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Association between Pre-Pregnancy Diabetes Mellitus and Pre-Conception Folic Acid Supplement Use by Hispanic Ethnicity: Findings from Georgia, New York City and Puerto Rico PRAMS 2016-2018

By

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MPH, Emory University, 2021

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By

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Bachelor of Arts
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Thesis Committee Chair: Vijaya Kancherla, PhD

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Abstract

Association between Pre-Pregnancy Diabetes Mellitus and Pre-Conception Folic Acid Supplement Use by Hispanic Ethnicity: Findings from Georgia, New York City and Puerto Rico PRAMS 2016-2018

By Iridian Alexandra Guzman

BACKGROUND: In the US all women of reproductive age are recommended to consume 400 mcg of folic acid daily to prevent neural tube defects (NTDs). Both Hispanic ethnicity and pre-pregnancy diabetes are associated with increased risk of NTDs. Preconception folic acid supplement use has been shown to attenuate the risk of NTDs among women with pre-pregnancy diabetes. The purpose of this study was to assess the association between pre-conception folic acid use and pre-pregnancy diabetes particularly among Hispanic women in the US.

METHODS: Using data from three-state based Pregnancy Risk Assessment Monitoring System (PRAMS) 2016-2018, we examined the association between preconception folic acid supplement use and pre-pregnancy diabetes mellitus stratified by Hispanic ethnicity. We used multivariable logistic regression to estimate the adjusted odds ratio (aORs) and 95% confidence intervals. All analyses accounted from PRAMS complex survey design.

RESULTS: Our study found that 44% of non-Hispanic women with pre-pregnancy diabetes and 29% of Hispanic women with pre-pregnancy diabetes reported recommended intake of folic acid supplements (4-7 times/week) before pregnancy. There was no significant association between pre-pregnancy diabetes and preconception folic acid supplement use overall. The prevalence odds of not taking preconception folic acid supplements were lower for women with pre-pregnancy diabetes compared to women without pre-pregnancy diabetes (aOR=0.39; 95% CI, 0.05, 3.25) among Hispanics who received preconception folic acid advice from a health provider and among those who did not receive preconception folic acid advice the odds were higher (aOR=1.50; 95% CI, 0.27, 8.52). In our site-specific analysis, we noted that Hispanic women in Puerto Rico had a higher prevalence odds of not taking preconception folic acid supplement when they had pre-pregnancy diabetes compared to when they did not (aOR=7.60; 95% CI, 1.73, 33.46).

CONCLUSIONS: Overall, there was no association between pre-pregnancy diabetes and preconception folic acid supplement use. However, some differences were noted by advice from a health provider and site. Mandatory fortification of corn masa products should be implemented. Until then, culturally tailored education on preconception folic acid supplement use from providers or community health workers needs to expand to reach Hispanic women in the US and Puerto Rico.

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CHAPTER I: BACKGROUND

Neural Tube Defects

Neural tube defects (NTDs), largely comprising of spina bifida, anencephaly and encephalocele, are major structural birth defects affecting the central nervous system characterized by the failure of neural tube to close completely around 4th week of gestation, a time when most women are unaware of their pregnancies (1). NTDs have a multifactorial etiology due to both genetic and environmental factors (2, 3). NTDs can cause serious health problems for infants including paralysis, bowel and urinary dysfunction, unconsciousness, deafness, mortality, among other things (4-7). Despite the increase in survival rates for patients born with an NTD (8), these serious health problems can often lead to complications that require patients to undergo intensive medical treatments (9). For instance, a cross-sectional study conducted using data 2009-2013 data from the National Spina Bifida Patient Registry found that from the 4,664 spina bifida patients in the database 81.5% of them had completed surgical procedures including gastrointestinal, neurologic, orthopedic, skin, urologic, and other (6). Among cases who underwent surgical procedures, approximately 50% of them happened when the patient was <1 year old (6). The estimated sum of charges for all spina bifida related hospital admissions and emergency room visits in 2014 was approximately $2 billion, compared to $1.2 billion in 2006 (adjusting for inflation) (10). In the United States (US) from 2014-2017, the average infant mortality rate due to NTDs was 9.0 per 100,000 live births (7).

Prevalence of NTDs in the US

A study pooling data from eight different population-based birth defects surveillance programs with prenatal ascertainment found that in the US, the total prevalence of spina bifida and anencephaly after mandatory fortification (1999-2011) were 4 and 2.9 per 10,000 live births, respectively (11). When examined by maternal ethnicity/race, the prevalence of NTDs has remained stable following mandatory fortification for all Hispanics, non-Hispanic White, and non-Hispanic Black (11) . Even after mandatory fortification Hispanics continue to have the highest prevalence of NTDs, where in 2011 the reported total prevalence of NTDs among non-Hispanic Black was approximately 4 per 10,000 live births compared to 5 per 10,000 live births among non-Hispanic White and 6.5 per 10,000 live births among Hispanics (11).

Risk Factors for NTDs

Non-genetic modifiable risk factors of NTDs include pre-pregnancy obesity (BMI ≥30.0), pre-pregnancy diabetes type I or type II, gestational diabetes, lack of any and folic acid supplementation during preconception period and pregnancy, low dietary folate intake, and anticonvulsant medication or any hot tub or sauna use during the month before pregnancy and the first month of pregnancy (3, 12). Genetic non-modifiable risk factors include infant sex, family history of NTDs, and maternal Hispanic ethnicity (3, 12). These risk factors account for less than half of NTDs, suggesting that other unidentified genetic or nongenetic risk factors account for most NTD cases (3).

NTDs and Hispanic Ethnicity

There is a disproportionately higher prevalence of NTDs among Hispanic populations in the US. Hispanic women in the US are more likely to deliver infants with NTDs compared to their white counterparts (13-20). In a study examining the association between race/ethnicity and major birth defects in the US from 1999-2007, using data from 12 population-based surveillance systems, Hispanic mothers were the only racial/ethnic group in the study that had a significantly higher prevalence of having a pregnancy affected by spina bifida and anencephaly compared to non-Hispanic whites after adjusting for maternal age and US state of residence (20). A case-control study of 538 infants born with NTDs in California found that the odds of neural tube defects among infants of Mexican descent was 1.9-times greater compared to infants of Caucasian decent (13). When examined by Mexican mother's birthplace they found that compared to infants of Caucasian descent, the odds of NTDs among infants born to Mexican mothers who were Mexico-born was 2.4-times greater, while the odds among infants born to Mexican mothers who were US-born was 1.1-times greater. These results suggest that NTDs are more common among infants born to Mexican mothers who were born in Mexico than in infants born to Mexican mothers who were born in the US and Caucasian mothers. Similar effects of nativity status on risk of NTDs in Hispanic populations have been found in other studies (21). Additionally, a cross-sectional study using medical records from six hospitals in Brooklyn found that prevalence of three types of NTDs, anencephaly, myelomeningocele and occipital encephalocele combined was higher among infants born to Puerto Rican mothers compared to non-Puerto Rican white or black mothers (16). In this study Puerto Rican ethnicity was classified based on mother's place of birth and did not include Puerto Rican mothers that were born in the US. Puerto Rican mothers who were born in the US were classified as white therefore, the study did not stratify Puerto Rican ethnicity groups by mother's nativity status as it was done in the previous study for Mexican mothers.

NTDs and maternal pre-pregnancy diabetes

Maternal pre-pregnancy diabetes is one of the modifiable risk factors of NTDs. Infants born to women with type 1 and type 2 diabetes mellitus have an increased risk for NTDs (22, 23). Infants born to mothers with pre-pregnancy diabetes are 3.17-times more likely to be born with an isolated birth defect and 8.62-times more likely to be born with multiple birth defects compared to infants born to mothers without pre-pregnancy diabetes (24). Although studies have shown that the diabetes crude attributable risk (cAR) for pre-pregnancy diabetes among cases of isolated NTDs is low (cARs=0.29%) (3), most women of reproductive age are undiagnosed with diabetes prior to becoming pregnant.

The biological mechanisms underlying the association between pre-pregnancy diabetes and NTDs are complex and not completely understood. Maternal diabetes has been shown to induce hypoxia, oxidative stress, and other metabolic disruptions in the embryo that alter biological pathways and molecules leading to developmental defects in an embryo (25). It has been suggested that maternal diabetes leads to increased glucose levels which increase oxidative stress through the production of reactive oxygen species (ROS). The ROS produced leads to membrane damage and activates programmed cell death, apoptosis. Abnormal apoptosis results in malformation in major organ systems, such as the neural tubes, for a developing fetus (26). Epigenetic mechanisms that modify the expression of genes involved in embryogenesis have also been proposed. Pre-pregnancy diabetes may alter the embryonic epigenome which can modify the mechanisms involved in DNA methylation and histone acetylation, in turn these modifications may particularly impact genes involved in morphogenesis (27, 28). While the mechanisms remain not completely understood, epidemiological evidence suggests that the risk of NTDs among is higher among children born to mother with diabetes compared to those without (29) suggesting that more needs to be done to prevent NTDs among diabetic women.

