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RESEARCH ARTICLE

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# Periconceptional folic acid supplement use among women of reproductive age and its determinants in central rural Germany: Results from a cross sectional study

**Clara Wegner**[1] | **Vijaya Kancherla**[2] | **Anke Lux**[3] | **Andrea Köhn**[1] | **Dirk Bretschneider**[4] | **Kristina Freese**[5] | **Mathias Heiduk**[6] | **Anke Redlich**[7] | **Daniela Schleef**[8] | **Gerhard Jorch**[9] | **Anke Rissmann**[1]

[1]Malformation Monitoring Centre Saxony-Anhalt, Medical Faculty Otto-von-Guericke University Magdeburg, Magdeburg, Germany

[2]Department of Epidemiology, Emory University Rollins School of Public Health, Atlanta, Georgia

[3]Institute for Biometrics and Medical Informatics, University Magdeburg, Magdeburg, Germany

[4]Department of Pediatrics, Hospital Marienstift Magdeburg, Magdeburg, Germany

[5]Department of Obstetrics and Gynecology, Hospital Marienstift Magdeburg, Magdeburg, Germany

[6]Department of Pediatrics, Hospital Magdeburg gGmbH, Magdeburg, Germany

[7]Department of Obstetrics and Gynaecology, University Hospital Magdeburg, Magdeburg, Germany

[8]Department of Obstetrics and Gynecology, Hospital Magdeburg GmbH, Magdeburg, Germany

[9]Department of Paediatrics, University Hospital Magdeburg, Magdeburg, Germany

**Correspondence**
Anke Rissmann, Malformation Monitoring Centre Saxony-Anhalt, Medical Faculty Otto-von-Guericke University Magdeburg, Magdeburg,

## Abstract

**Background:** Prevalence of neural tube defects (NTD) has not decreased in Germany despite longstanding recommendations for folic acid supplementation. To examine the prevalence of periconceptional folic acid supplement use and associated factors among German women of reproductive age.

**Methods:** Cross-sectional survey was conducted in hospital-based maternity units in rural Germany. A sample of 1,004 women of reproductive age, either pregnant or in their early postpartum period, took interviewer/self-administered paper-based survey questionnaire. Prevalence of periconceptional folic acid supplement use was assessed, where periconception was defined as 1 month prior to and 3 months post-conception. Prevalence odds ratios (POR) and 95% confidence intervals (CI) using crude and adjusted logistic regression analysis were estimated to examine determinants of folic acid supplement use.

**Results:** Prevalence of folic acid supplement use was 41.5% (95% CI: 37.7%, 45.7%). Multivariable analysis showed lack of educational qualifications, unplanned pregnancy, later diagnosis of pregnancy, increased parity, and not having an awareness of importance of folic acid for optimal pregnancy outcomes were associated with not taking periconceptional folic acid supplements. Books, doctors, friends, media, were sources of information.

**Conclusion:** Periconceptional folic acid is sub-optimal in rural Germany and thus failing to prevent NTDs. Targeted promotion of folic acid supplement use should be conducted periodically by gynecologists and primary care physicians during annual medical screenings. Mandatory folic acid fortification of staple foods is a complementary approach to overcome limitations of individual behaviors of folic acid supplement intake, and should be considered as it has been proven effective in multiple countries.

Clara Wegner and Vijaya Kancherla contributed equally as first authors.

Germany.
Email: anke.rissmann@med.ovgu.de

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Otto-von-Guericke University Medical Faculty

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folic acid, folic acid supplementation, periconceptional, preconception, reproductive age women, unplanned pregnancy

## 1 | INTRODUCTION

Neural tube defects (NTDs), like spina bifida and anencephaly, are major birth defects resulting from the failure of closure of the neural tube around 28th day after conception, a period when most women are not aware of their pregnancies (Botto, Moore, Khoury, & Erickson, 1999). Infants with anencephaly die at or shortly after birth; infants with spina bifida are affected with life-long morbidity and disability, and several die under age 5 years due to health complications (Blencowe, Kancherla, Moorthie, Darlison, & Modell, 2018; Sutton, Daly, & Kirke, 2008).

