Vitamin E concentration in breast milk in different periods of lactation: Meta-analysis

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Objective: This study systematized information about vitamin E concentration in healthy breast milk during different stages of lactation in order to support the strategies of protecting postpartum women and infants.

Methods: Studies published before April 30th, 2021, which detected vitamin E concentration in breast milk of healthy women by High Performance Liquid Chromatography (HPLC) or Ultra High Performance Liquid Chromatographic (UHPLC), were evaluated. The databases of CNKI (Chinese), WanFang Data (Chinese), VIP (Chinese), PubMed, Cochrane Library, Web of Science and Embase were searched. The random effect models were used to conduct meta-analysis by the statistical software package Stata 14.0.

Results: In all 4,791 searched publications, 53 with full text were selected, which included 46 descriptive studies, 1 case-control study, 1 non-randomized controlled trial, and 5 randomized controlled trials. The pooled mean of vitamin E concentration was 10.57 mg α-TE/L (95%CI 8.94–12.20) in colostrum, 4.03 mg α-TE/L (95%CI 3.29–4.77) in transitional milk and 3.29 mg α-TE/L (95%CI 2.95–3.64) in mature milk. Subgroup analysis showed that vitamin E concentration of colostrum in Asian countries was lower than that in Western countries in colostrum and transitional milk.

Conclusions: Vitamin E concentration in breast milk decreased during lactation until the mature milk was produced. The vitamin E concentration of colostrum in Asian countries was evidently lower than that in Western countries. The vitamin E concentration in mature milk is similar in different regions. The concentration of vitamin E in breast milk started to be stable from about 2 to 3 weeks postpartum until 4 or 6 months postpartum, but it needs additional evidence to support.

Keywords: vitamin E, alpha-tocopherol, breast milk, lactation, meta-analysis
Introduction

Breast milk is important for infant growth and development, which is the most convenient and accessible source of nutrition for infants in the first 6 months of life. The exclusive breastfeeding is recommended for the first 6 months and then continued breastfeeding alongside appropriate complementary foods from thereafter to 24 months. Consequently, studying the composition of breast milk is of crucial importance (1, 2).

Vitamin E, also known as tocopherol, functions as a potent antioxidant, which protects cells from oxidative damage and maintains normal immunity. It is closely related to the development of respiratory, immune and cognitive systems in infants (3). It comprises a group of compounds possessing tocopherol and tocotrienol and their derivatives. Vitamin E includes four tocopherols and four tocotrienols designated as α-, β-, γ-, and δ- tocopherol, which is preferentially recognized by the α-tocopherol transfer protein (TTP) in the human body, is the compound playing the highest vitamin E activity (4, 5).

The nutritional supplement of vitamin E to the fetus through the placenta is limited during pregnancy. Therefore, postpartum breastfeeding has become a significant source for infants to obtain vitamin E. This way of vitamin E supplementation could help infants defend oxygen toxicity in the extrauterine environment and protect the lipoproteins and polyunsaturated fatty acids present in the cellular membranes against peroxidation (6). As described above, the content of vitamin E in breast milk is extremely vital for babies.

This review systematically searched and analyzed three databases for Chinese language articles, four databases for English language articles to obtain more comprehensive information. The aim of the present meta-analysis was to systematize information about vitamin E concentration in breast milk during different periods of lactation, which might be useful to establish support strategies to protect postpartum women and infants.

Materials and methods

This meta-analysis was conducted according to the norms of Meta-Analysis of Observational Studies in Epidemiology (MOOSE) (7), with the following questions: What are the vitamin E concentrations in different periods of lactation of healthy breast milk? Do the vitamin E concentrations in breast milk of normal mothers vary in different regions?

Search strategy

Studies published before May 2021 were searched by three independent reviewers in databases of CNKI (Chinese), WanFang Data (Chinese), VIP (Chinese), PubMed, Cochrane Library, Web of Science and Embase. The following key words were used (Table 1). Authors were contacted when full-text of articles were not available.

Eligibility criteria

We adopted as inclusion criteria the studies that:

- language was Chinese or English;
- involved lactating mothers aged from 18 to 45 years old in addition to infants aged from 0 to 48 months;
- either mothers or infants were medically certified as healthy;
- involved intervention studies and observational studies (cross-sectional study, case-control study, cohort study). Lactating mothers in control group in randomized controlled trials, who did not intake special dietary or participate in dietary supplementation, were included in this meta-analysis;
- the concentration of vitamin E in breast milk was detected by High Performance Liquid Chromatography (HPLC) or Ultra High Performance Liquid Chromatographic (UHPLC).