In recent years, the prevalence of diabetes among women of reproductive age in the US has increased (30, 31) presenting a pregnancy risk for women and their infants. Epidemiologic studies have shown that from 2000 to 2010, there was a 37% increase in overall age-standardized prevalence of pre-pregnancy diabetes mellitus among US women of childbearing age (31). Furthermore, Hispanic women in the US are more likely to have undiagnosed diabetes mellitus. A study using data from the National Longitudinal Study of Adolescent to Adult Health (Add Health) found that among non-pregnant Hispanic women ages 24-32 the prevalence of diabetes was 7.5% and 48.1% of them were undiagnosed (32). Undiagnosed diabetes is more than 2-times higher among Hispanic women compared to Caucasian women (22.8%). This presents an additional risk among Hispanic women who may become pregnant and are unaware of their condition and thus unable to take the necessary measures to prevent any adverse pregnancy outcomes such as NTDs (33).
There is limited research on the effects of maternal pre-pregnancy diabetes mellitus on risk of NTDs among Hispanic women. A case-control study on NTDs among births in Harris County Taxes found no association between maternal pre-pregnancy diabetes and risk of one type of NTD, anencephaly (19). The association could not be examined for spina bifida because there were no diabetic mothers among the spina bifida cases. In general, the results of this study were limited by the precision of the data. Additionally, a case-control study of Mexican American women using data from the Texas Department of Health's Neural Tube Defect Project found that the risk of NTDs among infants born to mothers with

hyperinsulinemia was 1.73-times higher compared to infants born to control mothers after adjusting for obesity, maternal age, education, previous miscarriage, and vitamin use (34). While hyperinsulinemia alone is not considered diabetes, it often leads to the development of type 2 diabetes. One limitation of this study is that hyperinsulinemia was measured 5-6 weeks postpartum. The researchers stated that postpartum hyperinsulinemia is highly suggestive of preconception hyperinsulinemia. Nonetheless, we cannot be confident that postpartum levels truly reflect preconception levels. More research collecting information on pre-pregnancy diabetes and NTDs among Hispanic women is needed to better understand how this disease effects reproductive outcomes among this population.

Folic acid

Folic acid is a micronutrient and a water-soluble vitamin (vitamin B9). Folic acid is a synthetic form of folate that is used in supplements and in other fortified food products such as rice, pasta, bread, and some breakfast cereals. Research has shown that in the early developmental stages of pregnancy, folic acid may play an important role in the formation of neural tube although the exact mechanisms remain unknown (35, 36). In 1965, it was first hypothesized that there could be a relationship between folate deficiency and NTDs as a result of multiple observations in the increased number of malformations in infants born to mothers who were diagnosed with deficient folate metabolism (37). Similar findings were observed in animal studies where pregnant animals were deprived of folic acid.

In 1992, the US Public Health Service recommended that all women of reproductive age consume 400 ug of folic acid daily in order to prevent pregnancies affected by neural tube defects (38). Following this recommendation in 1998, the US implemented a public health intervention that required the fortification of enriched cereal grain products.

Manufactures were required to fortify these products with 140 mcg of folic acid per 100 grams of flour. Women in the US have access to three main sources of folic acid: fortified enriched cereal grain products, fortified ready-to-eat cereals, and dietary supplements. Recent research has shown that women whose only source of folic acid were enriched cereal grain products had lower daily total folic acid intake, lower red blood cell folate concentrations, and higher predictive NTDs prevalence compared to women who consumed additional folic acid from diet and supplements (39). These results highlight the importance of folic acid supplement use among women to achieve the recommended daily consumption of folic acid.

Folic acid use and race/ethnicity in the US

Race and ethnicity differences in the recommended daily consumption of folic acid have also been noted. In a study using data from the 2001-2002 National Health and Nutrition Examination Survey (NHANES), researchers found that 21% of Hispanic women consumed ≥400 ug folic acid from supplement and/or fortified foods compared to 40.5% of non-Hispanic white women of reproductive age (40). Similar results were found in a study using data from the 2009 Pregnancy Risk Assessment Monitoring System (PRAMS) survey, where 34.2% of non-Hispanic white women reported folic acid supplement use during the month before pregnancy compared to 22.5% of Hispanic women (41). A more recent cross-sectional study using data from the 2009-2011 Georgia PRAMS surveys found that Hispanic women are 2.15-times more likely to not use pre-conceptional folic acid supplements compared to non-Hispanic white women (42). A study conducted in Puerto Rico has also shown low prevalence of preconception folic acid consumption including consuming a multivitamin containing folic acid among women of reproductive age (43). Similar findings are observed even among Hispanics in Puerto Rico who are aware of the best time to begin folic acid supplementation use (44). Suggesting that overall, many Hispanic women in the US and Puerto Rico are not meeting the daily recommended consumption of folic acid even after the 1992 folic acid recommendations and the 1998 fortification of food products intervention. Public Health professionals have suggested that the failure to fortify corn masa food products in the US may be setting back efforts to increase folic acid consumption among Hispanic women of reproductive age (45). The low prevalence of pre-conceptional folic acid supplement use, in addition to lack of fortification of corn masa and lower acculturation levels to other fortified US staples (e.g., enriched wheat and/maize) have shown to impact the lower geometric mean red blood cell folate concentrations among Hispanic women placing their offspring at significantly higher risk of NTDs compared to other race/ethnic groups (40, 42, 45, 46).

Folic acid supplement use among diabetic women of reproductive age

Whether preconception folic acid use attenuates the risk of NTDs among diabetic women is not completely understood. Animal studies have shown that folate supplements do not significantly reduce NTD rates in rats with hyperglycemic conditions (47). Nonetheless, a study among US women of reproductive age has suggested that pre-conceptional use of multivitamins that may contain folic acid among diabetic women reduce the risk of selected birth defects (48). Furthermore, a global meta-analysis on preconception care and risk of birth defects among infants born to women with diabetes mellitus found in their post hoc analysis that that lowest risk for birth defects was observed among the participants that participated in the Bay Area Diabetes and Early Pregnancy Program in California that reported including the use of preconception folic acid in their preconception care program

(49, 50). Suggesting that including folic acid supplement use in the preconception care of diabetic women is necessary to reduce the risk of birth defects.

Data on the adherence to the recommended daily preconception folic acid consumption among women of reproductive age with pre-pregnancy diabetes is limited and inconsistent. It has been noted that women with pre-pregnancy diabetes are more likely to have unplanned pregnancies and not have access to proper preconception care, thus decreasing the likelihood that they are consuming the recommended dose of folic acid before becoming pregnant (51, 52). A cross-sectional study using data from the Texas Behavioral Risk Factor Surveillance System (BRFSS) found no association between pre-pregnancy diabetes and the use of daily folic acid supplements after adjusting for race/ethnicity, age, education, and household income or knowledge that folic acid prevents birth defects and recommendation from a health care provider (53). On the other hand, a study conducted using data from the National Birth Defects Prevention Study found that 4.2% of women with pre-pregnancy diabetes had an average daily intake of folate that was lower than 253 ug during the year before they became pregnant (54). This percentage was significantly lower compared to women without pre-pregnancy diabetes, suggesting that women with pre-pregnancy diabetes had relatively better intake of folate. In this study they created the cutoffs for low and high intake of folate based on the distribution of the nutritional factor among the sample and not based on the folic acid recommendations for women of reproductive age in the US. Women consuming between 253 mcg and 399 mcg of folic acid are still not meeting the recommended daily consumption of 400 mcg of folic acid to prevent NTDs, thus from this study it is unclear whether women with pre-pregnancy diabetes are meeting these recommendations. There is a need to further understand the relationship between pre-pregnancy diabetes and NTDs, as well as examine the current pre-conception health behaviors, such as folic acid consumption, among Hispanic women with pre-pregnancy diabetes.

Promotoras de salud model to communicate folic acid message to Hispanic women

Promotoras de salud are community health workers who contribute to the improvement of health education and health information access of low-income, Spanish speaking, and underserved Hispanic/Latino communities. The interpersonal relationship between a promotora de salud and community members helps drive a change in positive behaviors to improve health outcomes. Recently, the promotora de salud model has been adapted to communicate the folic acid message to Hispanic/Latina women in the US. Promotoras received an 8-hour training, in Spanish, on folic acid which was facilitated by the Centers for Disease Control and Prevention. Each promotora was equipped with a binder that consisted of educational materials on folic acid and NTDs. After the training, intervention sites were recruited from locations throughout the country were a large population of Hispanics congregated. Within these locations promotoras reached Spanish-speaking women to gauge interest and eligibility before registering them for an education session. A study evaluating the use of this model showed that 5% of participants reported consuming folic acid supplements before participating in the education session and 55% reported consuming folic acid supplements after participating in the education session (55). Additionally, the majority of participants reported taking folic acid vitamin supplement because the promotora had recommended it (55). Understanding the relationship between pre-conceptional folic acid supplement use and pre-pregnancy diabetes mellitus among Hispanic women may help determine if Hispanic women with pre-gestational diabetes should be specifically targeted by public health intervention programs like the promotora de salud model to improve intake of folic acid among this vulnerable group.

Conclusions

Our literature review highlights the importance of preconception folic acid supplement use for reducing adverse pregnancy outcomes such as NTDs. All women of child-bearing age should consume the at least 400 mcg/day of folic acid before and during early pregnancy. This is particularly important among women who have greater risks of NTDs such as Hispanic women and women with pre-pregnancy diabetes. Given that pre-pregnancy diabetes is prevalent among Hispanic women of reproductive age and that many of them go undiagnosed emphasizes the importance of understanding the current preconception behaviors of Hispanic women with pre-pregnancy diabetes.

