

Using meta-research methods to examine the inclusion of women, pregnant women, and women-specific health outcomes in studies that contributed to the dietary reference intakes for one-carbon metabolism micronutrients

Carolyn Brandt,¹ Dina Moradian,¹ Bethany Harker,² Emily Hogan,¹ Negeena Azad,¹ Padmini Kucherlapaty,³ Emily Smith,^{1,3} Matthew Barberio,¹ Siran He^{1,3}

Affiliations: ¹ Department of Exercise and Nutrition Sciences, The Milken Institute School of Public Health, The George Washington University, Washington D.C., U.S.A., ² Department of Public Health, The Milken Institute School of Public Health, The George Washington University, Washington D.C., U.S.A. ³ Department of Global Health, The Milken Institute School of Public Health, The George Washington University, Washington D.C., U.S.A.



ABSTRACT

Purpose: Maternal micronutrient deficiencies occurring during periconceptional, pregnancy, and postpartum periods are a leading cause of adverse pregnancy outcomes globally. The Dietary Reference Intakes (DRIs) are a set of reference values used to assess and guide nutrient intakes of healthy individuals. However, the current DRIs for pregnancy and lactation may be limited in their methods and included populations. The present study analyzed the current DRIs for their inclusion of pregnant women and geographic representativeness. **Methods:** Meta-research methods were applied to the DRI report for vitamins B6, B12, folate, and choline in four steps: search, screening, full-text data extraction, and data analysis. For each target micronutrient, sections that contributed data to setting the average requirement were focused on, "Selection of Indicators for Estimating the Requirement," "Findings by Life Stage and Gender Group," and "Tolerable Upper Intake Limit" for adults, pregnancy, and lactation sub-sections. Screening involved reviewing the reference list to determine whether a reference directly contributed to setting the DRI. Full-text data extraction of primary data was conducted in areas of: 1) administrative information; 2) study methods; 3) human population characteristics; and 4) non-human subjects. Descriptive analyses were performed to describe the inclusion of women, pregnant women, geographic patterns, and demographic diversity. **Results:** For Vitamin B12, 100% of indicator studies and 71% of life stages studies included women, with a total of 3,246 women participants. However, none of the indicator studies and 15% of life stages studies included pregnant women, with a total of 556 pregnant women participants. None of the indicator studies and 8% of life stages studies reported health measurements specific to women, pregnancy, or lactation. Geographically, 54% of studies were conducted in the United States, and 18% took place in low-and middle-income countries. Data analysis is ongoing for the remaining micronutrients. **Conclusions:** Preliminary findings indicate that the body of evidence informing the current DRIs are limited in their inclusion of women and pregnant women. Numerous adverse pregnancy and birth outcomes are preventable through optimal maternal nutrition. Therefore, it is critical to ensure that the DRIs are suitable for their intended population. Despite their original intent for use in North America, the DRIs are widely adopted globally. Thus, geographic representation of the studies underlying the DRIs have implications for generalizability.

BACKGROUND

- **Women and pregnant people are historically underrepresented in medical research.** Over 90% of clinically approved drugs still lack information on safety, efficacy, and pharmacokinetics in pregnancy.¹
- **The Dietary Reference Intakes (DRIs),** developed at the Institute of Medicine, are a general term for a set of reference values used to assess and guide nutrient intakes of healthy individuals.²
- **DRIs are used** to guide global nutrition policy, diet assessments, and pregnancy vitamin and mineral supplement recommendation levels.
- **Maternal micronutrient deficiencies** occurring during periconceptional, pregnancy, and postpartum periods are a leading cause of adverse pregnancy outcomes globally.³
- **One-carbon metabolism micronutrients,** including folate, choline, vitamin B6, and B12, are essential during pregnancy; deficiencies in these nutrients are associated with adverse outcomes including maternal preeclampsia and neural tube defects in the offspring.⁴
- **We aimed at systematically investigating the body of evidence that informed the DRI values in terms of:**

- **The inclusion of pregnant people and women of reproductive age, and**
- **The geographic representation of these studies**

