Periconceptional use of vitamin A and the risk of giving birth to a child with nonsyndromic orofacial clefts—A meta-analysis

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Abstract

Background: We conducted a meta-analysis of observational epidemiological studies to evaluate the association between periconceptional use of vitamin A and the risk of giving birth to a child with nonsyndromic orofacial clefts (NSOFCs).

Methods: We carried out a systematic literature search of Embase, PubMed, Web of Science, Google Scholar, and OpenGrey from inception to June 30, 2021. Two reviewers independently evaluated the studies that met the inclusion criteria and filled out an abstraction form for each study. Study quality was assessed using the Newcastle-Ottawa Assessment Scale (NOS). Adjusted estimates were pooled with an inverse variance weighting using a random-effects model. Heterogeneity and publication bias were assessed using the Cochran’s Q test and funnel plot, respectively.

Results: A total of six case–control studies with moderate risk of bias were included. The pooled OR showed a 20% reduction in the risk of NSOFCs for periconceptional use of vitamin A which was not statistically significant (OR = 0.80; 95% CI 0.54–1.17, p = 0.25). For nonsyndromic cleft lip with or without cleft palate (NSCL/P), the studies were homogenous, and the pooled estimate showed a 13% risk reduction, which was significant (OR = 0.87; 95% CI 0.77–0.99, p = 0.03). For nonsyndromic cleft palate only (NSCPO), the pooled estimate showed a 33% lower likelihood, which was not statistically significant (OR = 0.67; 95% CI 0.42–1.08, p = 0.10).

Conclusion: Our results suggest a possible protective effect for the periconceptional use of vitamin A on the risk of NSCL/P. This finding should be investigated further in prospective studies across multiple populations.

KEYWORDS
craniofacial birth defects, multivitamins, orofacial clefts, retinol, vitamin A
1 | BACKGROUND

Orofacial clefts (OFCs) are the most common congenital birth defects of the head and neck (Mai et al., 2014), with an estimated prevalence that ranges between 1 in 500 and 1 in 2500 (Mossey & Modell, 2012). OFCs can be broadly classified into syndromic orofacial clefts (SOFCs) and nonsyndromic orofacial clefts (NSOFCs) based on the presence or absence of other structural or cognitive impairments (Calzolari et al., 2007). The NSOFCs represent the most cases of OFCs and, depending on the affected structure(s), can be further classified into cleft lip (CL), cleft lip and palate (CLP), and cleft palate only (CPO) (Carinci, Scapoli, Palmieri, Zollino, & Pezzetti, 2007). Due to the closely related embryological basis between CL and CLP, they are usually grouped together as CL with or without cleft palate (CL/P; Carinci et al., 2007). The treatment is primarily surgical to correct the structural defects and improve aesthetics. However, restoring optimal function requires other care such as orthodontics, nursing, and speech therapy, among others (Nahai, Williams, Burstein, Martin, & Thomas, 2005). The comprehensive care requirement and the integration of affected individuals and families pose an economic burden on the family and society, especially in resource-limited environments.

The etiology of NSOFCs is multifactorial and the role of several exogenous factors such as maternal nutrition, including multivitamins, medications, and drugs used during the periconceptional period is well documented (Kawalec, Nelke, Pawlas, & Gerber, 2015). The periconceptional period (3 months before pregnancy and the first trimester) is a critical period of embryonic development during which tissues and organs are formed in utero (embryogenesis) (Steegers-Theunissen, Twigt, Pestinger, & Sinclair, 2013). Embryogenesis requires the establishment of an accurate methylation pattern in a process called fetal programming (Kwon & Kim, 2017). Fetal programming is achieved by gene expression patterns, which are crucial for the developing baby's proper structural and functional development (Lau & Rogers, 2004). Although most human traits are determined by the genes located in the deoxyribonucleic acid (DNA), gene expression patterns are affected by environmental factors (Reik et al., 2003). This alteration of gene expression by environmental factors (epigenetics) is achieved through DNA methylation, chromatin remodeling, and histone modification (Joshi, Chellappan, & Kuksal, 2020). Insufficient or deficient dietary nutrients during embryogenesis result in a permanent alteration to specific structures by affecting the programming process (Barker, 1990). Maternal nutrition is among the most important environmental variables that decide the fate of the developing embryo (Graham, 2000).