Study Rationale and Objectives

There are no current published studies on pre-conception folic acid supplement use among Hispanic women of reproductive age with pre-pregnancy diabetes. Understanding women's adherence to adequate pre-conception folic acid supplement use guidelines is important to determine where interventions should be better implemented. The goal of this study is to assess whether pre-pregnancy diabetes among women of reproductive age women who have had live births in Georgia, Puerto Rico, and New York City is associated with the intake of adequate preconception folic acid supplements, and by Hispanic ethnicity. Using data from three state-based PRAMS surveys (Georgia, Puerto Rico, and New York City) from years 2016-2018, we examined the prevalence of preconception folic acid supplement use for women with and without pre-pregnancy diabetes by Hispanic ethnicity. These three study sites were selected to increase the potential sample size of Hispanic women given the increasing populations of Hispanics in Georgia and the large population of Hispanics in Puerto Rico and New York City. Theoretically, these sites could also represent distinct sub-populations within the larger sample of Hispanics. For instance, Hispanic populations in Georgia mostly comprise of Mexican, Puerto Rican, and Central American populations (56), in Puerto Rico the Hispanic population is predominantly Puerto Rican (57), and in New York City it is predominantly Puerto Rican and Dominican (57). This provides an opportunity to understand within-group heterogeneity that would be missed if we assumed all Hispanic populations were the same.

Research Questions

1. Is there an association between pre-conceptional folic acid supplement use and pre-pregnancy diabetes mellitus in the study target group of reproductive-aged women in selected states of the US?
2. Is the association between pre-conceptional folic acid supplement use and pre-pregnancy diabetes mellitus modified by Hispanic ethnicity overall and by the study sites?

CHAPTER II: MANUSCRIPT

INTRODUCTION

Neural tube defects (NTDs), largely comprising of spina bifida, anencephaly, and encephalocele, are major structural birth defects affecting the central nervous system; their prevalence has been shown to vary by race/ethnicity as Hispanic women in the United States (US) at a high risk of having their pregnancies affected by NTDs compared to other race/ethnic groups (13-20). The total prevalence of NTDs during the post-fortification period (1999-2011), was approximately 6.5 per 10,000 live births among Hispanics which was higher compared to non-Hispanic White (~5 per 10,000 live births) and non-Hispanic Black (~4 per 10,000 live births) (11). In 1992, the US Public Health Service recommended that all women of reproductive age consume 400 mcg of folic acid daily in order to prevent pregnancies affected by neural tube defects (38). Following this recommendation in 1998 the US implemented a public health intervention that required the fortification of enriched cereal grain products. Manufactures were required to fortify these products with 140 mcg of folic acid per 100 grams of flour. Since then, there have been consistent declines in major NTDs among non-Hispanic White and Hispanic births (58, 59). Strikingly, the prevalence of major NTDs continues to be higher among Hispanic women compared to non-Hispanic White and non-Hispanic Black women (11, 59).

Researchers have suggested that the failure of nation-wide voluntary folic acid fortification of corn masa flour and tortillas might be holding back public health efforts to reduce NTDs, particularly among infants born to Hispanic mothers (45, 60). Previous studies have found that Hispanic women are 2.15-times more likely to not use pre-conceptional folic acid supplements compared to non-Hispanic white women (42). The low prevalence of pre-conceptional folic acid supplement use, in addition to lack of fortification of corn masa and lower acculturation levels to other fortified US staples (e.g., enriched wheat and/maize) have shown to impact the lower geometric mean red blood cell folate concentrations among Hispanic women(61) placing their offspring at significantly higher risk of NTDs compared to other race/ethnic groups (40, 42, 45, 46).

Pre-pregnancy diabetes mellitus is another well-established risk factor for NTDs (24, 47, 62). Approximately 78% of women with pre-pregnancy diabetes who become pregnant report the pregnancy being unplanned compared to only 48% of non-diabetic women (63). Diabetic women of reproductive age are also more likely to lack access to prenatal care (52), and may have trouble managing their blood sugar before pregnancy (64). Pre-conception care programs for diabetic women focus on glucose monitoring and control, which has shown to be effective in reducing birth defects (65). Nonetheless, birth defects among infants born to mothers with pre-pregnancy diabetes continue to occur. Epidemiologic studies have shown that from 2000 to 2010, there was a 37% increase in overall age-standardized prevalence of pre-pregnancy diabetes mellitus among US women of childbearing age (31). Additionally, the prevalence of undiagnosed diabetes is higher for Hispanic women compared to non-Hispanic white women (33). A recent study has suggested that pre-conceptional folic acid supplement use among diabetic women of reproductive age might attenuate the risk of spina bifida-affected pregnancy associated with maternal diabetes mellitus (66). Furthermore, studies have shown that diabetic women who do not use pre-conceptional folic acid supplements have greater odds of an adverse pregnancy outcomes compared to their counterparts who do (48).

The objective of this study was to use a population-based Pregnancy Risk Assessment Monitoring System (PRAMS) data to examine the association between pre-pregnancy diabetes and preconception folic acid supplement use among pregnant women who delivered a liveborn infant by Hispanic ethnicity. Findings from our study will be useful to designing targeted educational programs on the importance of folic acid for Hispanic populations, and advocate for the mandatory fortification of corn masa with folic acid in the US.

METHODS

We analyzed 2016-2018 data from three state-based PRAMS: Georgia, New York City, and Puerto Rico. PRAMS was implemented in 1987 as a population-based surveillance system of behaviors, attitudes, and experiences before, during, and after pregnancy of mothers who give birth to a live-born infant. Since then, this has been an ongoing research project between the US Centers for Disease Control and Prevention (CDC) and state health departments. Currently, there are 51 participating states and areas including 47 states, the District of Columbia, New York City, Puerto Rico, and the Greater Plains Tribal Chairman's Health Board. Participating sites are responsible for their PRAMS data collection activities following a standard data collection protocol that provides flexibility to tailor projects to their individual needs. As of 2018 PRAMS surveillance cover approximately 83% of all US births. Detailed PRAMS methodology is available elsewhere (67), and may be also accessed at https://www.cdc.gov/prams/methodology.htm (accessed 1/23/2021).

For the current analysis, we included non-Hispanic and Hispanic women of reproductive age (18-45 years) who were residents of the three states who participated in the PRAMS survey between the years 2016 and 2018. Women who did not meet the age criteria, and who did not provide information on pre-conceptional folic acid supplement use, pre-gestational diabetes mellitus or Hispanic ethnicity were excluded from the analysis (Figure 1).

Pre-pregnancy diabetes among participants was assessed using PRAMS core question four: “During the 3 months before you got pregnant with your new baby, did you have any of the following health conditions?” condition a being “Type 1 or Type 2 diabetes (not gestational diabetes or diabetes that starts during pregnancy)”. Participants could respond yes or no to each of the conditions stated in this question.

Pre-conceptional folic acid supplement use among study participants was assessed using the reported answers to PRAMS core question five: “During the month before you got pregnant with your new baby, how many times a week did you take a multivitamin, a prenatal vitamin, or a folic acid vitamin?” The responses to this question included “I didn’t take a multivitamin, prenatal vitamin, or folic acid vitamin in the month before I got pregnant”, “1 to 3 times a week”, “4 to 6 times a week”, and “every day of the week”. Following Mukhtar et al., we recategorized the responses to this question and created a yes or no dichotomous variable for pre-conceptional folic acid supplement use. Under the assumption that women who reported consuming prenatal supplement vitamins 1 to 3 times a week did not meet the recommended daily dose of folic acid, “I didn’t take a multivitamin, prenatal vitamin, or folic acid vitamin in the month before I got pregnant” and “1 to 3 times a week” were combined to create “Pre-conceptional folic acid supplement use - No”. Consequently, “4 to 6 times a week” and “every day of the week” were combined to create “Pre-conceptional folic acid supplement use - Yes”.

Maternal ethnicity was examined in the current analysis as non-Hispanic and Hispanic using birth certificate question: “Mother of Hispanic origin? (Check the box that best describes whether the mother is Spanish/Hispanic/Latina. Check the “No” box if mother is not Spanish/Hispanic/Latina). Participant’s response is categorized as yes, no, not recorded, or unknown in the PRAMS analytic research file.

We considered selected covariates for the analysis *a priori* based on previous literature. Covariates in our analysis included PRAMS site (Georgia, Puerto Rico, New York City), maternal race (White, Black, Other), maternal age (in years) (18-19, 20-29, 30-39, ≥40), maternal education (less than 12th grade, 12th grade, some college, college degree or more), annual household income level twelve months before pregnancy (US$) (≤20,000, 20,001-60,000, ≥60,001), pre-pregnancy health insurance (Private, Medicaid, Other, None), maternal body max index (BMI, kg/m^2) (<18.5, 18.5-24.9, 25.0-29.9, 30.0+), smoking three months before pregnancy (Yes, No), drinking three months before pregnancy (Yes, No), electronic cigarette use three months before pregnancy (Yes, No), pre-pregnancy high blood pressure or hypertension (Yes, No), pre-pregnancy depression (Yes, No), pre-conception folic acid advice from healthcare provider (Yes/No) , Pregnancy intention (Later, Sooner, Then, Did not want then or any time, Was not sure).