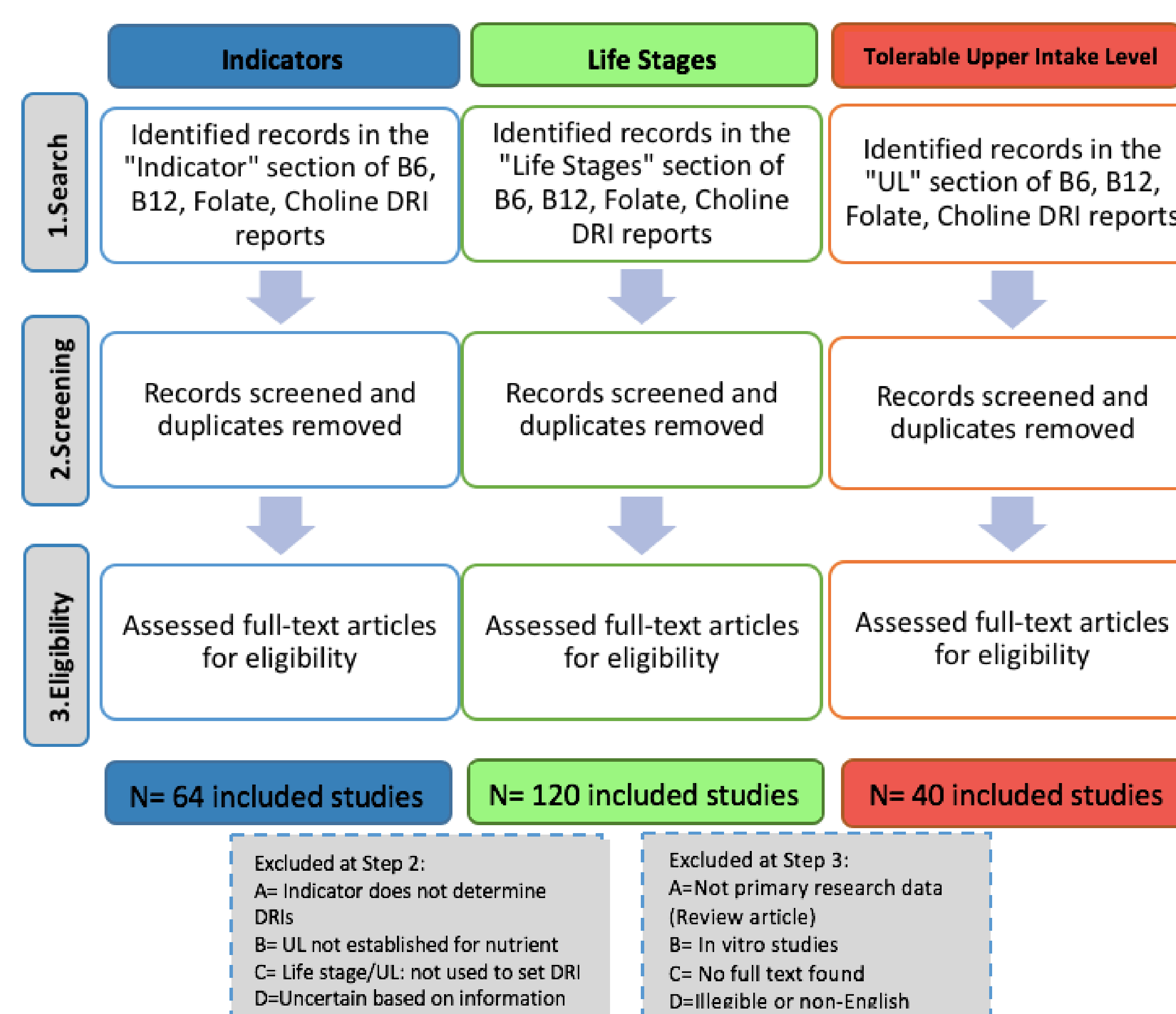
METHODS

• Meta-research methods were applied to the DRI report for Vitamin B6, Vitamin B12, Folate, and Choline in four steps: search, screening, full-text data extraction, and data analysis.

- 1. Search**
 - All studies which potentially contributed to the 1998 DRI report for B6, B12, folate, and Choline were searched.
- 2. Screening**
 - A panel of five experts reviewed the reference list to determine whether a reference directly contributed to setting the DRI for that micronutrient.
 - 224 human or animal primary studies, and 206 only human primary studies which were considered as contributing to the DRIs were ultimately included for Vitamins B12, B6, Folate, and Choline.