Randomized clinical trials have unequivocally demonstrated a significant reduction in the risk of NTDs with maternal periconceptional intake of folic acid (Czeizel, Dudas, & Metneki, 1994; MRC Vitamin Study Research Group, 1991). Periconceptional folic acid supplementation reduces both first and recurrent occurrence of NTDs (De-Regil, Pena-Rosas, Fernandez-Gaxiola, & Rayco-Solon, 2015). Folic acid intake may also provide protection for other selected congenital anomalies (Bulloch et al., 2018; Czeizel, Dobó, & Vargha, 2004; De-Regil et al., 2015; Tolarova & Harris, 1995).

According to the Food Fortification Initiative (www.ffinetwork.org), the United States and over 80 other countries in the world, but not including most countries in Europe, have implemented mandatory fortification of staple foods with folic acid, and several countries with effective fortification policies have reported a reduction in the prevalence of NTDs during the post-fortification period (Atta et al., 2016; Castillo-Lancellotti, Tur, & Uauy, 2013). National guidelines in Germany and other countries in Europe recommend that women who are capable of becoming pregnant should take 400 μg/day oral folic acid supplementation for primary prevention of NTDs since 1994 (Koletzko & Kries, 1995). Numerous campaigns have been targeted to women of reproductive age in European countries to promote folic acid supplement use, and yet the compliance is low, particularly among women from low socioeconomic status (Bestwick, Huttly, Morris, & Wald, 2014; Bitzer, von Stenglin, & Bannemerschult, 2013; Dante et al., 2015; Ray, Singh, & Burrows, 2004; Tort, Lelong, Prunet, Khoshnood, & Blondel, 2013). Women start taking folic acid only after the pregnancy test is positive, which is usually around the time neural tube closes, and it is too late to prevent NTDs. Thus, the public health strategy of voluntary intake of folic acid supplements by women of reproductive age has had very little impact, as shown in the prevalence trends of NTDs in Europe (Khoshnood et al., 2015).

Numerous studies have estimated the prevalence of folic acid use among women of reproductive age in countries of European countries, some including large urban cities in Germany (Bestwick et al., 2014; Birkenberger, Henrich, & Chen, 2019; Bitzer et al., 2013; Heinz, Kästner, Seewald, & Pötzsch, 2006; Knudsen et al., 2004; McKeating et al., 2015; Toivonen et al., 2018; Tort et al., 2013). However, there are no current studies on the periconceptional folic acid use in rural regions of Germany. We aimed at investigating the current prevalence of periconceptional folic acid supplement use and associated predictors among pregnant women and women who were in their early postpartum period in a central rural region of Saxony-Anhalt, Germany. Saxony-Anhalt is one of the two regions in Germany with active birth defects surveillance systems that tracks the total prevalence of NTDs since 1980. Since 2000, the registry covers the entire state of Saxony-Anhalt with over 2 million inhabitants and annual births at a rate of about 17,000 children. The surveillance system is multicentric and based on population, tracking all live births, still births, elective terminations for fetal anomalies for birth defects, including NTDs. Figure S1 displays the prevalence of NTDs for the time period of 2000 up to 2017 in the region surveyed by Saxony-Anhalt Birth Defects Registry in Germany. Current study findings have a potential to guide our understanding of prevalence of NTDs in this rural surveillance region.

## 2 | METHODS

Our study used a cross-sectional research design. We conducted a survey using an interviewer/self-administered paper-based interview. Participants were given a choice to either complete the survey on their own, or CW assisted the participants with the survey as needed. Only one interviewer (CW) was involved in administering the survey, and thus, the process of data collection did not vary due to multiple interviewers. Data were collected from January until July 2019 in all maternity

departments in Magdeburg, Saxony-Anhalt, including the university hospital. Including all maternal departments in the city allowed us to obtain a representative sample of participants from all socioeconomic strata in Magdeburg.

Pregnant women and women in their early postpartum period (up to 4 days after delivery), seeking medical care at the hospitals, were interviewed. The questionnaire covered knowledge and use of folic acid as well as sociodemographic data, including age, educational level, marital status, pregnancy planning, past history of congenital malformations, miscarriages, and sources from where participants received knowledge on folic acid before pregnancy, among other questionnaire items. Correct periconceptional folic acid intake was defined, according to the current guidelines, as starting supplementation of 400 μg folic acid supplement pill daily starting 1 month before conception and for at least 12 weeks of pregnancy (first trimester).