Statistical Analysis

We compared demographic, lifestyle, and health-related characteristics among the groups of women with and without preconception folic acid use using descriptive measures of frequencies and percentages. We further compared maternal characteristics among the groups of women with and without preconception folic acid use, stratified by Hispanic ethnicity. Differences between groups were examined using Rao Scott Chi-square test (P-value <0.05). We used multivariable logistic regression to assess the adjusted odds ratios (aORs) and 95% confidence intervals (CIs) and estimate the association between maternal pre-conceptional folic acid supplement use and maternal pre-pregnancy diabetes mellitus stratified by Hispanic ethnicity. Several modeling criteria were applied, including backward selection procedure where covariates that were least significant (P>0.10) were dropped from the model, and using *a priori* variable selection criterion where covariates were selected based on the literature review. Additionally, we ran the full model for Hispanic and Non-Hispanic women stratified by whether they received pre-conception folic acid advice from a health provider as well as the full model for Hispanics stratified by PRAMS state. All analyses were conducted using SAS statistical software version 9.4 to account for PRAMS' complex survey sampling design.

RESULTS

Overall, there were 7991 women in Georgia, Puerto Rico, and New York City who participated in PRAMS from 2016-2018. Among them, 117 (1.5%) were excluded because they did not meet the age eligibility. Another 284 (3.6%) were excluded because they had missing information on pre-conception folic acid supplement use, pre-pregnancy diabetes mellitus, or Hispanic ethnicity. Thus, our analytic sample consisted of 7590 participants from the three PRAMS sites (Figure 1).

Overall, 3.4% of all participants in our analytic sample reported to have pre-pregnancy diabetes mellitus; about one third of all the participants included in this analysis reported consuming the recommended daily use of 400 mcg of folic acid supplement pill 4 to 7 times per week during their preconception period (Table 1). Pre-pregnancy diabetes mellitus was reported in 3% of participants with low folic acid intake (0-3 times per week) and 4.1% of women with recommended folic acid intake (*P*=0.0459; cOR=0.72; 95% CI=0.52, 0.99). Apart from reported pre-pregnancy diabetes mellitus status, participants with and without the recommended intake of folic acid supplement use differed significantly by site, race, Hispanic ethnicity, age, education, household income, pre-pregnancy health insurance, BMI, smoking before pregnancy, drinking before pregnancy, and pregnancy intension (Table 1). The two groups also differed significantly in receiving pre-conception folic acid intake advice from health providers, where participants who took recommended folic acid were more likely to get advice from their health provider compared to participants who did not (62% vs. 28%) ($P<0.001$) (Table 1).

When stratified by Hispanic ethnicity, there was a significant unadjusted association between pre-pregnancy diabetes mellitus and preconception folic acid use among Hispanics (cOR=0.49; 95% CI, 0.27, 0.88) (Table 2), while this association was not significant among non-Hispanics (cOR=0.83; 95% CI, 0.57, 1.21) (Table 2). While the inverse association between pre-pregnancy diabetes and preconception folic acid supplement persisted among Hispanics after controlling for potential confounders applying three different model selection criteria, in the range of 0.75 and 0.84, their 95% CI included null (Table 3). Among non-Hispanics, there was a positive but non-significant association, between pre-pregnancy diabetes and preconception folic acid supplement in our multivariable analysis, with effect estimates in the three model selection process ranging between 1.24 and 1.32 (Table 3).

Separately for Hispanics and non-Hispanics, we further stratified our results by whether or not a woman received preconception folic acid advice from a healthcare provider, we observed a shift in the measure of association among Hispanic women (Table 4). Among Hispanic women who received preconception folic acid advice from the healthcare provider, the adjusted odds ratio showed a higher likelihood of taking preconception folic acid supplements if the woman had pre-pregnancy diabetes (aOR=0.39; 95% CI=0.05, 3.25), while the same was not true for Hispanic women who did not receive preconception folic acid advice the odds were higher (aOR=1.50; 95% CI=0.27, 8.52), although neither estimates of association were statistically significant (Table 4). For non-Hispanic women, the association remained close to null, whether or not women received preconception folic acid advice from their healthcare provider (Table 4).

To evaluate for effect modification by some unmeasured factor that aligns with geographic region and individual subgroups of Hispanics in the three study sites, we examined the association between pre-pregnancy diabetes and preconception folic acid use by PRAMS state/site, for Hispanic women alone (Table 5). Among Hispanics, stratified by PRAMS site, we found no significant association between pre-pregnancy diabetes and preconception folic acid supplement use in Georgia (aOR=0.03; 95% CI = <0.001, 1.20) and New York City (aOR=1.01; 95% CI=0.33, 3.64); however, in Puerto Rico, the odds of not taking preconception folic acid supplement were significantly higher for women with pre-pregnancy diabetes compared with women without pre-pregnancy diabetes (aOR=7.60; 95% CI=1.73, 33.46) (Table 5).

DISCUSSION

Our population-based study using PRAMS data from Georgia, New York City and Puerto Rico showed the association between pre-pregnancy diabetes and preconception folic acid supplement use varied by Hispanic ethnicity, as well as by advice received by healthcare provider for folic acid and by study site. PRAMS allowed us to have relatively accurate measures of our primary exposure, outcome, and potential covariates compared to some other surveys in the US. Our study found that when stratified by receiving preconception folic acid advice from a provider, Hispanic women with pre-pregnancy diabetes who did not receive preconception folic acid advice from a health provider those were less likely to report recommended intake of folic acid supplements compared to those without pre-pregnancy diabetes, although not statistically significant. Site-specific results also highlighted large differences in findings between Georgia, New York City and Puerto Rico, where among Hispanic women in Puerto Rico, the odds of not taking preconception folic acid were higher for women with pre-pregnancy diabetes compared to women without pre-pregnancy diabetes. Our results highlight important issues related to two major preconception health indicators, including diabetes mellitus and folic acid supplement use, among Hispanics.

A study conducted using the Texas Behavioral Risk Factor Surveillance System (BRFSS), similar to our finding, reported no significant difference in the reported daily folic acid supplement use between non-diabetic and diabetic non-pregnant women of reproductive age, and that diabetic women were less likely to be aware that folic acid prevents birth defects and to recall a medical provider ever recommending supplement use (53). Contrary to what we found, data from the National Health and Nutrition Examination Survey (NHANES) found that women of reproductive age in the US with diabetes were less likely to use a supplements containing folic acid although these results were based on small sample sizes and were suggested to be imprecise (68). Neither of the two aforementioned studies examined differences between non-Hispanic women and Hispanic women. Additionally, both BRFSS and NHANES surveys do not focus on women who have had live births thus making it difficult to obtain adequate self-reported data on maternal behaviors and experiences before pregnancy.

We noted in our study that only a small proportion of women of reproductive age who have had live births reported having pre-pregnancy diabetes or being told by a provider that they had diabetes before pregnancy. While this is consistent with published literature, it is also shown in the past that a large proportion of women of reproductive age go undiagnosed with diabetes, and particularly, Hispanic women of reproductive age are highly likely to have undiagnosed diabetes mellitus before pregnancy (32, 33). Thus, our findings should account for this underreporting of the main exposure variable. Future studies should focus on collecting data prospectively to have a more precise estimate of women with diabetes prior to becoming pregnant and their adherence to preconception folic acid supplement use.

Our study adds to the growing body of literature that suggests that adherence to preconception folic acid supplements is low among Hispanic women so other interventions such as the mandatory fortification of corn masa products is needed to more effectively increase folic acid intake among this high-risk group. In 2016, the FDA allowed the voluntary fortification of corn masa flour and tortillas (69). Nonetheless, studies conducted suggest that the voluntary fortification of corn masa has failed to increase the availability of corn masa and tortilla products fortified with folic acid (45, 60). Additionally, a study assessing the RBC folate concentrations of Hispanic women of reproductive age found that these concentrations did not differ pre and post-FDA approval of voluntary corn masa fortification (61). Mandatory folic acid fortification of corn masa flour is needed to improve blood folate concentrations among Hispanic women, and until then, our study findings support improving culturally sensitive pre-pregnancy care and preconception folic acid advice from a provider or community health worker among Hispanic women are needed to improve recommended intake of preconception folic acid supplements, in particular among those with pre-pregnancy diabetes.

Our study has some limitations. Given the cross-sectional nature of PRAMS we are not able to make any causal associations. Data on maternal behaviors and attitudes before, during, and after pregnancy are self-reported and prone to recall or social desirability bias. Reporting of preconception folic acid supplement use, smoking, electronic cigarette use, and alcohol is likely affected by social desirability bias. Additionally, there's potential for nondifferential misclassification of exposure since a large percent of women of reproductive age are not diagnosed with diabetes before pregnancy. It is likely that there are some women who reported not being told by a provider that they had diabetes 12 months prior to their pregnancy who had diabetes but were not diagnosed. This could affect our measure of association towards the null. Another limitation of this study is that PRAMS data includes only women who had live births thus we lack information on maternal characteristics and behaviors for women who had pregnancies that ended in termination or spontaneous abortion, this can result in selection bias since we are not including women who often time fall under the more high-risk group.