Vitamin A is a fat-soluble vitamin that can be obtained from the diet in the form of provitamin A (carotenoids) from plant products or as preformed vitamin A (retinol and retinyl esters) from animal products (Finnell et al., 2004; Tang, 2010). Additionally, preformed vitamin A can also be gotten directly from supplements together with other vitamins (as multivitamins) or in isolation (vitamin A supplements). The absorption and conversion of dietary carotenoids into vitamin A occurs in the small intestine (Tang, 2010). The absorption process is influenced by food formulation, processing, and fat contents (Furr & Clark, 1997). Furthermore, the absorption and conversion of carotenoids is less efficient in the presence of vitamin A from other sources regulating the plasma level of vitamin A in humans (Tang, 2010). Vitamin A plays a crucial role during embryogenesis, most importantly in the modulation of the upper lip and palate morphogenesis (Finnell et al., 2004). Studies in experimental animals have linked excess or deficiency of vitamin A to an increased risk of OFCs (Finnell et al., 2004). While the teratogenic effect of excess vitamin A has been reported in animal studies, the threshold at which vitamin A becomes teratogenic in humans remains controversial (Bastos Maia et al., 2019). Furthermore, fetal vitamin A (retinol) levels do not increase significantly following maternal supplementation (Miller, Hendrickx, Mills, Hummler, & Wiegand, 1998). This is because while the placenta can transfer teratogenic compounds and continue to produce teratogens through ongoing oxidative metabolism and isomerization (Miller et al., 1998), the mean serum levels of vitamin A remain within the physiologic range even at a dosage of 30,000 IU (9,000 μg/day) (The recommended daily dose during pregnancy is 800 μg/day) (WHO, 2004).

Over the years, human epidemiological studies have focused largely on multivitamins (with or without vitamin A as a component; Czeizel, Dobó, & Vargha, 2004; Itikala, Watkins, Mulinare, Moore, & Liu, 2001; Shaw, Wasserman, O’Malley, Tolarova, & Lammer, 1995). The few human studies that evaluated the specific effect of vitamin A (Johansen, Lie, Wilcox, Andersen, & Drevon, 2008; Mitchell, Murray, O’Brien, & Christensen, 2003; Werler, Lammer, Rosenberg, & Mitchell, 1990) reported a largely nonsignificant protective effect of vitamin A on the risk of NSOFCs. Only one study reported a statistically significant protective effect of vitamin A on CPO (Johansen et al., 2008). Further, studies have shown that vitamin A deficiency during pregnancy is likely to have different phenotypic effects depending on the stage of fetal development (Bastos Maia et al., 2019). Hence, this meta-analysis of observational epidemiological
studies aims to evaluate the association between vitamin A use during the periconceptional period and the risk of giving birth to a child with NSOFCs among pregnant women. We hypothesize that the use of vitamin A (dietary intake or supplement) during the periconceptional period will reduce the risk of NSOFCs or a subphenotype (CL/P and CPO).

2 | METHODS

2.1 | Search strategy

We carried out a systematic literature search of Embase, PubMed, Web of Science, Google Scholar, and OpenGrey using the following search terms: “Vitamin A,” “Retinol,” “beta-carotene,” “alpha-carotene,” and “multivitamins” in combination with “orofacial cleft,” “craniofacial birth defects,” “congenital oral defects,” “oral cleft,” “cleft lip,” and “cleft palate.” The search included all the articles from the inception of the databases to June 30th, 2021. An additional manual search of references from selected studies was also conducted. From our search, only one article was not in English, and after going through its abstract, which was available in English, it did not meet our inclusion criteria. Our search included both published articles and gray literatures. A study was included if it was an original human observational epidemiological study (cross-sectional, case–control, or cohort study), evaluating the association between orofacial cleft or craniofacial birth defects including OFCs and vitamin A (dietary, supplement, or both) used at anytime within the periconceptional period (3 months before pregnancy and first 3 months of pregnancy). Included studies must provide the result for vitamin A specific effect on the risk for NSOFCs. Studies were excluded if they were animal or experimental study, shared population with another included study, case report, case series, review, or quasi-experimental studies. Studies without relevant quantitative information or without adequate data for odds ratio or relative risk calculations were also excluded.