The studies were excluded that:

- lactating mothers were active smokers, or with chronic conditions (such as gestational diabetes or mastitis), or undergoing pharmacotherapy;
- lactating mothers received interventions from special diets or dietary supplements;
- lactation stages were not described distinctly;
- the main outcomes did not have values;
- included conference papers, reviews, ecological studies, case reports, editorials, letters, commentary, short surveys, and notes.

Study selection and data extraction

The workflow is presented in Table 1. First, duplicate studies were removed manually or by using Endnote. Next, titles and abstracts screening were performed in order to exclude the irrelevant studies. Full-text articles which needed further investigation were assessed by eligibility criteria.

Two researchers screened information and extracted the data independently, and disagreements were resolved by consensus. When a consensus could not be reached, the third reviewer was consulted. The following information was extracted from the final included articles, which included the first author, year of publication, country, lactation stage, sample
size, relevant characteristics of mother (age, gestational weeks etc.) and data of vitamin E concentration.

Assessment of study quality

The quality of studies was assessed according to the Joanna Briggs Institute (JBI) critical appraisal checklist (8–10). This assessment tool was chosen as it has been widely used in systematic reviews.

Statistical analysis

Data conversion

Total vitamin E activity was calculated as follows (11–13):

\[
\alpha - TE = (mg\alpha - tocopherol \times 1.0) + (mg\beta - tocopherol \times 0.5) + (mg\gamma - tocopherol \times 0.1) + (mg\delta - tocopherol \times 0.03) + (mg\gamma - tocotrienol \times 0.3) + (mg\beta - tocotrienol \times 0.05).
\]

The vitamin E data reported in different units were converted to mg α-TE/l uniformly. For instance, millimoles could be converted to milligrams by multiplying by molecular weight. Breast milk data used per kilogram could be converted to per liter by dividing by 1.032.

Data consolidation

Data in different studies presented in non-consistent forms, such as median, minimum/maximum values, and/or quartiles. Therefore, sample mean and standard deviation were estimated to pool results in a consistent format (14, 15).

If multiple data existed in the same lactation period in one study, the weighted mean (Means) and standard deviation (SDs) could be calculated with the following formula:

\[
\text{Means} = \frac{(n_1 \times M_1 + n_2 \times M_2 + n_3 \times M_3 + \cdots + n_i \times M_i)}{(n_1 + n_2 + n_3 + \cdots + n_i)}
\]

\[
A_i = S_i^2(\frac{n_i}{n_i - 1}) + M_i^2 \times \frac{1}{n_i}
\]

\[
\text{SDs} = \sqrt{\frac{\sum A_i - (\sum M_i)^2}{N - 1}}
\]

Where: \(n_i\) = Sample size of individual studies, \(M_i\) = Mean of individual studies, \(S_i\) = Standard deviation of individual studies.

Meta-analysis

The meta-analysis was performed by Stata software (version 14.0). The program of “metan” was used to pool vitamin E concentration in the format of means with 95% confidence intervals (95% CIs). The \(I^2\) and the Cochran Q test were used to assess heterogeneity. \(I^2 > 50\%\) was considered to have substantial heterogeneity, and the random effect model was chosen. Otherwise, the fixed-effect model was used. The publication bias was evaluated by Egger’s test and trim-and-fill analysis. \(P\)-value <0.05 was considered as statistically significant. The trim-and-fill analysis was a non-parametric method for approximating the number of missing studies that might help in reducing and correcting publication bias in meta-analysis.

The possible sources of heterogeneity were identified by the multivariable meta-regression model. Subgroup
analyses were conducted based on publication year, country of study, region and research type. Sensitivity analysis was also conducted to examine the effect of every study on the final results.

Result

Data search results and included studies

Four thousand and seven hundred and ninety one studies were found from all databases. Then, 4,527 studies were reserved after duplicates were removed and 4,415 articles were excluded by checking the titles and abstracts. For the remaining 112 articles, the full texts were rigorously reviewed. After the screening, 53 papers were included in this study (Figure 1).