Despite the limitations, our study has many strengths. PRAMS is a nationally representative population-based dataset with a large sample size. PRAMS data are weighted to represent the target population and account for sampling, non-response, and noncoverage with omitted records due to delays in processing and other PRAMS survey limitations. This, along with our inclusion of three PRAMS sites, increases the generalizability of our results. PRAMS collection of quality data on a wide range of core and standard topics allows us to have reliable measures of preconception folic acid supplement use and other maternal health behaviors prior to pregnancy that allow us to extensively evaluate potential confounders in our analysis. Additionally, using PRAMS data we minimize recall bias since interviews are conducted within a few months of delivery. Lastly, the standardized methods used for data collection allows us to compare results with other states.

In summary, our study shows that relying on preconception folic acid supplement use to prevent NTDs among Hispanic women with pre-pregnancy diabetes is ineffective due to low adherence of folic acid supplement use in this group. There are variations in the association between pre-pregnancy diabetes mellitus and preconception folic acid use by the three site we examined, which indicate some role of Hispanic sub-populations that we could not further study due to paucity of information on sub-typing of various Hispanic groups. Future studies should improve the assessment of temporal relationship between pre-pregnancy diabetes and preconception folic acid use, which was not possible in the current study which was based on a cross-sectional survey. A combination of efforts to improve preconception screening of women of reproductive age to identify those with diabetes mellitus, and advocate for the mandatory fortification of corn masa along with culturally tailored educational materials on the importance of preconception folic acid supplements through providers or community health works, are needed to improve recommended folic acid intake supplement intake among Hispanic women, and especially focusing on women in Puerto Rico.

Figure 1. Study Sample Selection using Pregnancy Risk Assessment Monitoring System Phase 8 (2016-2018)

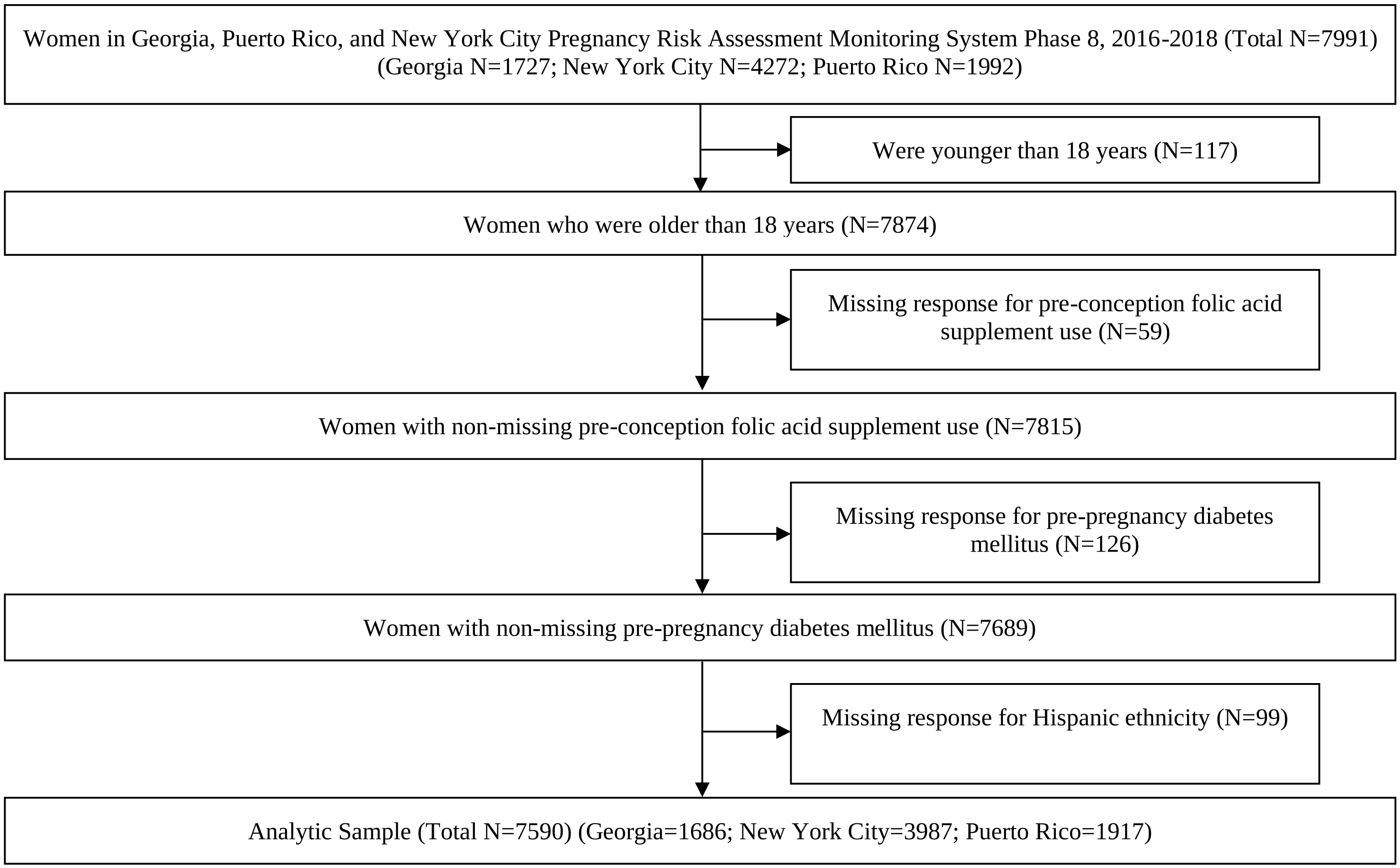

Table 1. Preconception Folic Acid Use and Selected Maternal Characteristics, Georgia, Puerto Rico, and New York City PRAMS, 2016 to 2018

		Preconception folic acid supplement use			
		No	**Yes**		
Maternal Characteristics	**Total (N=7590) n (%)**	**(0-3 times/week) (n=4941) n (%)**	**(4-7 times/week) (n=2649) n (%)**	**Crude OR (95% CI)**	***P*[a]**
Pre-pregnancy diabetes mellitus					0.0459
Yes	385 (3.4)	233 (3.0)	152 (4.1)	0.72 (0.52, 0.99)	
No	7205 (96.6)	4708 (97.0)	2497 (96.0)	Reference	
State/Site					<.0001
Georgia	1686 (41.6)	1116 (43.3)	570 (38.6)	1.32 (1.13, 1.54)	
Puerto Rico	1917(6.3)	1476 (7.6)	441 (3.9)	2.26 (1.93, 2.64)	
New York City	3987 (52.1)	2349 (49.1)	1638 (57.5)	Reference	
Race					<.0001
White	4341 (53.6)	2819 (51.4)	1522 (57.5)	Reference	
Black	1907 (26.6)	1310 (29.0)	597 (22.4)	1.45 (1.21, 1.73)	
Other	1303 (19.8)	783 (19.6)	520 (20.1)	1.09 (0.93, 1.29)	
Hispanic Ethnicity					<.0001
Non-Hispanic	4352 (72.2)	2517 (67.9)	1835 (80.0)	Reference	
Hispanic	3238 (27.8)	2424 (32.1)	814 (20.0)	1.90 (1.65, 2.19)	
Age at birth (years)					<.0001
18-19	249 (3.2)	197 (3.7)	52 (2.2)	2.25 (1.38, 3.66)	
20-29	3465 (46.2)	2544 (51.9)	921 (36.0)	1.92 (1.67, 2.23)	
30-39	3496 (46.0)	2009 (41.0)	1487 (54.8)	Reference	
≥40	380 (4.7)	191 (3.4)	189 (7.0)	0.65 (0.48, 0.88)	
Education					<.0001
Less than 12th grade	978 (14.3)	730 (16.9)	248 (9.7)	2.69 (2.25, 3.24)	
12th grade	1905 (26.3)	1379 (29.5)	526 (20.6)	3.27 (2.63, 4.06)	
Some college	2060 (24.4)	1498 (27.1)	562 (19.8)	2.57 (2.15, 3.09)	
College degree or more	2633 (35.0)	1326 (26.5)	1307 (49.9)	Reference	