Two reviewers independently evaluated the studies that met the inclusion criteria and filled out an abstraction form for each of the studies. The information contained in the abstraction form included: study authorship, year of publication, study location, study design, study population, sample size, source of vitamin A, duration of exposure, the dosage of vitamin A, and how it was calculated, outcome ascertainment method, cleft phenotypes, and confounders adjusted for. Study quality was assessed using the Newcastle–Ottawa Assessment Scale (NOS; Wells et al., 2000). The NOS scale has three domains (selection of participants, comparability, and exposure/outcome assessment) with a maximum score of 9. Each item under the domains has a maximum score of 1, except for the comparability domain, which has item and a maximum score of 2. These scores are assigned based on how well a study fulfills the individual items using a set of standardized criteria. Studies were classified based on the total quality score using arbitrary cut-offs (≤3 = low-quality (high-risk of bias), 4–6 = moderate quality (moderate risk of bias), and 7–9 = high-quality (low-risk of bias)). A third reviewer checked the abstraction forms from the two independent reviewers for discrepancies, and all discrepancies were resolved by consensus.

Adjusted odds ratios were used for the analyses. These adjusted estimates were pooled with a generic inverse variance weighting method using a random-effects model to estimate the summary measure of effects in the main and subgroup analyses. Funnel plots were created using the effects of vitamin A on all NSOFCs for five studies (excluding one study, which reported only the subphenotype specific results) to visually assess publication bias by checking for asymmetry. Cochran’s Q test was used to assess the heterogeneity of the included studies, and a p-value < .2 indicates potential heterogeneity. Additionally, $I^2$ was calculated to assess the degree of heterogeneity. Subgroup analyses were conducted for the subphenotypes of OFCs (CL/P and CPO) as these have been shown to be etiologically distinct and are in line with our hypothesis, which suggests the possibility of a phenotype-specific effect. Revman (Review Manager from the Cochrane Collaboration) meta-analytic software was used for the analyses (RevMan, 2020). Systematic review registration: International prospective register of systematic reviews (PROSPERO CRD42021268825).

3 | RESULTS

A total of six studies were included in the meta-analysis. The systematic literature search resulted in a total of 605 potentially eligible studies after we removed the duplicates. Primarily, we identified 517 studies through PubMed, 31 via Embase, 35 via Google Scholar, 304 through Web of Science, and seven by reference search of selected articles (total of 894 with duplicates). Following abstract and title screening, 579 studies were excluded. We then excluded 18 more studies based on our inclusion and exclusion criteria. Two studies were further excluded as they only presented mean differences in vitamin A without any association data (Figure 1).