## 2.1 | Statistical analysis

Our sample size analysis was based on known population prevalence of folic acid supplement intake in the European women of reproductive age. We estimated that a sample size of 1,000 participants would give us expected prevalence with 99.9% confidence bounds around the estimated prevalence (ignoring non-response). With a power set at 80% and Type 1 error set at 0.05, a sample size of 1,000 participants can detect a crude prevalence odds ratio (POR) of at least 1.50 for selected predictors at the reference proportions.

Data were analyzed using the SAS version 9.4 (SAS Institute Inc., Cary, NC). Descriptive statistics were computed by calculating frequencies and percentages for responses. Comparison of characteristics between participants who reported periconceptional folic acid use and non-use were conducted using chi square test. Fisher exact test was applied for comparisons when a cell size were small ($n \leq 5$). Because the study used a cross-sectional design with a dichotomous dependent variable (periconception folic acid supplement use vs. no use), we conducted unadjusted and adjusted logistic regression to examine the association between each predictor variable with the outcome. Similarly, we conducted logistic regression analysis to examine information sources that predicted periconceptional folic acid use. As the study used cross-sectional study with no established temporal relation between the outcome and predictor variables, POR were effect estimates of choice. Thus, crude and adjusted PORs and 95% confidence intervals (CI) were estimated. All predictor variables were decided upon based on the literature review. Variable selection for multivariable models was examined using different methods and estimates were compared: (a) backward logistic regression; (b) using 10% change-in-estimate criterion; and (c) a priori criterion based on review of existing literature. As expected, these different regression analyses yielded same results. We report our findings based on a priori criterion, which was based on previous literature, and arbitrarily determined to follow highest plausible social determinants of health model, and best support our study interpretation. Significance for all statistical tests was set at $p < .05$.

Ethical approval for the study was obtained from the Medical Faculty Otto-von-Guericke University Magdeburg Ethics Committee (188/18) on 17th December 2018. The study was conducted according to good clinical practice guidelines and the principles of the Declaration of Helsinki.

# 3 | RESULTS

A total of 1,004 women, including 228 pregnant and 776 women in early postpartum, participated in the study. The overall response rate was 94.3%. The early postpartum interviews constituted 37.7% of all births that occurred in the city of Magdeburg during the study period, January and June 2019. The median age of the women interviewed was 31 years (standard deviation = 5.1 years). Nearly half of the surveyed women were pregnant with their first child or had just given birth to their first child, and third had one previous child. About three quarters (73.8%, $n = 717$) of women had planned their pregnancy. Of the women surveyed, majority (95%) reported that they were aware of the importance of folic acid during pregnancy (Table 1).

Overall, 41.5% ($n = 417$) of participants reported taking folic acid supplements during their periconceptional period. There was no significant difference in periconceptional folic acid use among participants who were pregnant during the interview and those that were in their early postpartum phase ($p = .8842$). Thus, the prevalence of periconceptional folic acid use among study participants was 41.5% (95% CI: 37.7%, 45.7%). The mean period of folic acid intake was 32 weeks of pregnancy. 91.3% ($n = 917$) of women used folic acid at some point during the advised period, but for most of the women (47.4%, $n = 476$) the folic acid use began after pregnancy notification; in 86.3% ($n = 404$) of cases after the fifth week of pregnancy.

Descriptive characteristics of all participants, and those stratified by periconceptional folic acid users and non-users are presented in Table 1. We found that