Study characteristics

Of the 53 included articles, 46 were descriptive studies (6, 16–60), 1 was a case-control study (61), 1 was a non-randomized controlled trial (62), and 5 were randomized controlled trials (63–67). A summary of these findings was presented in Table 2 and Supplementary Tables S1–S4.

It should be noticed that 7 studies reported vitamin E concentrations in breast milk from mothers of preterm and full-term infants both. However, the results of normal mothers who gave birth to full-term infants were used only in present study. Moreover, the data of vitamin E concentrations in healthy control group were chosen in case-control study, non-randomized controlled or randomized controlled trials.
| Reference          | Country   | Region         | Type of study                  | Colostrum | | | Transitional milk | | | Mature milk | | | Study quality |
|--------------------|-----------|----------------|--------------------------------|-----------|---|---|----------------|---|---|----------------|---|---|---------------|
|                     |           |                | Sample size | Concentration (mg α-TE/l) | Sample size | Concentration (mg α-TE/l) | Sample size | Concentration (mg α-TE/l) |                |               |              |               |
| Lennart et al. (16) | Sweden    | Western country | cross-sectional study         | 6         | 10.00 ± 5.50 | 10            | 4.80 ± 1.80 | 24            | 3.20 ± 1.80 | Medium               |
| Chappell et al. (17) | Canada    | Western country | cross-sectional study         | 12        | 15.00 ± 2.50 | 12            | 1.50 ± 6.34 | 12            | 3.19 ± 1.35 | Medium               |
| Chappell et al. (18) | Canada    | Western country | longitudinal study           | 12        | 15.48 ± 8.80 | 25            | 8.33 ± 9.82 | 34            | 3.19 ± 1.35 | Medium               |
| Haug et al. (19)    | Germany   | Western country | longitudinal study           | 25        | 8.33 ± 9.82 | 25            | 8.33 ± 9.82 | 34            | 3.19 ± 1.35 | Medium               |
| Moffatt et al. (20) | America   | Western country | cross-sectional study         | 5         | 3.12 ± 0.58 | 5             | 3.12 ± 0.58 | 5             | 3.12 ± 0.58 | Medium               |
| Boersma et al. (21) | Saint Lucia | Western country | longitudinal study           | 13        | 22.39 ± 14.3 | 11            | 13.59 ± 8.65 | 12            | 8.24 ± 4.8  | High                  |
| Zheng et al. (47)   | China     | Asian country   | cross-sectional study         | 43        | 6.94 ± 3.51 | 43            | 6.94 ± 3.51 | 43            | 6.94 ± 3.51 | Medium               |
| Zheng et al. (48)   | China     | Asian country   | cross-sectional study         | 38        | 3.45 ± 1.18 | 5             | 1.32 ± 0.59 | 5             | 1.32 ± 0.59 | Medium               |
| Zheng et al. (49)   | China     | Asian country   | cross-sectional study         | 71        | 5.57 ± 2.70 | 71            | 5.57 ± 2.70 | 71            | 5.57 ± 2.70 | Medium               |
| Barua et al. (22)   | Bangladesh | Asian country   | cross-sectional study         | 61        | 2.04 ± 0.86 | 61            | 2.04 ± 0.86 | 61            | 2.04 ± 0.86 | High                  |