Four of the included studies were conducted outside the United States; that is, in the Netherlands, Denmark, and Norway (Bille et al., 2007; Johansen et al., 2008;
Krapels et al., 2004; Mitchell et al., 2003). Most (5/6) (Johansen et al., 2008; Krapels et al., 2004; Mitchell et al., 2003; Wallenstein, Shaw, Yang, & Carmichael, 2013; Werler et al., 1990). Five of the included studies were case–control studies with diet as the major source of vitamin A. Four of the studies had vitamin supplements as additional sources (Bille et al., 2007; Johansen et al., 2008; Mitchell et al., 2003; Werler et al., 1990). Four of the included studies (Bille et al., 2007; Johansen et al., 2008; Krapels et al., 2004; Wallenstein et al., 2013) specified the dosage of vitamin A; two used quartile, one used percentile and the last dichotomized vitamin A exposure into yes or no. The quartile and percentile were calculated based on the distribution of vitamin A among control mothers. There was considerable variability in the duration of exposure to vitamin A reported by four
| First author and year published | Location | Study design | Study population | Sample size | Duration of exposure | Source of vit A | Dosage information | Cleft phenotype | Outcome ascertainment | Confounder considered |
|--------------------------------|----------|--------------|------------------|-------------|----------------------|----------------|-------------------|----------------|----------------------|---------------------|
| Johansen et al. (2008)         | Norway   | Case–control | Cases–hospital, controls–general population | Cases–287 (CL/P), CPO–115, control-693 | First 3 months of pregnancy | Diet and supplement | Calculated in quartiles based on the distribution among controls | Isolated CLP, CPO, CLP | Birth registry, medical record, mothers report | Maternal energy intake, dietary folate, folic acid supplementation, alcohol consumption, smoking, working during first trimester, educational level, father's income, year of birth |
| Krapels et al. (2004)          | The Netherlands | Case–control | Cases–hospital, controls–general population | 153–CL/P, 29–CPO | 3 months before and 3 months after conception | Diet | Calculated in quartiles based on the distribution among controls | Isolated CL/P, isolated CPO | Medical report | Maternal age, parity, periconceptional smoking, alcohol consumption, folic acid supplementation |
| Werler et al. (1990)           | Boston, Philadelphia, Toronto and Iowa | Case–control | Hospital–both cases and controls | 1,332–oral clefts, 2,609–controls | Not stated | Diet and supplements | Not stated | Orofacial clefts | Surveillance | Geographic region, interview year, age, education, race, religion, smoking, alcohol, history of infections during pregnancy (measles and rubella) |
| Wallenstein et al. (2013)      | California, U.S. | Case–control | Hospital–both cases and controls | 502–CL/P, 199–CP, 626–controls | 2 months before and 2 months after conception | Diet | Calculated in percentiles based on the distribution among controls | CL/P, CPO | Medical records, clinical examination | Energy intake, maternal race/ethnicity, age, education, prepregnancy BMI, gravidity, periconceptional cigarette smoking, and alcohol |

(Continues)
**TABLE 1** (Continued)

| First author and year published | Location | Study design | Study population | Sample size | Duration of exposure | Source of vit A | Dosage information | Cleft phenotype | Outcome ascertainment | Confounder considered |
|--------------------------------|----------|--------------|------------------|-------------|----------------------|----------------|-------------------|-----------------|----------------------|------------------------|
| Mitchell et al. (2003)          | Denmark  | Case–control | Cases–hospital, controls–hospital | Cases–222 (CL/P), CPO–80, control–567 | Not stated | Diet and supplements | Not stated | Isolated CLP, isolated CPO | Birth registry | Nil                   |
| Bille C (2007)                  | Denmark  | Case–cohort  | Cases–Hospital and general population, control–general population | Cases–192 (CL/P) and CPO control–880 | First trimester | Diet and supplements | Categorized as dichotomous (yes and no) | Isolated CL with or without P, isolated CPO | Birth registry | Parental age and social class |