METHODS CONTINUED

Figure A: Meta-analysis workflow



*Indicators for B6 also included studies for preeclampsia

3. Data Abstraction

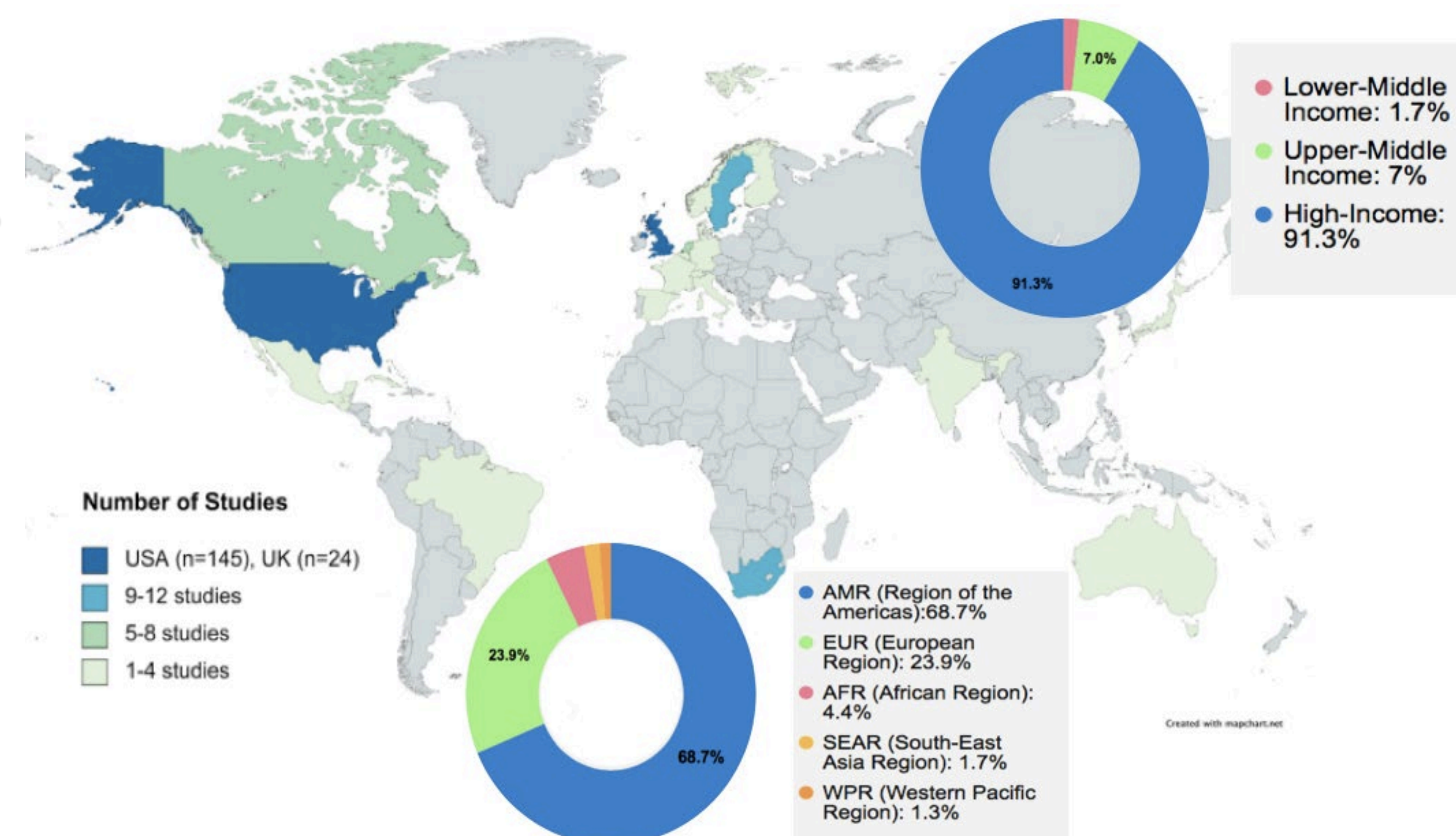
- Full-text data extraction of primary data from each study was performed in areas: 1) administrative information and study identification; 2) study methods; 3) human population characteristics; and 4) non-human subjects.

4. Data Analysis

- Descriptive analyses were performed to describe the inclusion of women, pregnant women, women of reproductive age, geographic patterns, and whether health outcomes specific to women/pregnancy/lactation were included.
- For all characteristics analyzed, we focused on collecting data for the number and proportion of studies. Total sample size of women was also calculated.

RESULTS

Figure B: Number of research studies by country, proportion occurring in each World Health Organization region, & proportion occurring in countries by their World Bank Income Group



- Less than 2% of the studies included in the DRIs for one-carbon metabolism micronutrients were conducted in Lower-Middle Income countries. No studies were conducted in Low-Income countries.

