can lead to micronutrient deficiencies, including vitamin B12 and folate, which are often observed in individuals with a high BMI [50]. Specifically, folate deficiency can reduce methyl group availability, resulting in higher homocysteine levels. This condition is known as a risk factor for different adverse health outcomes, including neurological disorders, vascular diseases, and reproductive health [51]. High maternal homocysteine levels are also associated with pregnancy complications, posing a threat to the health of the maternal–fetal dyad in the short and long term [52]. For instance, pregnant women with obesity have increased risks related to pregnancy, delivery, and postpartum, such as pregnancy-induced hypertension and GDM, preeclampsia, and cesarean section [53]. Still, cardiometabolic and neurodevelopment impairment has been detected in the offspring of women with obesity, other than higher incidence of large for gestational age (LGA) babies, perinatal mortality, and congenital anomalies, including NTDs [54]. The existing body of literature reveals a paucity of studies delving into the effect of FA supplementation on NTDs incidence. Notably, out of the studies included in this systematic review, only two investigated health outcomes in newborns [33, 34]. However, they evaluated anthropometric measurements at birth, such as weight, height, and head circumference, as well as the incidence of macrosomia, without addressing the occurrence of NTDs [33, 34].

Two randomized controlled trials included in the present review evaluated the efficacy of FA supplementation combined with Myo-inositol on the incidence of GDM [33, 34], indicating a positive impact. However, it was unclear whether the effect was due to one molecule or both, or their potential synergistic effect. In the last decades, research has emphasized the role of inositol in different forms, such as Myo-inositol and D-chiro-inositol, in improving insulin sensitivity and related conditions such as diabetes mellitus and reproductive disorders [55]. One study not included in this systematic review, revealed that administering Myo-inositol during the first trimester of pregnancy to

women with a BMI > 30 kg/m^2 and pre-gestational diabetes, decreased the occurrence of GDM in the treated group (Myo-inositol 2 g and 200 μg FA twice a day) compared to the control (200 μg FA twice a day), by enhancing insulin sensitivity (P = 0,001; OR = 0,34, 95% CI: 0,17–0,68) [55]. Conversely, despite being affected by obesity, women in this study did not adhere to the recommended higher dosage of 5 mg [56]. Similar to FA, Myo-inositol has emerged as a contributing factor in reducing the prevalence of NTDs. Studies in mice have demonstrated that mothers with significantly lower blood inositol concentration levels had a 2.6-fold increased risk of having NTDs affected offspring [57]. Further research is needed to deepen understanding of the role of inositol in preventing NTDs and its interaction with folate metabolism.

During the study selection process, the authors recorded that most of the included studies focused on supplementation practice once pregnancy has already begun, investigating the pre-gestational FA protocol, retrospectively [27–34]. The authors highlighted the lack of comprehensive data on women of reproductive age, despite the well-established importance of raising serum folate levels before pregnancy. Concerning dietary habits, Mohd-Shukri et al. [31] reported that pregnant women with very severe obesity exhibited significantly lower dietary folate intake; this was also confirmed by Redfern and colleagues [32]. Notably, these studies referred to different RNI values regarding folate (600 μg/day *vs.* 300 μg/day), even though they were both conducted in the UK [31, 32]. Folate is essential for synthesizing nucleic acids and amino acids, and it plays a crucial role in cell growth and differentiation during the periconceptional period [58]. Daily intakes of 800 μg to 5 mg of folic acid from supplementations have been linked to an increased risk of perinatal mortality and cancer development [59]. Therefore, it is crucial to establish precise and consistent guidelines to better provide healthcare professionals addressing the dietary needs of pregnant women.

This systematic review included studies from European countries that adhered to a policy of voluntary fortification. Mandatory fortification has been implemented in different non-European countries, such as the USA in 1998, followed by Canada, Israel, Chile, and others. In Europe, the proposal for mandatory fortification has been placed forward by the UK and Ireland, which registered a high incidence of NTDs [60]. Fortification aims to contrast folate deficiency, particularly in unplanned pregnancies, without replacing periconceptional supplementation. Notably, fortification in the USA has demonstrated a reduction in NTDs incidence by 25–30%, approximately 50% of the preventable fraction with folic acid [61].

Voluntary fortification is an alternative approach, where fortified foods are available on the market and promoted by public and private initiatives. However, this method requires well-informed citizens and faces challenges in effectively controlling and monitoring intake levels over an extended period [62]. Despite the widespread use of dietary supplements, even among non-fertile women, concerns have been raised about potential excessive FA intake [63]. However, as noted in the present systematic review, European pregnant women are not particularly adherent to recommendations during the period of greatest need [27–34]. All the included studies highlighted the influence of different factors on the poor adherence of women with obesity to the recommended higher dose of FA. These include age, level of education, smoking, alcohol consumption, and pregnancy planning. Notably, the latter emerges as a pivotal determinant in compliance with FA supplementation, particularly during the preconception period [29]. From the studies conducted so far, it is not possible to make definitive considerations about the pre-pregnancy period due to insufficient comprehensive data. There is a need to conduct longitudinal cohort studies, rather than retrospective ones, on a larger sample size using validated and targeted questionnaires, to collect a greater quantity of data that can be used in clinical practice.

Conclusion

The literature analysis demonstrates that pregnant women with overweight/obesity frequently do not adhere to current FA supplementation recommendations. Furthermore, there is an urgent need to standardize the recommendations across European countries. To date, the scientific community should: i) conduct higher quality clinical trials to ascertain if the highest recommended dose (5 mg) is the most suitable and safe for both women with obesity and their offspring; ii) educate women of childbearing age, particularly those with excessive weight, on the significance of commencing FA supplementation before pregnancy, as neural tube closure occurs around the 28th day of gestation; iii) encourage women of childbearing age with obesity to embrace a healthy lifestyle and argument the consumption of folate-rich foods before conception; iv) promote the implementation of effective food fortification policies with folic acid through the active engagement of healthcare providers, to achieve equitable primary prevention of NTDs across countries.

In conclusion, women of childbearing age with excess weight should be monitored assessing serum folate, RBC folate, and homocysteine levels to gain a better understanding of one-carbon metabolism and devise tailored supplementation protocols. These improvements should

be supported by educational policies involving cooperation among healthcare professionals, medical doctors, policymakers, and citizens, to enhance awareness among women of childbearing age about their pivotal role in supporting health across generations.

Supplementary Information

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Supplementary material 1.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Competing interest
The authors declare no competing interests.

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