**TABLE 2** Quality of the included studies using the Newcastle Ottawa assessment scale

| Quality score domains | Participants selection | Comparability | Exposure/outcome | Total |
|-----------------------|------------------------|---------------|------------------|-------|
|                       | Adequate case definition | Control selection | Control definition | Study controls for folic acid and/or other vitamins | Exposure ascertainment | Same method of ascertainment | Nonresponse rate | Total score |
| Johansen              | 1                      | 0             | 1                | 1 | 0 | 1 | 0 | 5 |
| Krapels               | 0                      | 1             | 1                | 1 | 0 | 1 | 0 | 5 |
| Mitchell              | 1                      | 1             | 0                | 1 | 0 | 1 | 1 | 5 |
| Wallenstein           | 1                      | 0             | 0                | 1 | 0 | 1 | 1 | 5 |
| Werler                | 1                      | 1             | 0                | 1 | 0 | 1 | 1 | 5 |
| Bille                 | 1                      | 0             | 1                | 1 | 0 | 1 | 1 | 5 |
studies (Bille et al., 2007; Johansen et al., 2008; Krapels et al., 2004; Wallenstein et al., 2013). Although these four studies used the term “periconceptional” for the duration, the definition of this term differed between studies. One study (Mitchell et al., 2003) matched cases to controls by site and place of birth, while others presented the adjusted estimate after controlling for potential confounders (Table 1). All the included studies had moderate quality with the same total score, and thus, we were unable to stratify by quality (Table 2).

Five studies assessed all NSOFCs irrespective of the phenotype; two of which calculated the dosage of vitamin A from the distribution among controls, and one dichotomized vitamin A exposure. Using the adjusted OR for the studies (comparing the largest quartile/percentile), we calculated the pooled OR using a random-effects model. This showed a 20% reduction in the risk of NSOFCs for periconceptional use of vitamin A, which was not statistically significant (OR = 0.80; 95% CI 0.54–1.17, p = .25; Figure 2). There was moderate heterogeneity among the included studies, with an I² value of 30%. Visualization of the funnel did not suggest the presence of publication bias (Figure 3). All the included studies reported a nonsignificant odds ratio for the effects of vitamin A on NSOFCs, making publication bias highly unlikely.

For the subgroup analysis, we identified studies where the effects, of vitamin A on NSCL/P and NSCPO were presented separately (four studies). For NSCL/P, the studies were homogenous, with an I² of 0%, and the pooled estimate showed a 13% reduction in the risk, which was significant (OR = 0.87; 95% CI 0.77–0.99, p = .03). In contrast, we found evidence (p = .09, I² = 54%) for between-study heterogeneity in the NSCPO subgroup analysis. The pooled OR using a random-effect model showed a 33% lower likelihood of NSCPO, which was not statistically significant (OR = 0.67; 95% CI 0.42–1.08, p = .10) (Figure 3b).

### DISCUSSION

Following the advocacy for the use of vitamin supplements during the periconceptional period, studies investigating the effects of folic acid and other components of multivitamins on the risk of congenital birth defects, especially NSOFCs, have gained traction. Like the uncertainty concerning the protective effects of folic acids on NSOFCs risk, the evidence for vitamin A remains unclear. To the best of our knowledge, this is the first meta-analysis to evaluate the effect of periconceptional use of vitamin A on the risk of NSOFCs. Our results showed a nonsignificant protective effect of vitamin A on the risk of giving birth to a child with NSOFCs among pregnant women. When we performed the analysis separately for the subphenotypes (NSCL/P and NSCPO), we found a significant protective effect of vitamin A on the risk of NSCL/P and a nonsignificant effect on the risk of NSCPO. A similar finding was seen in a meta-analysis conducted on the effect of folic acid fortification and the prevalence of NSOFCs, where a significant effect was seen only with the NSCL/P subphenotype (Millacura, Pardo, Cifuentes, & Suazo, 2017). This observation could be explained by the underlying differences between these two subphenotypes (Fogh-Andersen, 1967). For instance, NSCL/P occurs during lip and primary palate formation, while NSCPO occurs during the formation of the secondary palate (Leslie & Marazita, 2013). Also, NSCL/P are more common in males while NSCPO are commoner in females (Grosen et al., 2010). These differences point to distinct genetic, embryologic, and possibly exogenous factors.