| Barbasa et al. (23) | Spain     | Western country | longitudinal study           | 8         | 14.40 ± 6.50 | 8             | 3.10 ± 1.40 | 8             | 3.10 ± 1.40 | Medium               |
| Ortega et al. (24)  | Brazil    | Western country | longitudinal study           | 57        | 1.80 ± 0.68 | 57            | 0.96 ± 0.31 | 57            | 0.96 ± 0.31 | High                  |
| Zheng et al. (Chinese) (50) | China | Asian country | cross-sectional study | 12 | 9.12 ± 1.40 | 12 | 9.12 ± 1.40 | 12 | 9.12 ± 1.40 | High |
| Zheng et al. (Chinese) (67) | China | Asian country | randomized controlled trial | 30 | 7.30 ± 3.29 | 30 | 7.30 ± 3.29 | 30 | 7.30 ± 3.29 | Medium |
| Macias et al. (25)  | Cuba      | Western country | longitudinal study           | 21        | 11.80 ± 6.30 | 21            | 5.00 ± 3.00 | 21            | 2.70 ± 1.10 | High                  |
| Olafsdottir et al. (26) | Iceland | Western country | cross-sectional study         | 77        | 4.4 ± 1.85  | 77            | 4.4 ± 1.85  | 77            | 4.4 ± 1.85  | High                  |
| Zhu et al. (Chinese) (51) | China | Asian country | longitudinal study | 77 | 4.4 ± 1.85 | 77 | 4.4 ± 1.85 | 77 | 4.4 ± 1.85 | High |
| Schweiger et al. (27) | Germany  | Western country | longitudinal study           | 40        | 8.98 ± 3.74 | 40            | 4.47 ± 1.64 | 40            | 3.31 ± 1.13 | High                  |
| Sakurai et al. (28) | Japan     | Asian country   | cross-sectional study         | 21        | 22.01 ± 13.39 | 21          | 5.69 ± 2.20 | 21          | 5.69 ± 2.20 | High                  |
| Romeu-Nadal et al. (29) | Spain | Western country | cross-sectional study         | 6         | 5.95 ± 2.65 | 6             | 5.23 ± 2.67 | 103           | 2.98 ± 1.28 | High                  |
| Tokusoglu et al. (30) | Turkey   | Western country | cross-sectional study         | 10        | 3.89 ± 0.16 | 10            | 3.89 ± 0.16 | 10            | 3.89 ± 0.16 | Medium               |
| Szklári-László et al. (33) | Hungary | Western country | cross-sectional study         | 92        | 9.84 ± 2.13 | 18            | 3.12 ± 1.20 | 18            | 3.12 ± 1.20 | High                  |
| Grazyna et al. (31) | Poland    | Western country | cross-sectional study         | 12        | 4.19 ± 2.20 | 18            | 4.19 ± 2.20 | 18            | 4.19 ± 2.20 | High                  |
| Molto-Puigmarti et al. (32) | Spain | Western country | longitudinal study           | 10        | 3.78 ± 2.48 | 10            | 3.78 ± 2.48 | 10            | 3.78 ± 2.48 | Medium               |
| Tijerina-Sáenz et al. (34) | Canada | Western country | cross-sectional study         | 60        | 2.27 ± 0.92 | 60            | 2.27 ± 0.92 | 60            | 2.27 ± 0.92 | Medium               |
| Orhon et al. (61)   | Turkey    | Western country | case-control study           | 20        | 13.27 ± 0.69 | 20            | 13.27 ± 0.69 | 20            | 13.27 ± 0.69 | High                  |
| Garcia et al. (62)  | Brazil    | Western country | non-randomized controlled trial | 74 | 10.81 ± 7.42 | 74            | 10.81 ± 7.42 | 74            | 10.81 ± 7.42 | High                  |