**TABLE 1** Characteristics of the survey participants by periconceptional folic acid use, year 2019

| Characteristics | All participants ($n$ = 1,004) | | Periconceptional folic acid users ($n$ = 417) | | Periconceptional folic acid non-users ($n$ = 587) | | |
|---|---|---|---|---|---|---|---|
| | *n* | % | *n* | % | *n* | % | *p*-value* |
| Age at interview (years) | | | | | | | |
| <18 | 9 | 0.91 | 0 | 0 | 9 | 1.57 | <.0001 |
| 18–<25 | 116 | 11.79 | 19 | 4.61 | 97 | 16.96 | |
| 25–<30 | 254 | 25.81 | 95 | 23.06 | 159 | 27.80 | |
| 30–<35 | 389 | 39.53 | 187 | 45.39 | 202 | 35.31 | |
| 35–<40 | 193 | 19.61 | 101 | 24.51 | 92 | 16.08 | |
| 40+ | 23 | 2.34 | 10 | 2.43 | 13 | 2.27 | |
| Highest qualification | | | | | | | |
| Professional degree | 342 | 34.58 | 131 | 31.41 | 211 | 36.82 | <.0001 |
| College degree | 165 | 16.68 | 89 | 21.39 | 76 | 13.26 | |
| University degree | 325 | 32.86 | 176 | 42.31 | 149 | 26.00 | |
| Other qualification | 46 | 4.65 | 9 | 2.16 | 37 | 6.46 | |
| No qualification | 111 | 11.22 | 11 | 2.64 | 100 | 17.45 | |
| Marital status | | | | | | | |
| Unmarried | 520 | 51.95 | 185 | 44.36 | 335 | 57.36 | <.0001 |
| Married | 435 | 43.46 | 220 | 52.76 | 215 | 36.82 | |
| Divorced | 46 | 4.60 | 12 | 2.88 | 34 | 5.82 | |
| Pregnancy planning | | | | | | | |
| Planned | 717 | 73.84 | 400 | 97.32 | 317 | 56.61 | <.0001 |
| Unplanned | 254 | 26.16 | 11 | 2.68 | 243 | 43.39 | |
| Pregnancy diagnosis time during gestation | | | | | | | |
| 1–4 weeks | 249 | 25.33 | 113 | 27.49 | 136 | 23.78 | <.0001 |
| 5–8 weeks | 626 | 63.68 | 282 | 68.61 | 344 | 60.14 | |
| 9 weeks and above | 108 | 10.99 | 16 | 3.89 | 92 | 16.08 | |
| Parity | | | | | | | |
| 0 | 487 | 49.24 | 235 | 57.18 | 252 | 43.60 | <.001 |
| 1–2 | 432 | 43.68 | 163 | 39.66 | 269 | 46.54 | |
| 3 or above | 70 | 7.08 | 12 | 3.16 | 57 | 9.86 | |
| Previous history of congenital anomalies | | | | | | | |
| No | 957 | 96.86 | 389 | 95.81 | 568 | 97.59 | .1378 |
| Yes | 31 | 3.14 | 17 | 4.19 | 14 | 2.41 | |
| Previous history of having a pregnancy affected by neural tube defects | | | | | | | |
| No | 1,001 | 99.70 | 416 | 99.76 | 585 | 99.66 | 1.000 |
| Yes | 3 | 0.30 | 1 | 0.24 | 2 | 0.34 | |
| Previous history of miscarriages | | | | | | | |
| No | 768 | 78.69 | 298 | 74.50 | 470 | 81.60 | .0077 |
| Yes | 208 | 21.31 | 102 | 25.50 | 106 | 18.40 | |
| Awareness of folic acid use during pregnancy | | | | | | | |
| No | 52 | 5.18 | 2 | 0.48 | 50 | 8.53 | <.0001 |
| Yes | 951 | 94.82 | 415 | 99.52 | 536 | 91.47 | |

*Note*: Frequencies and percents may not equal to total or add up to 100% due to missing responses.
*$p$-Values significant at <.05 comparing periconceptional folic acid users to non-users; Fisher exact $p$-values reported when cell sizes were five or less.

periconceptional folic acid use was more frequent in older women and women with high educational qualification. In addition, married women and women with awareness of folic acid were more likely to take folic acid in the periconceptional period compared to their counterparts. Additionally, planned pregnancies and an early pregnancy diagnosis improved the probability of taking folic acid during periconceptional period. The likelihood of taking periconceptional folic acid was similar when we compared women with previous history of congenital anomalies to those without. We had very scarce sample of participants who reported having a previous history of NTDs, with one participant among users and two among non-users, limiting our ability to study this association further. Thus, age, educational qualification, marital status, pregnancy planning, gestational age when the pregnancy was diagnosed, parity, previous history of miscarriages, and awareness of folic acid use during pregnancy, were factors that were significantly different between the two study groups in our descriptive analysis ($p < .05$) (Table 1).