RESULTS CONTINUED

Figure C: Characterization of Included Study Population

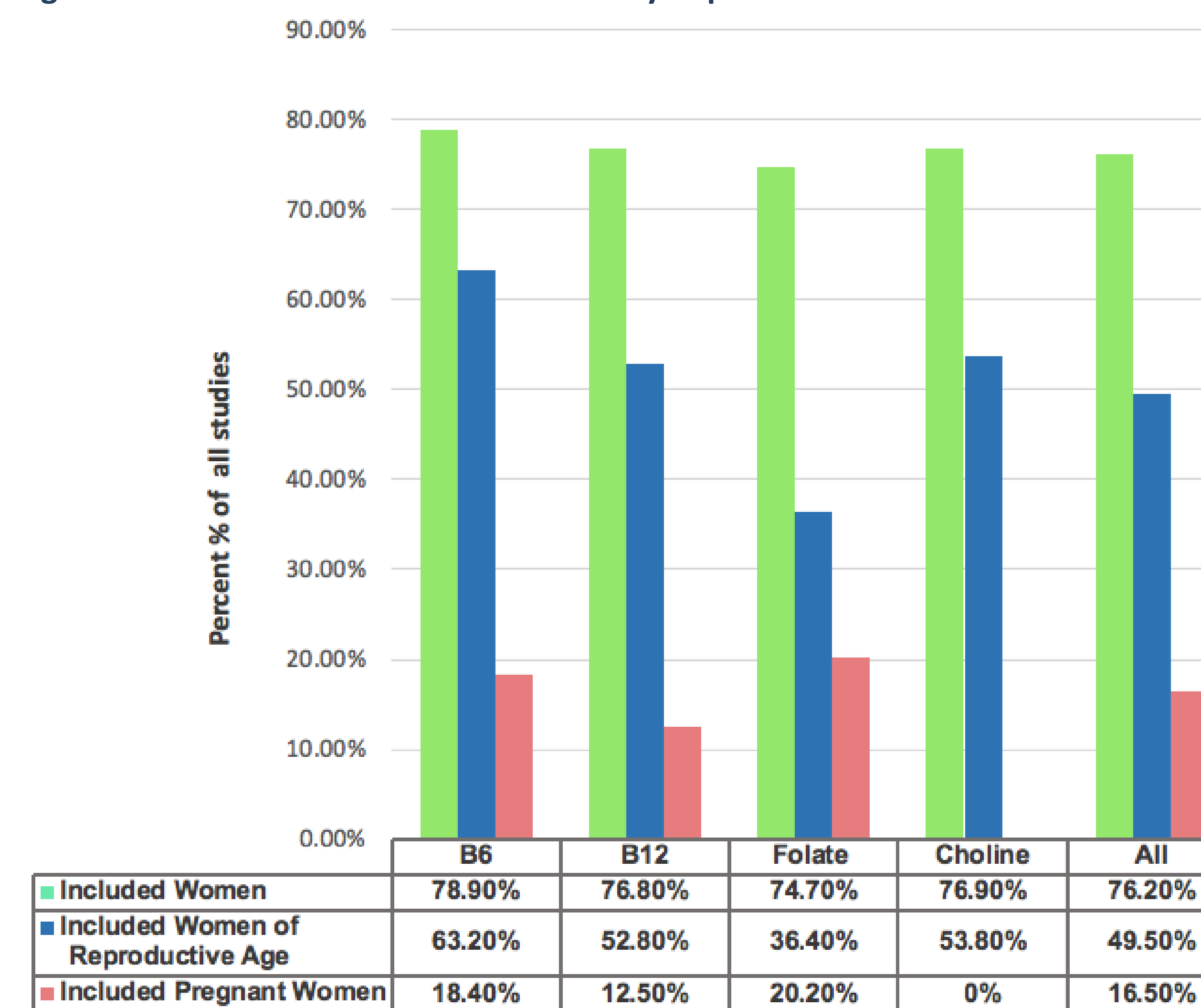
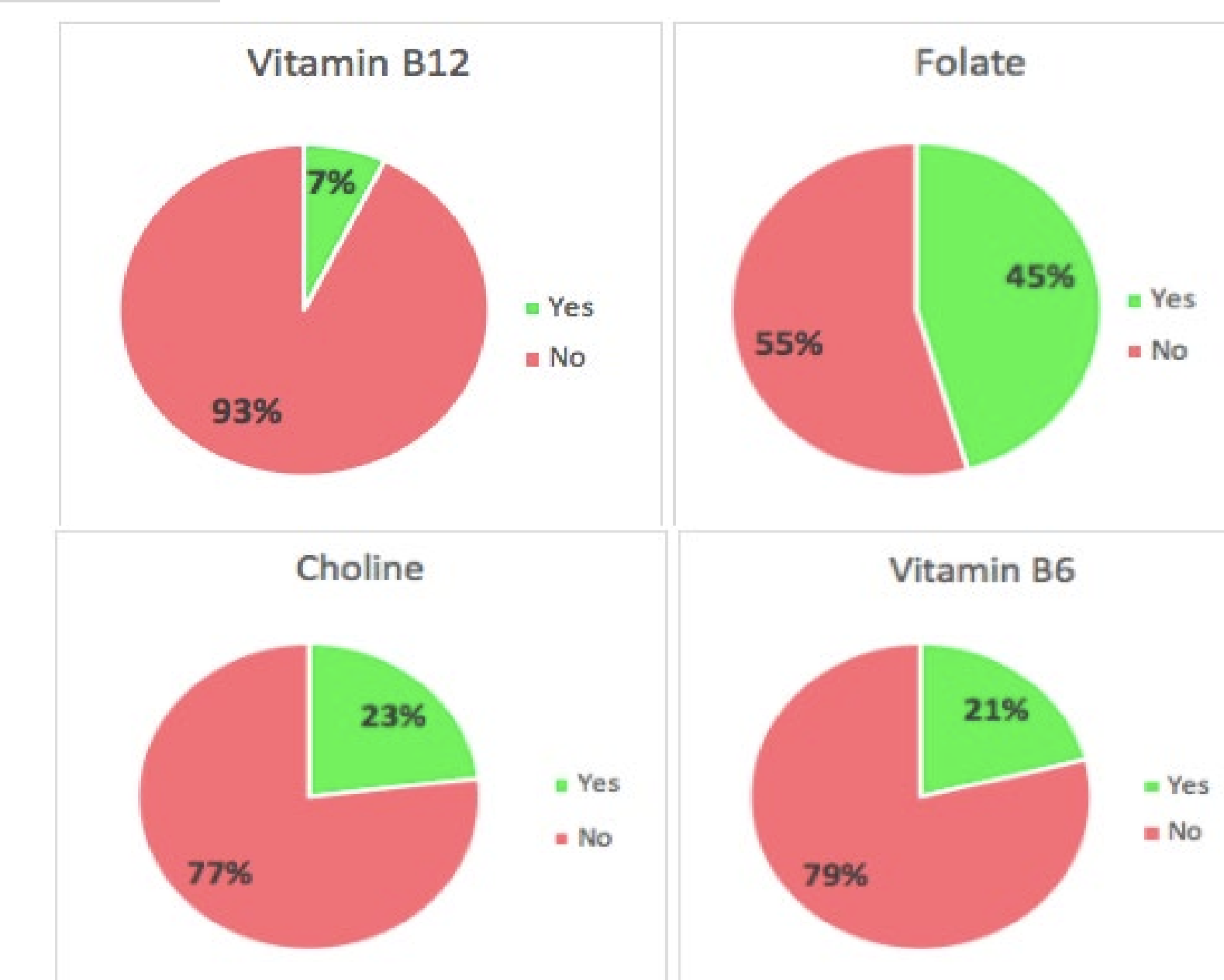