Maternal Characteristics	Total (N=7590) n (%)	Preconception folic acid supplement use: No (0-3 times/week) (n=4941) n (%)	Yes (4-7 times/week) (n=2649) n (%)	Crude OR (95% CI)	*P*[a]
Household Income (US$)					<.0001
≤20,000	2679 (33.3)	2018 (38.8)	661 (24.1)	3.55 (2.95, 4.27)	
20,001-60,000	2010 (34.7)	1396 (39.2)	614 (27.2)	3.17 (2.63, 3.83)	
≥60,001	1741 (32.0)	732 (22.0)	1009 (48.7)	Reference	
Pre-pregnancy health insurance					<.0001
Private	3663 (55.1)	2036 (48.1)	1627 (67.6)	Reference	
Medicaid	2555 (26.9)	1875 (29.5)	680 (22.2)	1.87 (1.60, 2.19)	
Other	72 (1.1)	47 (1.2)	25 (0.9)	3.20 (2.53, 4.06)	
None	926 (16.9)	741 (21.2)	185 (9.3)	1.73 (0.99, 3.02)	
BMI (kg/m^2)					<.0001
Underweight (<18.5)	367 (4.2)	236 (4.2)	131 (3.9)	1.38 (0.99, 1.19)	
Normal (18.5-24.9)	3316 (46.6)	1993 (42.7)	1323 (53.6)	Reference	
Overweight (25.0-29.9)	1953 (26.2)	1317 (27.7)	636 (23.6)	1.47 (1.25, 1.74)	
Obese (30.0+)	1901 (23.0)	1361 (25.4)	540 (18.9)	1.68 (1.40, 2.03)	
Smoking (three months before pregnancy)					<.0001
Yes	636 (9.4)	483 (11.3)	153 (6.0)	1.98 (1.50, 2.63)	
No	6838 (90.6)	4385 (88.7)	2453 (94.0)	Reference	
Drinking (three months before pregnancy)					0.0015
Yes	3398 (47.3)	2137 (45.3)	1261 (50.9)	0.80 (0.69, 0.92)	
No	4008 (52.7)	2684 (54.7)	1324 (49.1)	Reference	
Electronic cigarette use (three months before pregnancy)					0.0669
Yes	134 (2.2)	101 (2.5)	33 (1.5)	1.72 (0.96, 3.08)	
No	7304 (97.8)	4752 (97.5)	2552 (98.5)	Reference	
Pre-pregnancy hypertension					0.5680
Yes	656 (5.3)	407 (5.2)	249 (5.6)	0.92 (0.69, 1.23)	
No	6912 (94.7)	4519 (94.8)	2393 (94.4)	Reference	

Maternal Characteristics	Total (N=7590) n (%)	Preconception folic acid supplement use: No (0-3 times/week) (n=4941) n (%)	Yes (4-7 times/week) (n=2649) n (%)	Crude OR (95% CI)	***P***[a]
Pre-pregnancy depression					0.2986
Yes	597 (8.1)	399 (8.4)	198 (7.4)	1.15 (0.89, 1.50)	
No	6967 (91.9)	4529 (91.6)	2438 (92.6)	Reference	
Pre-conception folic acid advice from health provider					<.0001
Yes	1938 (41.0)	721 (25.8)	1262 (61.7)	0.22 (0.18, 0.26)	
No	3098 (59.0)	2348 (74.2)	750 (38.3)	Reference	
Pregnancy intention					
Later	1708 (21.1)	1362 (26.3)	346 (12.1)	2.89 (2.36, 3.54)	
Sooner	1014 (13.4)	468 (8.3)	546 (22.4)	0.49 (0.41, 0.60)	
Then	3221 (45.1)	1838 (40.3)	1383 (53.5)	Reference	
Did not want then or any time	464 (6.5)	374 (7.9)	90 (4.0)	2.59 (1.79, 3.74)	
Was not sure	1006 (13.9)	779 (17.2)	227 (8.0)	2.87 (2.26, 3.63)	

[a]Statistical significance is defined at $p<0.05$ (Rao-Scott Chi Square test). N=number; CI=Confidence Interval; OR= Odds Ratio; BMI=Body Mass Index; kg=Kilograms; m=Meter; PRAMS=Pregnancy Risk Assessment Monitoring System. Other race/ethnicity includes American Indian, Chinese, Japanese, Filipino, Hawaiian, Other Non-White, Alaska Native, Other Asian, and Mixed Race. Private pre-pregnancy health insurance includes insurance paid by job, parent, health care exchange, and state specific TRICARE or military. Other pre-pregnancy health insurance includes insurance paid by state specific SCHIP/CHIP, and state specific other state plan. None pre-pregnancy health insurance includes no insurance, and state specific IHS/Tribal. Frequencies might not equal totals due to missing data. Reported ORs and CIs are weighted.

Table 2. Preconception Folic Acid Use and Selected Maternal Characteristics by Hispanic Ethnicity, Georgia, Puerto Rico, and New York City PRAMS, 2016 to 2018

	Hispanic			**Non-Hispanic**		
	Preconception folic acid supplement use			**Preconception folic acid supplement use**		
	No	**Yes**		**No**	**Yes**	
	(0-3 times/week) (n=2424)	**(4-7 times/week) (n=814)**	**Crude OR**	**(0-3 times/week) (n=2517)**	**(4-7 times/week) (n=1835)**	**Crude OR**
Maternal Characteristics	**n (%)**	**n (%)**	**(95% CI)**	**n (%)**	**n (%)**	**(95% CI)**
Pre-pregnancy diabetes mellitus*						
Yes	75 (2.3)	30 (4.6)	0.49 (0.27, 0.88)	158 (3.4)	122 (4.0)	0.83 (0.57, 1.21)
No	2349 (97.7)	784 (95.4)	Reference	2359 (96.6)	1713 (96.0)	Reference
State/Site*a						
Georgia	205 (24.8)	47 (18.7)	1.58 (1.05, 2.37)	911 (52.1)	523 (43.5)	1.42 (1.19, 1.68)
Puerto Rico	1442 (23.0)	424 (18.9)	1.46 (1.20, 1.78)	34 (0.3)	17 (0.2)	1.45 (0.68, 3.10)
New York City	777 (52.2)	343 (62.4)	Reference	1572 (47.6)	1295 (56.3)	Reference
Race*a						
White	1848 (67.5)	575 (62.9)	Reference	971 (44.0)	947 (56.2)	Reference
Black	201 (6.5)	87 (10.4)	0.58 (0.39, 0.88)	1109 (39.3)	510 (25.4)	1.98 (1.62, 2.42)
Other	348 (26.0)	143 (26.7)	0.90 (0.69, 1.19)	435 (16.7)	377 (18.4)	1.16 (0.94, 1.42)
Age at birth (years)*a						
18-19	140 (4.9)	32 (4.7)	1.32 (0.71, 2.46)	57 (3.1)	20 (1.6)	2.62 (1.29, 5.34)
20-29	1371 (53.3)	361 (42.7)	1.56 (1.22, 1.99)	1173 (51.2)	560 (34.3)	1.99 (1.66, 2.37)
30-39	830 (37.6)	385 (47.0)	Reference	1179 (42.7)	1102 (56.8)	Reference
≥40	83 (4.2)	36 (5.6)	0.92 (0.51, 1.67)	108 (3.0)	153 (7.3)	0.55 (0.39, 0.79)

	Hispanic			Non-Hispanic		
	Preconception folic acid supplement use			Preconception folic acid supplement use		
	No (0-3 times/week) (n=2424)	Yes (4-7 times/week) (n=814)	Crude OR	No (0-3 times/week) (n=2517)	Yes (4-7 times/week) (n=1835)	Crude OR
Maternal Characteristics	**n (%)**	**n (%)**	**(95% CI)**	**n (%)**	**n (%)**	**(95% CI)**
Education[*a]						
Less than 12th grade	436 (27.9)	117 (21.7)	2.22 (1.57, 3.13)	294 (11.7)	131 (6.7)	3.08 (2.28, 4.15)
12th grade	670 (28.5)	184 (24.8)	1.99 (1.43, 2.78)	709 (30.0)	342 (19.5)	2.71 (2.18, 3.36)
Some college	806 (27.4)	211 (25.4)	1.87 (1.36, 2.56)	692 (26.9)	351 (18.4)	2.58 (2.07, 3.22)
College degree or more	507 (16.2)	302 (28.1)	Reference	819 (31.4)	1005 (55.4)	Reference
Household Income (US$) [*a]						
≤20,000	1304 (54.1)	342 (45.7)	2.42 (1.68, 3.49)	714 (32.4)	319 (19.1)	3.45 (2.74, 4.35)
20,001-60,000	566 (35.1)	204 (32.1)	2.25 (1.50, 3.35)	830 (40.8)	410 (26.1)	3.20 (2.58, 3.97)
≥60,001	144 (10.8)	135 (22.2)	Reference	588 (26.8)	874 (54.8)	Reference
Pre-pregnancy health insurance[*a]						
Private	762 (32.6)	366 (44.8)	Reference	1274 (55.3)	1261 (73.0)	Reference
Medicaid	1129 (33.9)	296 (32.1)	1.46 (1.12, 1.89)	746 (27.5)	384 (19.8)	1.84 (1.51, 2.23)
Other	18 (1.4)	7 (1.5)	1.33 (0.51, 3.48)	29 (1.1)	18 (0.9)	1.69 (0.85, 3.37)
None	406 (32.1)	89 (21.6)	2.05 (1.44, 2.91)	335 (16.1)	96 (6.3)	3.35 (2.40, 4.68)
BMI (kg/m^2) [*a]						
Underweight (<18.5)	114 (2.6)	39 (2.3)	1.35 (0.68, 2.70)	122 (5.0)	92 (4.2)	1.47 (1.01, 2.13)
Normal (18.5-24.9)	948 (39.2)	355 (47.6)	Reference	1045 (44.4)	968 (55.1)	Reference
Overweight (25.0-29.9)	706 (32.9)	233 (29.1)	1.37 (1.04, 1.81)	611 (25.2)	403 (22.3)	1.41 (1.15, 1.73)
Obese (30.0+)	641 (25.3)	184 (21.0)	1.48 (1.09, 2.00)	720 (25.4)	356 (18.4)	1.71 (1.36, 2.15)