In the overall NSOFCs cleft analyses, the moderate statistical heterogeneity (I² = 30%) observed was due mainly to the Werler study (Werler et al., 1990), which reported a nonsignificant increase in the risk of oral clefts among mothers who used vitamin A. The study did not provide information about vitamin A dosage or duration.

| Study or Subgroup | log(ODds Ratio) | SE  | Weight % | IV, Random, 95% CI | Odds Ratio | Odds Ratio |
|-------------------|----------------|-----|-----------|---------------------|------------|------------|
| Bille et al.(2007)| -.15082        | .229| 34.7      | .86 [.55, 1.35]     |            |            |
| Johansen et al.(2008)| -.73397       | .444| 15.0      | .48 [.20, 1.15]     |            |            |
| Krapels et al.(2004) | -.35667       | .457| 14.3      | .70 [.29, 1.71]     |            |            |
| Mitchell et al.(2003) | -.41552       | .309| 25.0      | .66 [.36, 1.21]     |            |            |
| Werler et al.(1990) |  .83291       | .538| 11.0      | 2.30 [.80, 6.60]    |            |            |
| **Total (95% CI)** |                |     | 100.0%    | **.80 [.54, 1.17]** |            |            |

| Heterogeneity: Tau² = 0.06; Chi² = 5.75, df = 4 (p = .22); I² = 30% |
| Test for overall effect: z = 1.15 (p = .25) |

**FIGURE 2** Shows the studies odds ratios as well as the pool odds ratio for the association between periconceptional use of vitamin A and NSOFCs
Participants were restricted to only mothers taking preformed vitamin A from supplements (retinol, retinol acetate, and retinol palmitate) daily for at least 1 week within the first trimester. This could potentially select mothers with very high-vitamin A levels due to the increased bioavailability of vitamin A from preformed sources compared to provitamin A carotenoids. Furthermore, this study was conducted prior to the folic acid fortification of foods across most countries. Although the study participants were asked about folic acid intake, it
was not adjusted for in the results. For the CLP subgroup analyses, the reported ORs were similar across all the included studies despite the difference in vitamin A source, duration, and covariates adjusted for. The low-heterogeneity might be because of the ability to regulate plasma concentration of vitamin A in humans and the lack of significant difference between crude and adjusted ORs in the included studies. Whereas for CPO subgroup analyses, Bille et al. (2007) and Johansen et al. (2008) reported more protective ORs compared to Mitchell et al. (2003) and Wallenstein et al. (2013). A possible explanation could be the difference in controls used in these studies. The Bill et al. and Johansen et al. studies recruited controls from the general populations, while the Mitchel and Wallenstein studies recruited hospital-based controls. This perhaps could introduce recall bias where mothers recruited in hospitals whose child may have some other health conditions are more likely to recall in detail food, and supplements consumed compared to mothers recruited from the general population. Additionally, it is possible that the smaller sample sizes for the cleft palate only phenotype in all the included studies introduced random errors into the estimates, contributing to the heterogeneity.

In this study, we included only studies that presented vitamin A specific results among those looking at the association between diet, multivitamins, or both and OFCs. We did this to identify vitamin A-specific effect after adjusting for other components in multivitamins, especially folic acid, which has been well documented to protect against OFCs when taken during the periconceptional period (Botto, Olney, & Erickson, 2004; van Rooij et al., 2004). Despite this targeted approach and the use of adjusted odds ratio in our meta-analysis, the effect of unmeasured confounders (dietary habits, socioeconomic status, previous reproductive history, family history of OFC, health behavior, and other micro/macro nutrients present in multivitamins) cannot be completely ruled out. For example, the components of multivitamins, including vitamin A, vary by region (Martinez-Frias & Salvador, 1990). The majority (5/6) of the studies pooled together were case-control studies without standardization of the vitamin A dosage or duration. Also, our results are prone to recall bias because all the studies assessed vitamin A exposure via questionnaires administered to mothers after birth which could have biased the reported associations.

Furthermore, all the included studies are of moderate quality, with a total quality score of 5. This was due to multiple factors randomly distributed across the studies, except for exposure ascertainment, which was self-reported in all. Finally, while it is possible to estimate vitamin A consumption from dietary foods as done in most of the included studies, cooking methods may significantly impact the retained vitamin content. Thus, further studies should assess this.