(Continued)
| Reference                  | Country      | Region          | Type of study                   | Colostrum | Transitional milk | Mature milk | Study quality |
|---------------------------|--------------|-----------------|--------------------------------|-----------|-------------------|-------------|---------------|
|                          |              |                 |                                | Sample size | Concentration (mg α-TE/l) | Sample size | Concentration (mg α-TE/l) | Sample size | Concentration (mg α-TE/l) |
| Yu et al. (52)            | China        | Asian country   | cross-sectional study          | 7          | 3.04 ± 1.94       | 7           | 1.80 ± 0.62       | 66          | 2.42 ± 1.64       |
| Antonakou et al. (35)     | Greece       | Western country | cross-sectional study          | 16         | 3.85 ± 1.86       | 48          | 3.83 ± 1.45       | 48          | 3.60 ± 1.45       |
| Kasapova et al. (36)      | Czech Republic | Western country | cross-sectional study          | 48         | 3.88 ± 1.73       | 44          | 3.88 ± 1.45       | 44          | 3.60 ± 1.55       |
| Szlagaty-Sidoriewicz et al. (6) | Poland       | Western country | longitudinal study             | 49         | 8.69 ± 5.18       | 49          | 1.94 ± 2.41       | 49          | 2.42 ± 1.64       |
| Martysiak-Zurowska et al. (39) | Poland       | Western country | longitudinal study             | 17         | 10.13 ± 1.50      | 30          | 4.59 ± 0.93       | 46          | 2.64 ± 0.89       |
| de Lira et al. (37)       | Brazil       | Western country | cross-sectional study          | 103        | 11.24 ± 5.51      | 102         | 4.26 ± 2.25       | 102         | 3.05 ± 1.50       |
| Grilo et al. (38)         | Brazil       | Western country | cross-sectional study          | 71         | 10.94 ± 5.32      | 88          | 2.76 ± 0.91       | 88          | 2.49 ± 1.10       |
| Fang et al. (Chinese) (53) | China        | Asian country   | cross-sectional study          | 72         | 9.29 ± 3.33       | 77          | 4.26 ± 2.25       | 77          | 3.45 ± 1.64       |
| Clemente et al. (63)      | Brazil       | Western country | randomized controlled trial    | 72         | 16.54 ± 1.71      | 89          | 2.49 ± 1.10       | 89          | 2.49 ± 1.10       |
| Liu et al. (Chinese) (55)  | China        | Asian country   | cross-sectional study          | 5          | 2.13 ± 0.91       | 10          | 2.21 ± 1.12       | 10          | 2.49 ± 1.10       |
| Jiang et al. (54)         | China        | Asian country   | longitudinal study             | 102        | 6.32 ± 4.25       | 102         | 2.56 ± 2.25       | 102         | 2.49 ± 1.10       |
| Grilo et al. (64)         | Brazil       | Western country | randomized controlled trial    | 77         | 17.44 ± 6.46      | 77          | 5.99 ± 2.24       | 77          | 3.45 ± 1.64       |
| Xue et al. (56)           | China        | Asian country   | cross-sectional study          | 32         | 6.64 ± 3.2        | 32          | 6.64 ± 3.2        | 32          | 6.64 ± 3.2        |
| Kim et al. (60)           | Korea        | Asian country   | cross-sectional study          | 165        | 2.48 ± 1.01       | 165         | 2.48 ± 1.01       | 165         | 2.48 ± 1.01       |
| Silva et al. (42)         | Brazil       | Western country | cross-sectional study          | 100        | 17.44 ± 6.46      | 77          | 5.99 ± 2.24       | 77          | 3.45 ± 1.64       |
| Melo et al. (63)          | Brazil       | Western country | randomized controlled trial    | 103        | 15.80 ± 8.83      | 103         | 3.80 ± 1.40       | 103         | 3.80 ± 1.40       |
| Samano et al. (41)        | Mexico       | Western country | cross-sectional study          | 32         | 6.64 ± 3.2        | 32          | 6.64 ± 3.2        | 32          | 6.64 ± 3.2        |
| Wei et al. (57)           | China        | Asian country   | longitudinal study             | 103        | 7.50 ± 2.10       | 103         | 3.80 ± 1.40       | 103         | 3.80 ± 1.40       |
| Wu et al. (Chinese) (58)   | China        | Asian country   | longitudinal study             | 103        | 7.50 ± 2.10       | 103         | 3.80 ± 1.40       | 103         | 3.80 ± 1.40       |
| de Sousa Reboucas et al. (66) | Brazil       | Western country | randomized controlled trial    | 89         | 11.81 ± 5.33      | 89          | 4.69 ± 1.81       | 89          | 4.69 ± 1.81       |
| Machado et al. (43)       | Brazil       | Western country | cross-sectional study          | 89         | 11.81 ± 5.33      | 89          | 4.69 ± 1.81       | 89          | 4.69 ± 1.81       |
| da Mata et al. (44)       | Brazil       | Western country | cross-sectional study          | 103        | 3.06 ± 1.70       | 103         | 3.06 ± 1.70       | 103         | 3.06 ± 1.70       |
| Wu et al. (Chinese) (60)   | China        | Asian country   | longitudinal study             | 89         | 9.72 ± 5.22       | 89          | 4.58 ± 1.81       | 89          | 4.58 ± 1.81       |
| Wu et al. (59)            | China        | Asian country   | longitudinal study             | 89         | 9.72 ± 5.22       | 89          | 4.58 ± 1.81       | 89          | 4.58 ± 1.81       |
| Duan et al. (45)          | Korea        | Asian country   | longitudinal study             | 89         | 9.72 ± 5.22       | 89          | 4.58 ± 1.81       | 89          | 4.58 ± 1.81       |
| Zagierski et al. (46)     | Poland       | Western country | cross-sectional study          | 154        | 3.82 ± 1.22       | 154         | 3.82 ± 1.22       | 154         | 3.82 ± 1.22       |