Results from unadjusted and adjusted analyses are presented in Table 2. We regressed the probability of not taking periconceptional folic acid as the outcome to understand factors associated with it, and to guide targeted intervention strategies in the future. Our multivariable adjusted PORs showed that women with no educational qualifications or with a low qualification were 3.6-times more likely to not use folic acid compared to women with college degrees (95% CI: 1.30, 10.06). Also, highest positive association prevalence odds were noted for not taking periconceptional folic acid, with a 20-fold increased likelihood (aPOR 19.79; 95% CI: 10.07, 38.88), for women who did not plan their pregnancy compared to those who planned their pregnancy. Another significant determinant for not taking folic acid during periconceptional period was time of pregnancy diagnosis. Women who had their pregnancy diagnosed at or after ninth week of pregnancy were at a four-fold increased prevalence odds of not taking periconceptional folic acid compared to those who received their pregnancy diagnosis before ninth week of pregnancy (aPOR 4.02; 95% CI: 1.87, 8.63). Higher parity was also associated with an increased likelihood of not using periconceptional folic acid compared to nulliparity. Finally, women without an awareness of the importance of folic acid during pregnancy were more likely to not use folic acid compared to women who were knowledgeable about it (aPOR 8.85; 95% CI: 1.84, 42.56). We did not have adequate number of participants with the outcome to explore the association between previous history of NTD affected pregnancy and periconceptional folic acid use for the index pregnancy. Overall, the strongest determinants of periconceptional folic acid non-use were low or no educational qualification, pregnancy planning, and awareness of the importance of folic acid during pregnancy in our adjusted analysis.

We also conducted an analysis to examine from where participants received information on folic acid before their pregnancy, and how these information sources predicted periconceptional folic acid use. Table 3 summarizes this information, showing that overall, doctors (37.55%) and friends (13.15%) were the main sources of information for the majority of participants to get information about folic acid before they were pregnant. Some women reported that they received the information about folic acid from books (3.78%), media (4.68%), pharmacists (3.09%), and family members (3.78%). Partners were not key sources in receiving information about folic acid before pregnancy. Our multivariable analysis showed that books, doctors, friends, and media were significant predictors of periconceptional folic acid use (Table 3).

## 4 | DISCUSSION

Even though majority of women were knowledgeable about the importance of folic acid during pregnancy in our study sample, only about 40% of women in the study took folic acid supplements within the recommended periconceptional period. The German policy of advising women of reproductive age, who want to become pregnant, to start with folic acid supplementation before conception, therefore seems to be reasonably not effectively working to prevent NTDs at a critical period in pregnancy when the neural tube is formed, which is around 28th day of conception. Strongest risk factors that were associated with women not taking folic acid supplements as recommended, included education qualification, planning pregnancy in advance, having an early diagnosis of pregnancy, and knowledge of the importance of folic acid during pregnancy to prevent adverse birth outcomes. Partner and general education of the importance of folic acid may improve uptake, as most women did not report that their partners or families as sources of information about folic acid.

Despite extensive and continuous information campaigns in Europe, including Germany, about the necessity of periconceptional folic acid supplement use, total prevalence of NTDs (including elective terminations, stillbirths, and live births) in countries without mandatory folic acid fortification policy of staple foods has not decreased over the last 20 years (Khoshnood et al., 2015). Supplemental folic acid use and compliance of use varies substantially across European countries in the target