Figure D: Percent of Studies Reporting Health Outcomes Specific to Women/ Pregnancy/ Lactation: B12, Folate, Choline and B6

- The highest % of studies that included pregnant or lactating people were observed for folate, nearly double that of B12.
- No studies for selection of indicators or for establishing the upper level (UL) reported specific health outcomes for B12 or Choline.



DISCUSSION & CONCLUSION

1. Similar to their historical exclusion in medical research, we found that pregnant and lactating people have been excluded from clinical nutrition research that informs the DRIs for Vitamins B6, B12, Folate, and Choline, despite the importance of these micronutrients during and after pregnancy for optimal health. (Figure C)
2. The percent of studies reporting health outcomes specific to women/pregnancy/lactation, such as milk volume or low birth weight, varied significantly between the micronutrients analyzed. (Figure D)
 - No studies informing the selection of indicators or for establishing the upper level (UL) reported specific health outcomes for B12 or Choline, which is problematic as optimal biomarkers of micronutrient status may vary by reproductive state.
3. The nutrient reference values were originally intended for use in North America, however, the DRIs are widely adopted and used globally, and so global reference values require underlying high-quality data representative of the global population, rather than primarily the US, the UK, and high-income countries, which was the case for one-the carbon-metabolism micronutrients analyzed.

The current dietary reference intake values, which inform supplement formulations and nutrition policy in the US and globally, do not adequately include pregnant people for one-carbon metabolism micronutrients that are critical for a healthy pregnancy and birth outcomes. The DRIs demonstrate low geographic representativeness and may not be applicable to varying global population's needs.

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