*a* Data refer to healthy mothers of full-term infants.

*b* Data refer only to the control group.
Meta-analysis results

Results of syntheses

The pooled mean vitamin E concentration in colostrum was 10.57 mg α-TE/L (95%CI 8.94–12.20), transitional milk was 4.03 mg α-TE/L (95%CI 3.29–4.77), and mature milk was 3.29 mg α-TE/L (95%CI 2.95–3.64) (Table 3).

Forest plot showed that the minimum and maximum values of vitamin E content in colostrum were 2.13 mg α-TE/L (55) and 37.93 mg α-TE/L (32), in transitional milk were 1.32 mg α-TE/L (60) and 13.59 mg α-TE/L (21), in mature were 0.52 mg α-TE/L (63) and 9.84 mg α-TE/L (30) (Figure 2).

Heterogeneity

Publication year, region (Asia or not), country of study and research type were analyzed for the source of heterogeneity by meta-regression analysis (multivariable). Results showed region might be the source of heterogeneity in colostrum (Table 4). We provide summary estimates of vitamin E content; however, the $I^2$ statistic indicated that data were heterogeneous in many of our analyses and therefore these summary measures must be interpreted with appropriate caution.

Subgroup analyses

The pooled concentration of vitamin E in colostrum was 13.34 mg α-TE/L (95%CI 11.97–14.72) in Western countries (19 studies were included) and 7.18 mg α-TE/L (95%CI 5.84–8.52) in Asian countries (16 studies were included).

The result in transitional milk was 5.00 mg α-TE/L (95%CI 3.27–6.73) in Western countries (7 studies were included) and 3.61 mg α-TE/L (95%CI 2.90–4.32) in Asian countries (11 studies were included). The data in mature milk was 3.61 mg α-TE/L (95%CI 2.90–4.32) in Western countries (29 studies were included) and 2.97 mg α-TE/L (95%CI 2.59–3.35) in Asian countries (14 studies were included) (Figure 3).

TABLE 3 Meta-analysis summary.

| Periods of lactation | Number of studies | Sample size | Overall effect (95% CI) | Heterogeneity test | Egger's test |
|----------------------|-------------------|-------------|------------------------|-------------------|-------------|
| Colostrum milk       | 35                | 1,626       | 10.57 (8.94–12.20)     | 99.1              | 0.000       |
| Transitional milk    | 18                | 800         | 4.03 (3.29–4.77)       | 97.8              | 0.000       |
| Mature milk          | 42                | 2,562       | 3.39 (2.86–3.92)       | 99.6              | 0.000       |

Colostrum milk

Colostrum, which is generated from the first day until the seventh or tenth day following parturition, is the first milk lactated (68). The publication of World Health Organization (WHO) and United Nations Children’s Fund (UNICEF) have demonstrated that breastfeeding with colostrum milk within the first hour of new life could effectively decrease neonatal mortality. It undoubtedly highlights the significance of breastfeeding right away upon delivery (69).

It is reported that colostrum is characterized by the highest concentration of vitamin E. The significant reduction can be observed in transitional milk and mature milk. Given that the concentration of vitamin E in plasma of neonates is usually much lower than that of adults including their mothers, high vitamin E consumption from colostrum seems to provide a compensatory mechanism of antioxidative activity (6).
In this study, 35 evidence demonstrated the level of vitamin E in colostrum, 18 and 42 evidence reported the vitamin E concentration in transitional milk and mature milk, respectively. The results of the meta-analysis showed vitamin E concentration was significantly higher in colostrum (10.57 mg α-TE/L) than in transitional milk (4.03 mg α-TE/L) and mature milk (3.29 mg α-TE/L).

### TABLE 4 Meta-analysis summary.

| Periods of lactation | Publication year | Country | Coefficient | P  | Region | Coefficient | P  | Research type | Coefficient | P  |
|----------------------|------------------|---------|-------------|----|--------|-------------|----|---------------|-------------|----|
| Colostrum milk       |                  |         | 0.079       | 0.200 |         | -0.355      | 0.049 |               | 8.821       | 0.000       |
| Transitional milk    |                  |         | 0.023       | 0.679 |         | -0.023      | 0.861 |               | 1.656       | 0.367       |
| Mature milk          |                  |         | 0.004       | 0.888 |         | 0.013       | 0.826 |               | 0.613       | 0.414       |
Sub-group analysis showed the pooled concentration of vitamin E based on Western countries and Asian countries in colostrum (A), transitional milk (B) and mature milk (C). The trend of pooled results in different periods of lactation (D).