**TABLE 2** Unadjusted and adjusted analysis for predictors of periconceptional folic acid use in Germany

| Characteristic | Unadjusted POR (95% CI) | A priori model adjusted POR (95% CI)[a] |
|---|---|---|
| Age at interview (years) | | |
| <18 | — | — |
| 18–<25 | Reference | Reference |
| 25–<30 | 0.33 (0.19, 0.57) | 0.76 (0.36, 1.58) |
| 30–<35 | 0.21 (0.12, 0.36) | 0.53 (0.25, 1.10) |
| 35–<40 | 0.18 (0.10, 0.32) | 0.32 (0.15, 0.71) |
| 40+ | 0.26 (0.10, 0.67) | 0.44 (0.13, 1.48) |
| Highest qualification | | |
| Professional degree | 1.89 (1.30, 2.75) | 1.67 (1.07, 2.62) |
| College degree | Reference | Reference |
| University degree | 0.99 (0.68, 1.44) | 1.32 (0.83, 2.09) |
| Other qualification | 4.81 (2.19, 10.61) | 1.95 (0.67, 5.68) |
| No qualification | 10.65 (5.32, 21.31) | 3.62 (1.30, 10.06) |
| Marital status | | |
| Unmarried | 1.85 (1.43, 2.40) | 1.39 (0.99, 1.96) |
| Married | Reference | Reference |
| Divorced | 2.90 (1.46, 5.75) | 2.41 (0.98, 5.93) |
| Pregnancy planning | | |
| Planned | Reference | Reference |
| Unplanned | 27.88 (14.97, 51.92) | 19.79 (10.07, 38.88) |
| Pregnancy diagnosis time during gestation | | |
| 1–4 weeks | 0.99 (0.74, 1.33) | 1.04 (0.72, 1.51) |
| 5–8 weeks | Reference | Reference |
| 9 weeks and above | 4.71 (2.71, 8.20) | 4.02 (1.87, 8.63) |
| Parity | | |
| 0 | Reference | Reference |
| 1–2 | 1.54 (1.18, 2.00) | 2.12 (1.49, 3.02) |
| 3 or above | 4.09 (2.18, 7.66) | 2.71 (1.13, 6.50) |
| Previous history of congenital anomalies | | |
| No | Reference | Not included |
| Yes | 0.56 (0.28, 1.16) | |
| Previous history of having a pregnancy affected by neural tube defects | | |
| No | Reference | Not included |
| Yes | 1.42 (0.13, 15.74) | |
| Previous history of miscarriages | | |
| No | Reference | Reference |
| Yes | 0.66 (0.48, 0.90) | 1.49 (1.00, 2.22) |
| Awareness of folic acid use during pregnancy | | |
| No | 19.36 (4.68, 80.01) | 8.85 (1.84, 42.56) |
| Yes | Reference | Reference |

Abbreviations: CI, confidence interval; POR, prevalence odds ratio.

*Note*: Analyses were modeled for the event of not taking folic acid during periconceptional period.

[a]Variables in the adjusted analysis were controlled for all other variables in the model.

**TABLE 3** Sources of information about folic acid before pregnancy among study participants, and their association with periconceptional folic acid intake 2019

| Source of information about folic acid use before pregnancy | All participants ($n = 1,004$) | | Periconceptional folic acid users ($n = 417$) | | Periconceptional folic acid non-users ($n = 587$) | | Unadjusted POR (95% CI) | Adjusted POR (95% CI) |
|---|---|---|---|---|---|---|---|---|
| | *n* | % | *n* | % | *n* | % | | |
| Books | 38 | 3.78 | 25 | 6.00 | 13 | 2.21 | 0.36 (0.18, 0.70) | 0.28 (0.13, 0.61) |
| Doctor | 377 | 37.55 | 280 | 67.15 | 97 | 16.52 | 0.10 (0.07, 0.13) | 0.09 (0.07, 0.12) |
| Friends | 132 | 13.15 | 82 | 19.66 | 50 | 8.52 | 0.04 (0.26, 0.55) | 0.36 (0.23, 0.57) |
| Media | 47 | 4.68 | 31 | 7.43 | 16 | 2.73 | 0.35 (0.19, 0.65) | 0.43 (0.21, 0.90) |
| Partner | 15 | 1.49 | 8 | 1.92 | 7 | 1.19 | 0.62 (0.22, 1.72) | 1.07 (0.30, 3.75) |
| Pharmacist | 31 | 3.09 | 21 | 5.04 | 10 | 1.70 | 0.33 (0.15, 0.70) | 0.50 (0.20, 1.26) |
| Family | 38 | 3.78 | 24 | 5.76 | 14 | 2.39 | 0.40 (0.20, 0.78) | 0.58 (0.26, 1.33) |

Abbreviations: CI, confidence interval; POR, prevalence odds ratio.
*Note*: Analyses were modeled for the event of taking folic acid during periconceptional period.