In conclusion, our result suggests a possible protective effect for the periconceptional use of vitamin A on the risk of giving birth to a child with NSCL/P among pregnant women. However, future studies using standardized dose and definition for the periconceptional period (a period critical in the development of craniofacial structures) will be required to confirm our findings.

**CONFLICT OF INTEREST**
The authors have declared no conflicts of interest for this article.

**DATA AVAILABILITY STATEMENT**
Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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**REFERENCES**
Barker, D. J. (1990). The fetal and infant origins of adult disease. *British Medical Journal, 301*(6761), 1111.
Bastos Maia, S., Rolland Souza, A. S., Costa Caminha, M. F., Lins da Silva, S., Callou Cruz, R., Carvalho Dos Santos, C., & Batista Filho, M. (2019). Vitamin A and pregnancy: A narrative review. *Nutrients, 11*(3), 681. https://doi.org/10.3390/nu11030681
Bille, C., Olsen, J., Vach, W., Knudsen, V. K., Olsen, S. F., Rasmussen, K.,... Christensen, K. (2007). Oral clefts and lifestyle factors—A case-cohort study based on prospective Danish data. *European Journal of Epidemiology, 22*(3), 173–181. https://doi.org/10.1007/s10654-006-9099-5
Botto, L. D., Olney, R. S., & Erickson, J. D. (2004). Vitamin supplements and the risk for congenital anomalies other than neural tube defects. *American Journal of Medical Genetics. Part C: Seminars in Medical Genetics, 125*(1), 12–21. https://doi.org/10.1002/ajmg.c.30004
Calzolari, E., Pierini, A., Astolfi, G., Bianchi, F., Neville, A. J., & Rivieri, F. (2007). Associated anomalies in multi-malformed infants with cleft lip and palate: An epidemiologic study of nearly 6 million births in 23 EUROCAT registries. *American Journal of Medical Genetics. Part A, 143*(6), 528–537. https://doi.org/10.1002/ajmg.a.31447
Carinci, F., Scapoli, L., Palmieri, A., Zollino, I., & Pezzetti, F. (2007). Human genetic factors in nonsyndromic cleft lip and palate: An update. *International Journal of Pediatric Otorhinolaryngology, 71*(10), 1509–1519. https://doi.org/10.1016/j.ijporl.2007.06.007
Czeizel, A. E., Dobó, M., & Vargha, P. (2004). Hungarian cohort-controlled trial of periconceptional multivitamin supplementation shows a reduction in certain congenital abnormalities. *Birth Defects Research Part A: Clinical and Molecular Teratology, 70*(11), 853–861. https://doi.org/10.1002/bdra.20086
Leslie, E. J., & Marazita, M. L. (2013). Genetics of cleft lip and cleft palate. *American Journal of Medical Genetics. Part C: Seminars in Medical Genetics, 163*(C4), 246–258. https://doi.org/10.1002/ajmg.c.31381

Mai, C. T., Cassell, C. H., Meyer, R. E., Isenburg, J., Canfield, M. A., Rickard, R., ... National Birth Defects Prevention Network. (2014). Birth defects data from population-based birth defects surveillance programs in the United States, 2007 to 2011: Highlighting orofacial clefts. *Birth Defects Research. Part A: Clinical and Molecular Teratology, 100*(11), 895–904. https://doi.org/10.1002/bdra.23329

Martinez-Frias, M. L., & Salvador, J. (1990). Epidemiological aspects of prenatal exposure to high doses of vitamin a in Spain. *European Journal of Epidemiology, 6*(2), 118–123. https://doi.org/10.1007/bf00145783

Millacura, N., Pardo, R., Cifuentes, L., & Suazo, J. (2017). Effects of folic acid fortification on orofacial clefts prevalence: A meta-analysis. *Public Health Nutrition, 20*(12), 2260–2268. https://doi.org/10.1017/S1368946517000878

Miller, R. K., Hendrickx, A. G., Mills, J. L., Hummeler, H., & Wiegand, U. W. (1998). Periconceptional vitamin a use: How much is teratogenic? *Reproductive Toxicology, 12*(1), 75–88. https://doi.org/10.1016/s0890-6238(97)00102-0