Maternal Characteristics	Hispanic: Preconception folic acid supplement use: No (0-3 times/week) (n=2424) n (%)	Hispanic: Yes (4-7 times/week) (n=814) n (%)	Hispanic: Crude OR (95% CI)	Non-Hispanic: Preconception folic acid supplement use: No (0-3 times/week) (n=2517) n (%)	Non-Hispanic: Yes (4-7 times/week) (n=1835) n (%)	Non-Hispanic: Crude OR (95% CI)
Smoking (three months before pregnancy) [a]						
Yes	161 (6.1)	41 (4.8)	1.27 (0.75, 2.15)	322 (13.8)	112 (6.3)	2.36 (1.72, 3.26)
No	2235 (93.9)	767 (95.2)	Reference	2150 (86.2)	1686 (93.7)	Reference
Drinking (three months before pregnancy) [a]						
Yes	1009 (43.0)	333 (42.1)	1.04 (0.82, 1.31)	1128 (46.4)	852 (46.8)	0.76 (0.64, 0.90)
No	1373 (57.0)	472 (57.9)	Reference	1311 (53.6)	928 (53.2)	Reference
Electronic cigarette use (three months before pregnancy)						
Yes	34 (1.4)	8 (0.8)	1.82 (0.65, 5.04)	67 (3.1)	25 (1.7)	1.87 (0.98, 3.59)
No	2360 (98.6)	794 (99.2)	Reference	2392 (96.9)	1758 (98.3)	Reference
Pre-pregnancy hypertension*						
Yes	119 (2.9)	59 (5.5)	0.51 (0.30, 0.85)	288 (6.3)	190 (5.6)	1.12 (0.80, 1.56)
No	2300 (97.1)	752 (94.5)	Reference	2219 (93.7)	1641 (94.4)	Reference
Pre-pregnancy depression[a]						
Yes	152 (5.8)	63 (8.8)	0.63 (0.40, 1.02)	247 (9.7)	135 (7.1)	1.41 (1.04, 1.92)
No	2269 (94.2)	747 (91.2)	Reference	2260 (90.3)	1691 (92.9)	Reference
Pre-conception folic acid advice from health provider*[a]						
Yes	369 (32.1)	360 (58.8)	0.33 (0.24, 0.45)	352 (23.1)	902 (62.4)	0.18 (0.15, 0.23)
No	1112 (67.9)	208 (41.2)	Reference	1236 (76.9)	542 (37.6)	Reference

	Hispanic			Non-Hispanic		
	Preconception folic acid supplement use			Preconception folic acid supplement use		
Maternal Characteristics	No (0-3 times/week) (n=2424) n (%)	Yes (4-7 times/week) (n=814) n (%)	Crude OR (95% CI)	No (0-3 times/week) (n=2517) n (%)	Yes (4-7 times/week) (n=1835) n (%)	Crude OR (95% CI)
Pregnancy Intention[*a]						
Later	794 (29.6)	160 (18.3)	2.15 (1.57, 2.94)	568 (24.7)	186 (10.5)	3.16 (2.44, 4.09)
Sooner	181 (7.1)	100 (13.7)	0.69 (0.47, 1.01)	287 (8.9)	446 (24.5)	0.49 (0.39, 0.62)
Then	893 (43.1)	446 (57.2)	Reference	945 (39.0)	937 (52.6)	Reference
Did not want then or any time	185 (6.8)	28 (2.6)	3.46 (1.94, 6.17)	189 (8.3)	62 (4.4)	2.57 (1.67, 3.95)
Was not sure	319 (13.4)	62 (8.2)	2.17 (1.46, 3.23)	460 (19.1)	165 (8.0)	3.24 (2.44, 4.30)

[*]Indicates statistical significance defined at $p<0.05$ (Rao-Scott Chi Square test) among Hispanics.
[a]Indicates statistical significance defined at $p<0.05$ (Rao-Scott Chi Square test) among non-Hispanics.
Frequencies might not equal totals due to missing data. Reported ORs and CIs are weighted.

Table 3. Multivariable Analysis Assessing the Association between Preconception Folic Acid Supplement Use and Pre-Pregnancy Diabetes by Hispanic Ethnicity, Georgia, Puerto Rico, and New York City PRAMS, 2016 to 2018

	Hispanics			**Non-Hispanics**		
Maternal Characteristics	**Model 1 (full model) aOR (95% CI)**	**Model 2 (reduced model) (backward selection) aOR (95% CI)**	**Model 3 (reduced model) (a priori) aOR (95% CI)**	**Model 1 (full model) aOR (95% CI)**	**Model 2 (reduced model) (backward selection) aOR (95% CI)**	**Model 3 (reduced model) (a priori) aOR (95% CI)**
Pre-pregnancy Diabetes						
Yes	0.84 (0.34, 2.13)	0.75 (0.31, 1.81)	0.82 (0.33, 2.05)	1.24 (0.69, 2.23)	1.26 (0.70, 2.26)	1.32 (0.81, 2.16)
No	Reference	Reference	Reference	Reference	Reference	Reference
State/Site						
Georgia	1.20 (0.51, 2.85)	1.23 (0.53, 2.87)	1.20 (0.52, 2.77)	0.89 (0.68, 1.18)	0.89 (0.68, 1.16)	0.86 (0.66, 1.12)
Puerto Rico	2.12 (1.56, 2.88)	2.09 (1.56, 2.80)	1.98 (1.41, 2.78)	1.54 (0.66, 3.62)	1.33 (0.55, 3.19)	1.33 (0.55, 3.19)
New York City	Reference	Reference	Reference	Reference	Reference	Reference
Race						
White	–	–	–	Reference	–	–
Black	–	–	–	1.25 (0.90, 1.75)	–	–
Other	–	–	–	1.37 (0.98, 1.91)	–	–
Age at birth (years)						
18-19	0.42 (0.15, 1.22)	–	0.38 (0.13, 1.13)	1.02 (0.26, 4.02)	0.89 (0.25, 3.14)	0.86 (0.25, 2.97)
20-29	1.31 (0.87, 1.95)	–	1.26 (0.85, 1.87)	1.36 (1.00, 1.83)	1.33 (0.99, 1.80)	1.31 (0.98, 1.76)
30-39	Reference	–	Reference	Reference	Reference	Reference
≥40	1.27 (0.37, 4.41)	–	1.33 (0.39, 4.56)	0.48 (0.28, 0.84)	0.47 (0.27, 0.82)	0.47 (0.27, 0.82)
Education						
Less than 12th grade	2.21 (1.13, 4.30)	2.61 (1.39, 4.87)	2.25 (1.16, 4.38)	1.68 (0.89, 3.17)	1.80 (0.94, 3.44)	2.00 (1.07, 3.73)
12th grade	1.70 (0.98, 2.96)	1.78 (1.08, 2.96)	1.64 (0.93, 2.91)	1.08 (0.68, 1.70)	1.08 (0.70, 1.68)	1.14 (0.74, 1.77)
Some college	1.39 (0.84, 2.31)	1.51 (0.95, 2.41)	1.31 (0.76, 2.24)	1.45 (0.99, 2.11)	1.46 (1.00, 2.13)	1.45 (1.00, 2.09)
College degree or more	Reference	Reference	Reference	Reference	Reference	Reference

Maternal Characteristics	Hispanics: Model 1 (full model) aOR (95% CI)	Hispanics: Model 2 (reduced model) (backward selection) aOR (95% CI)	Hispanics: Model 3 (reduced model) (a priori) aOR (95% CI)	Non-Hispanics: Model 1 (full model) aOR (95% CI)	Non-Hispanics: Model 2 (reduced model) (backward selection) aOR (95% CI)	Non-Hispanics: Model 3 (reduced model) (a priori) aOR (95% CI)
Pre-pregnancy health insurance						
Private	Reference	–	–	Reference	–	–
Medicaid	1.07 (0.71, 1.62)	–	–	1.15 (0.77, 1.71)	–	–
Other	1.46 (0.30, 7.10)	–	–	0.99 (0.33, 3.00)	–	–
None	1.49 (0.68, 3.27)	–	–	1.97 (1.00, 3.88)	–	–
Drinking (three months before pregnancy)						
Yes	–	–	–	1.31 (0.97, 1.76)	–	–
No	–	–	–	Reference	–	–
Electronic cigarette use (three months before pregnancy)						
Yes	–	–	–	1.42 (0.61, 3.28)	–	–
No	–	–	–	Reference	–	–
Pre-pregnancy hypertension						
Yes	1.12 (0.55, 2.30)	–	–	–	–	–
No	Reference	–	–	–	–	–
Pre-pregnancy depression						
Yes	0.75 (0.35, 1.58)	–	–	1.34 (0.78, 2.30)	1.34 (0.78, 2.31)	–
No	Reference	–	–	Reference	Reference	–
Pre-conception folic acid advice from health provider						
Yes	0.32 (0.22, 0.47)	0.32 (0.21, 0.47)	0.31 (0.21, 0.46)	0.21 (0.16, 0.27)	0.21 (0.17, 0.27)	0.21 (0.17, 0.27)
No	Reference	Reference	Reference	Reference	Reference	Reference