population (Knudsen et al., 2004; McKeating et al., 2015; Tort et al., 2013). Currently, the knowledge regarding the compliance of German women is limited, and especially not representative or timely, of rural regions of Germany (Birkenberger et al., 2019; Heinz et al., 2006). A review of 34 studies conducted in countries worldwide between 1992 and 2001 showed, that nowhere the proportion of women taking folic acid supplements before pregnancy was greater than 50% and that overall it was about 25% (Ray et al., 2004). In Ireland, a survey of 42,362 women booking for antenatal care between 2009 and 2013 reported that 43.9% used folic acid before pregnancy (McKeating et al., 2015). In France, 14.8% of women giving birth in 2010 started FA use before pregnancy (Tort et al., 2013). This proportion was 31% in a cross-sectional study of nearly half a million women attending antenatal care in England in 2011–2012 (Bestwick et al., 2014). This variability may be partly due to the method and year of data collection as well as the impact of health care recommendations in each country. Nevertheless, many of these European studies show that majority of women who do not take folic acid periconceptionally, and our findings add to the evidence base with similar statistics, and focusing on a rural region.

The women's age, marital status, educational level and parity have been found to be associated with periconceptional FA use in other surveys as well as in our results (Mukhtar, Kramer, Oakley, & Kancherla, 2017; Obara et al., 2017; Yan et al., 2017). This may be partly due to more unplanned pregnancies and less knowledge of the benefits of folic acid supplementation in younger women. Limited access to medical information in less advantaged social classes might be another reason for insufficient folic acid intake and probably reflects socio-economic status as an example of health inequalities (Lindquist, Kurinczuk, Redshaw, & Knight, 2015). Lower consumption among women with high parity, independent of their social characteristics, is also reflected in many other studies (Birkenberger et al., 2019; de Walle & de Jong-van den Berg, 2008; Tort et al., 2013). This may be due to knowledge from previous pregnancies postponing the consultation of a doctor or the belief, that after the other children were not born with neural tube defect, any more pregnancies will be not affected either. Elective abortions requiring specific gynecology care present another opportunity for advising folic acid supplementation by doctors.

The frequency of unplanned pregnancies in our sample is similar to those referred in a German setting (Birkenberger et al., 2019), or in France (Tort et al., 2013) and some parts of the Netherlands (Friberg & Jørgensen, 2015). Unplanned pregnancies are more frequent in women with a low educational level, younger age and more than two children (Birkenberger et al., 2019; Goossens et al., 2016; Wellings et al., 2013). Planning pregnancy is an important condition for periconceptional folic acid use (Knudsen et al., 2004; Nilsen et al., 2006). Irrespective thereof, unplanned pregnancies have been shown to have a higher risk of exposure to prenatal risk factors for NTDs like smoking and unhealthy diets, and would profit in particular of a periconceptional folic acid use (Goossens et al., 2016). Moreover, data from the year 2000 of 1,224 women just after delivery, collected in the area our study took place and based on the same questionnaire we used, showed that only 4.0% took folic acid supplements during periconceptional period (Heinz et al., 2006). This proportion increased significantly over the last 19 years, but not in the group of women with

unplanned pregnancies. In 2000, none of the women with unplanned pregnancies took folic acid periconceptional, but in 2019, only 2.7% of women with unplanned pregnancies used folic acid periconceptional. This aspect shows the limitation of the current health care recommendations in Germany, targeting women with planned pregnancies, but not especially those of reproductive age who are at risk of unplanned pregnancies. Not specifically involving women with unplanned pregnancies in the current information campaigns in Europa might be one of the reasons, why the prevalence of NTDs in the EUROCAT did not decrease over the last 20 years in Europe (Khoshnood et al., 2015).

The fact that over 90% of all participants in our study reported using folic acid at some point of their pregnancy shows that the German public health recommendations are known. Also a large majority of participants had the knowledge of important of folic acid before their pregnancy and therefore in time to start with folic acid supplements. However, only a small proportion of women used folic acid supplementation as recommended in the periconceptional period. There is important know-do gap that needs to be addressed in Germany to promote timely intake of folic acid for primary prevention of NTDs. Partners, who may be present with these women, should also be educated about folic acid so they can serve as source of information on folic acid to the target group.