The studies that were chosen included 19 researches on the colostrum of Western lactating women and 16 studies of Asian lactating women. Subgroup analyses showed that Asian women had significantly lower levels of vitamin E in their colostrum than did Western women. The reason for this difference might be discovered through comparing results between original studies. Maternal characteristics, genetic background, dietary intake of vitamin E and the use of supplementation appeared to be the main factors for the discrepancy of vitamin E level in breast colostrum between different regions (2, 57, 65, 68).

It's worth noting that a discrepancy of vitamin E concentration could be observed in different research times. In recent 10 years, colostrum are explored in 8 studies in Western lactating women. The vitamin E concentrations (16.54 ± 1.71 mg/L, 12.02 ± 6.78 mg/L, 17.44 ± 6.46 mg/L, 15.8 ± 8.83 mg/L) (42, 63–65) in the latest 4 Brazilian studies from 2015 to 2017 were higher than those in the articles from Poland (8.69 ± 5.18 mg/L, 10.13 ± 1.5 mg/L) (6, 39) and Brazil (11.24 ± 5.51 mg/L, 10.94 ± 5.32 mg/L) (37, 38) both in 2013. The same phenomenon could be found in the research of China. Moreover, vitamin E levels in colostrum also could be found regional discrepancy in China (Supplementary Figure S1). Three researches of Wu et al. (58–60) observed the vitamin E values of colostrum in Shanghai (9.72 ± 5.22 mg/L, 10.12 ± 4.52 mg/L, 11.81 ± 5.33 mg/L) from 2019 to 2020 were much higher than Inner Mongolia (3.04 ± 1.94 mg/L) in 2009 (52), Hohhot (2.13 ± 0.91 mg/L) in 2013 (55), Hangzhou (4.40 ± 2.85 mg/L) in 2016 (54), Lanzhou (8.09 ± 4.85 mg/L) in
FIGURE 4
Sensitivity analysis showed the influential studies on the overall pooled effect for colostrum (A), transitional milk (B) and mature milk (C).

2016 (54), Beijing (6.53 ± 4.12 mg/L) in 2016 (54). The reason might be associated with the improved economic conditions and increased breastfeeding health awareness. Improving the nutritional status of breastfeeding mothers has an extremely important impact on the ideal breast milk of lactating mothers.

Transitional milk

The composition of milk gradually changes after childbirth. Breast milk produced from the eighth to the fifteenth day after delivery was known as transitional milk (68). The vitamin E concentration in transitional milk was lower than that in colostrum but higher than that in mature milk, which is similar to other researches (16, 21, 24, 25, 28, 33, 39, 42, 51, 54, 56–60).

The subgroup analyses observed that vitamin E concentration in transitional milk of Western lactating women was higher than that of Asian lactating women. Other important factors must be taken into account in addition to dietary restrictions and ethnicity. We found that the collection time of transitional milk was inconsistent in various studies. For example, the transitional milk is collected from the 21st to the 24th day postpartum (51), or the 8th to the 21th day postpartum (52, 55) in several prior studies in China. However, the latest studies in China (54, 56–60) revealed the collection time is from the 5th to 15th day postpartum, which is comparable to the majority of studies conducted in other nations (16, 21, 24, 25, 33, 39, 42). It might be an important reason resulting in the lower pooled vitamin E concentration of transitional milk in Asian countries. In order to increase the reliability of the results, more researches of transitional milk collected from the 5th to 15th day postpartum are needed.

Moreover, in a study of Saint Lucia (21), the result of vitamin E concentration in transitional milk was much higher...
(approximately two to three times) than that of other Western countries. However, the author did not mention the reason for this unusually high concentration. Due to the lack of transitional milk studies, the overall effect of meta-analysis of Western countries was 4.36 (95%CI 2.62–6.14) after excluding this abnormal value. One thing worth noting is the exclusion could cause a big discrepancy in results. Therefore, more data is needed to support the values as well.