Mitchell, L. E., Murray, J. C., O’Brien, S., & Christensen, K. (2003). Retinoic acid receptor alpha gene variants, multivitamin use, and liver intake as risk factors for oral clefts: A population-based case-control study in Denmark, 1991-1994. *American Journal of Epidemiology, 158*(1), 69–76. https://doi.org/10.1093/aje/kwg102

Mossey, P. A., & Modell, B. (2012). Epidemiology of oral clefts 2012: An international perspective. *Frontiers of Oral Biology, 16*, 1–18. https://doi.org/10.1115/000337464

Nahai, F. R., Williams, J. K., Burstein, F. D., Martin, J., & Thomas, J. (2005). The management of cleft lip and palate: Pathways for treatment and longitudinal assessment. *Seminars in Plastic Surgery, 19*(4), 275–285. https://doi.org/10.1055/s-2005-925900

Reik, W., Constancia, M., Crow, A., Anderson, N., Dean, W., Ferguson-Smith, A., ... Sibley, C. (2003). Regulation of supply and demand for maternal nutrients in mammals by imprinted genes. *The Journal of Physiology, 547*(Pt 1), 35–44. https://doi.org/10.1113/jphysiol.2002.033274

RevMan Training. (2020). Review Manager (Version 5.4). Shaw, G. M., Wasserman, C. R., O’Malley, C. D., Tolarova, M. M., & Lammer, E. J. (1995). Risks of orofacial clefts in children born to women using multivitamins containing folic acid periconceptionally. *The Lancet, 346*(8972), 393–396. https://doi.org/10.1016/s0140-6736(95)92778-6

Steegers-Theunissen, R. P. M., Twigt, J., Pestinger, V., & Sinclair, K. D. (2013). The periconceptual period, reproduction and long-term health of offspring: The importance of one-carbon metabolism. *Human Reproduction Update, 19*(6), 640–655. https://doi.org/10.1093/humupd/dmt041

Tang, G. (2010). Bioconversion of dietary provitamin a carotenoids to vitamin a in humans. *The American Journal of Clinical Nutrition, 91*(5), 1468s–1473s. https://doi.org/10.3945/ajcn.2010.28674G

van Rooij, I. A. L. M., Ocké, M. C., Straatman, H., Zelhuis, G. A., Merkus, H. M. W. M., & Steegers-Theunissen, R. P. M. (2004). Periconceptional folic acid intake by supplement and food reduces the risk of non-syndromic cleft lip with or without cleft palate. *Preventive Medicine, 39*(4), 689–694. https://doi.org/10.1016/j.ypmed.2004.02.036

Wallenstein, M. B., Shaw, G. M., Yang, W., & Carmichael, S. L. (2013). Periconceptional nutrient intakes and risks of orofacial clefts in California. *Pediatric Research, 74*(4), 457–465. https://doi.org/10.1038/pr.2013.115
Wells, G. A., Shea, B., O’Connell, D. A., Peterson, J., Welch, V., Losos, M., & Tugwell, P. (2000). The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Ottawa Hospital Research Institute: Oxford.
Werler, M. M., Lammer, E. J., Rosenberg, L., & Mitchell, A. A. (1990). Maternal vitamin A supplementation in relation to selected birth defects. *Teratology, 42*(5), 497–503. https://doi.org/10.1002/tera.1420420506
WHO. (2004). *Vitamin and mineral requirements in human nutrition*. Geneva: World Health Organization.

**How to cite this article:** Alade, A., Ismail, W., Nair, R., Schweizer, M., Awotoye, W., Oladayo, A., Ryckman, K., & Butali, A. (2022). Periconceptional use of vitamin A and the risk of giving birth to a child with nonsyndromic orofacial clefts—A meta-analysis. *Birth Defects Research, 114*(10), 467–477. https://doi.org/10.1002/bdr2.2005