With loopholes in solely depending on individual health behaviors, an alternate effective approach to increasing folic acid uptake in the target population should be considered. Policies promoting mandatory fortification of staple foods with folic acid have been shown to be highly effective (Atta et al., 2016; Castillo-Lancellotti et al., 2013) with high cost–benefit ratio (Grosse, Berry, Mick Tilford, Kucik, & Waitzman, 2016). Evidence on improved blood folate concentrations among women of reproductive age, and reduced prevalence of NTDs, in countries with mandatory fortification provides support for this approach, limiting socioeconomic disparities in folic acid supplement intake when done on an individual level (Atta et al., 2016; Pfeiffer et al., 2019). Therefore, the Scientific Advisory Committee on Nutrition (SACN) advising Public Health England concluded in 2017 that its previous recommendations (published in 2006 and 2009) remained unchanged and mandatory folic acid fortification of flour remained to be recommended to improve the folate status of women most at risk of NTD-affected pregnancies as long as the folic acid intake of 1 mg/day is not exceeded (Scientific Advisory Committee on Nutrition, 2017).

An important strength of our study is that the survey is the large sample size and a high response rate. Participants who were in their early postpartum period constituted 37% of all women giving birth in the study area during the study period. We minimized any bias in our selection process to make the survey representative of women within all educational levels. We collected data on several potential predictors for periconceptional folic acid use. Another strength of the study is the study region. The study was conducted in the one of the two birth defects surveillance regions in Germany. The Malformation Monitoring Centre in Saxony-Anhalt is an established birth defects surveillance system in the survey region that is conducting active surveillance of birth defects over the last 19 years, including NTDs, while tracking all pregnancy outcomes (i.e., elective terminations for fetal anomalies following prenatal diagnosis, fetal deaths/stillbirths and live births). Our study results showing low prevalence of periconceptional folic acid supplement use supports the trend reported by the birth defects registry in the region, with no change in NTD prevalence over time (Figure S1) (Bremer et al., 2018; Khoshnood et al., 2015). Thus, indicating that voluntary intake of folic acid supplements by women of reproductive age in the region, and possibly in whole of Germany, is not high, and the prevalence of NTD is higher compared to other places with more effective programs promoting folic acid intake among women of reproductive age. A major limitation of the study is that folic acid use is self-reported. We were unable to accurately collect information on compliance. Since majority of women were aware of the importance of folic acid during pregnancy, there is a potential for bias in over-reporting folic acid use. We expect that the true periconceptional folic acid use may be lower than what was reported in the survey. We were also unable to control for unmeasured confounders in our study on predictors of periconceptional folic acid use.

In conclusion, our results show that public health policy on folic acid supplementation to prevent NTDs cannot rely only on campaigns addressing women with planned pregnancies and those who attend antenatal screening programs and scanning during pregnancy. The World Health Organization recommends that, "All women, from the moment they begin trying to conceive until 12 weeks of gestation, should take a folic acid supplement (400 μg folic acid daily) "(available at: https://www.who.int/elena/titles/folate_periconceptional/en/). Thus, campaigns to promote folic acid should target specifically women who are capable of becoming pregnant and information should be provided by the gynecologist to every woman attending their yearly medical visits for health screen. Moreover, in face of 58.5% of women still not taking folic acid periconceptionally despite the 25 years of experience with recommendations in Germany similar to those of the WHO (Koletzko & Kries, 1995), adds value to the need for folic acid food fortification in Germany as a reasonable addition to folic acid supplementation programs. Mandatory fortification of

staple foods with folic acid should be a complementary approach to overcome the limitations of supplement programs along, which depend on individual health behaviors of women, and have rarely reached 100% effectiveness in any country in the past. Our findings bring to light gaps in the success of current folic acid supplementation programs in rural Germany, and call for needed improvements in education about folic acid in various settings, and a parallel consideration of other complementary approaches to the intervention urgently as a preventive strategy for NTDs.

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## CONFLICT OF INTEREST

The authors have no financial relationships relevant to this article to disclose.

## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

## ORCID

*Vijaya Kancherla* https://orcid.org/0000-0002-2803-8030

*Anke Rissmann* https://orcid.org/0000-0002-9437-2790

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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