**Mature milk**

After transition milk, variations in the composition of breast milk continue to occur, until third week postpartum. During this period, the composition of milk becomes more stable, which is mature milk (68).

The concentration of vitamin E in mature breast milk samples from Western countries were near to the values of Asian samples. It was speculated that individual or dietary factors might have little influence on mature breast milk. This speculation was supported by a study, which demonstrated maternal supplementation with R, R, R-α-tocopherol could increase vitamin E level of colostrum and transitional milk rather than mature milk (71). It is worth noting that infants with an estimated daily intake of 780 mL/day may not get enough vitamin E from mature milk to meet their nutritional needs (42, 56). Consequently, the implementation of procedures to increase the level of vitamin E in milk would be important especially for nursing mothers living in poor conditions of food safety.

Furthermore, Xue et al. (56) study the vitamin E concentration of breast milk during 12–240 day postpartum. It was found that the concentration of vitamin E in breast milk observed in 12–30th day postpartum (2.96 ± 2.11 mg/L) were similar to those collected in 31th-240th day postpartum (31–60th day: 2.96 ± 1.92 mg/L, 61–120th day: 2.45 ± 1.67 mg/L, 121–240th day: 2.71 ± 1.72 mg/L). It could be implied that vitamin E concentration in breast milk might reach a relatively stable level after 12th day postpartum. Another study observed in Japan in 2005 (28) showed that vitamin E concentration in breast milk in 21–89th day postpartum (2.97 ± 1.23 mg α-TE/L) were same as those in 90–180th day and 181–365th day postpartum (3.45 ± 1.39 mg α-TE/L and 2.52 ± 1.03 mg α-TE/L). The plateau of vitamin E concentration in breast milk appeared almost one week later than the result of Xue et al. It is speculated that the vitamin E of breast milk continues to decrease after childbirth, until approximately second to third week postpartum. The vitamin E concentration in mature milk becomes more stable. However, to support the start of the vitamin E stationary phase, more evidence should be done.

One Turkish study in 2008 (30) showed that the content of vitamin E in mature milk (9.84 ± 2.13mg/L) was significantly greater (more than three times) than the samples from other nations such as Greece (35) and Spain (32). As a result, the statistical data of this paper may be influenced by the potential confounders. According to a Brazil study in 2019, the α-tocopherol content of breast milk was only 0.56 ± 0.11mg/L from 17th to 28th days postpartum, significantly lower than other studies conducted there during the same time period (44, 66). It may be associated with lower sample size.

**Limitation**

There were some limitations to our study. First, the search was restricted to the studies published in English language and Chinese language, which may lead to publication bias. However, we have addressed the issue of publication bias during our analysis. Next, although subgroup and sensitivity analyses were performed, heterogeneity was still very large in the meta-analysis. Except for differences in region may lead to greater heterogeneity between studies especially in colostrum, the other factors could also contribute to heterogeneity. The underlying factors, including milk sample collection method, different techniques for nutrient measurements, postpartum milk sampling, time of milk sampling, duration of breastfeeding and so forth, might partly explain the large variation between studies in different periods of lactation. Therefore, more studies are necessary for reliable results.

**Conclusion**

Vitamin E concentration in breast milk decreased during lactation until the mature milk was produced. The higher value of vitamin E in colostrum might be important for
new-borns to defend early oxidative stress. The vitamin E concentration in colostrum from western countries was higher than from Asia, which might be related to dietary habits, individual variation, etc. More evidences of vitamin E concentration in transitional milk, especially the milk collected from the 5 to 15th day postpartum, are needed. The vitamin E content of mature milk was similar. It tended to be stable from about second week postpartum to 4–6th month postpartum. More results are needed to support this conclusion.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding authors.

Author contributions

YX, HZ, and AZ: applied the literature search and undertook the screening title and abstract screening. XW and XR: extracted the data and tabulated results. KL, YX, and XW: statistical analysis. YX and XW: wrote the initial version of the manuscript. YY: validation of the paper for important figures. JL and RX: critical revision of the paper for important intellectual content. All authors contributed to its final version and read and approved the final manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2022.1050011/full#supplementary-material
Nutrition and dietary factors on the concentration of vitamin A, alpha-tocopherol and total lipids in human milk through out early stages of lactation. 

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