Maternal Characteristics	Hispanics Model 1 (full model) aOR (95% CI)	Hispanics Model 2 (reduced model) (backward selection) aOR (95% CI)	Hispanics Model 3 (reduced model) (a priori) aOR (95% CI)	Non-Hispanics Model 1 (full model) aOR (95% CI)	Non-Hispanics Model 2 (reduced model) (backward selection) aOR (95% CI)	Non-Hispanics Model 3 (reduced model) (a priori) aOR (95% CI)
Pregnancy Intention						
Later	1.58 (0.98, 2.54)	1.58 (0.99, 2.52)	1.53 (0.95, 2.46)	2.17 (1.48, 3.18)	2.31 (1.58, 3.37)	2.42 (1.65, 3.53)
Sooner	0.71 (0.43, 1.19)	0.70 (0.43, 1.14)	0.70 (0.42, 1.16)	0.63 (0.47, 0.86)	0.63 (0.46, 0.86)	0.64 (0.47, 0.86)
Then	Reference	Reference	Reference	Reference	Reference	Reference
Did not want then or any time	5.50 (2.00, 15.2)	5.05 (1.88, 13.6)	5.03 (1.87, 13.5)	2.63 (1.26, 5.52)	2.85 (1.38, 5.89)	2.81 (1.39, 5.65)
Was not sure	0.96 (0.55, 1.66)	0.98 (0.56, 1.70)	0.90 (0.52, 1.57)	2.46 (1.58, 3.82)	2.52 (1.63, 3.90)	2.44 (1.59, 3.73)

Reported aOR and CI are weighted. aOR=adjusted Odds Ratio; CI=Confidence Interval

Table 4. Multivariable Analysis Assessing the Association between Preconception Folic Acid Supplement Use and Pre-Pregnancy Diabetes by Hispanic Ethnicity and Pre-Conception Folic Acid Advice from Health Provider Georgia, Puerto Rico, and New York City PRAMS, 2016 to 2018

	Hispanics		**Non-Hispanics**	
	Pre-conception folic acid advice from health provider		**Pre-conception folic acid advice from health provider**	
	Yes	**No**	**Yes**	**No**
	Full Model[1]	**Full Model[1]**	**Full Model[2]**	**Full Model[2]**
Maternal Characteristics	**aOR (95% CI)**	**aOR (95% CI)**	**aOR (95% CI)**	**aOR (95% CI)**
Pre-pregnancy Diabetes				
Yes	0.39 (0.05, 3.25)	1.50 (0.27, 8.52)	1.01 (0.44, 2.32)	1.40 (0.56, 3.52)
No	Reference	Reference	Reference	Reference

Reported aOR and CI are weighted. aOR=adjusted Odds Ratio; CI=Confidence Interval.
[1]Adjusted for state/site, maternal age at birth, maternal education, pre-pregnancy health insurance, pre-pregnancy hypertension, pre-pregnancy depression, and pregnancy intention.
[2]Adjusted for state/site, race, maternal age at birth, maternal education, household income, pre-pregnancy health insurance, drinking three months before pregnancy, electronic cigarette use three months before pregnancy, pre-pregnancy depression, and pregnancy intention.

Table 5. Multivariable Analysis Assessing the Association between Preconception Folic Acid Supplement Use and Pre-Pregnancy Diabetes by PRAMS State/Site for Hispanic Women, 2016 to 2018

	PRAMS State/Site		
	Georgia	**Puerto Rico**	**New York City**
Maternal Characteristics	**Full Model [1]** **aOR (95% CI)**	**Full Model [1]** **aOR (95% CI)**	**Full Model [1]** **aOR (95% CI)**
Pre-pregnancy Diabetes			
Yes	0.03 (<0.001, 1.20)	7.60 (1.73, 33.46)	1.01 (0.33, 3.64)
No	Reference	Reference	Reference

Reported aOR and CI are weighted. aOR=adjusted Odds Ratio; CI=Confidence Interval.
[1]Adjusted for maternal age at birth, maternal education, pre-pregnancy health insurance, pre-pregnancy hypertension, pre-pregnancy depression, preconception folic acid advice from medical provider, and pregnancy intention.

CHAPTER III: SUMMARY, PUBLIC HEALTH IMPLICATIONS, POSSIBLE FUTURE DIRECTIONS

Summary

The risk of NTDs has remained disproportionally high among Hispanic populations in the US compared to non-Hispanic white despite public health efforts to prevent NTDs through the mandatory fortification of grain products (11, 70). Despite the implementation of daily intake of folic acid recommendations among women of reproductive age, Hispanic women in the US are less likely to take preconception folic acid supplements(42, 71, 72). Additionally, data from NHANES showed that post-fortification red blood cell (RBC) folate concentrations were 8.2% lower in Hispanic women compared to non-Hispanic white women (73). Pre-pregnancy diabetes is also a well-established risk factor for NTDs (22-24, 29). In the US, Hispanic women of reproductive age have a greater prevalence of diabetes compared to non-Hispanic women, and a large percentage of them (48%) are undiagnosed (32). Whether preconception folic acid supplement use attenuates the risk of NTDs associated with pre-pregnancy diabetes is unknown. A study has suggested that pre-conceptional use of multivitamins that may contain folic acid among diabetic women reduce the risk of selected birth defects (48). Given the higher prevalence of NTDs among Hispanic women, the link between folic acid and NTDs, the link between pre-pregnancy diabetes and NTDs, and the higher prevalence of undiagnosed diabetes mellitus among Hispanic women of reproductive age it's important to understand the current use of preconception of folic acid supplement use among this high-risk group.

Based on our data from the PRAMS (2016-2018) in Georgia, Puerto Rico, and New York City, we identified the prevalence of preconception folic acid supplement use among Hispanic women of reproductive age who have had live births with pre-pregnancy diabetes to be lower compared to non-Hispanic women with pre-pregnancy diabetes. Although statistically insignificant, we found that among Hispanic women who reported not receiving preconception folic acid advice from a provider those with pre-pregnancy diabetes had higher odds of not taking preconception folic acid supplements compared to those without pre-pregnancy diabetes. Additionally, we found that among Hispanic women in Puerto Rico those with pre-pregnancy diabetes have higher odds of not taking preconception folic acid supplements compared to those without pre-pregnancy diabetes, although the precision of our estimate is limited. To our knowledge, few studies have looked at the association between pre-pregnancy diabetes and preconception folic acid supplement use by Hispanic ethnicity. This is the first study examining this association using PRAMS data among the high-risk population in selected US states, i.e., Hispanic ethnicity.

Public Health Implications

Women in the US have access to three main sources of folic acid: fortified enriched cereal grain products, fortified ready-to-eat cereals, and dietary supplements. Recent research has shown that women whose only source of folic acid were enriched cereal grain products had lower daily total folic acid intake, lower red blood cell folate concentrations, and higher predictive NTDs prevalence compared to women who consumed additional folic acid from diet and supplements (39). These results highlight the importance of folic acid supplement use among women to achieve the recommended daily consumption of folic acid. Although we observed no significant difference in preconception folic acid supplement use between Hispanic women with and without pre-pregnancy diabetes the percent of Hispanic women in our sample that reported preconception folic acid supplement were <50% for both exposure groups. This suggests that more work needs to be done to improve preconception folic acid supplement use among Hispanic women of reproductive age.

The lack of preconception folic acid supplement use along with the lower acculturation levels to fortified US staple foods among Hispanic women has become a barrier in further decreasing the difference in prevalence of NTDs among Hispanic and non-Hispanic white women. Previous researchers have estimated the effects of folic acid fortification of corn masa flour, a food staple with higher intake among Hispanic populations, on the increase in daily folic acid intake and prevention of NTDs among Hispanics. A model developed using data from NHANES, estimated that fortification of corn masa flour would increase total usual daily folic acid intake by approximately 20% among Mexican American women of reproductive age (15-44 years) (74). Additionally, corn masa fortification with folic acid is estimated to prevent approximately 40 infants of Hispanic ethnicity from having spina bifida or anencephaly suggesting an important benefit to the Hispanic population (75).

In 2016, the FDA introduced new regulations allowing the voluntary fortification of corn masa flour and tortillas (69). Nonetheless, studies conducted after the new FDA regulation was implemented suggest that the voluntary fortification of corn masa has failed to increase the availability of corn masa and tortilla products fortified with folic acid. Researchers found that within a sample of grocery stores in Atlanta, national brand products of soft corn tortillas and corn masa flour are either not fortified with folic acid or have very low concentrations of folic acid (60). Furthermore, a social media campaign launched to survey folic acid fortified corn masa and corn tortilla products nationwide found that of the forty-three corn masa flour or corn tortilla products shared from twenty-eight different US states, only three corn masa flour products included folic acid and none of the tortilla products were fortified (45). A study assessing the RBC folate concentrations of Hispanic women of reproductive age found that RBC folate concentrations did not differ pre and post-FDA approval of voluntary corn masa fortification (61). These results along with our observed findings of lower preconception folic acid supplement use among diabetic Hispanic women compared to diabetic non-Hispanic women from three different PRAMS sites suggest that mandatory fortification of corn masa flour and tortilla products in the US is needed in order to increase the total daily folic acid intake among all Hispanic women of reproductive age. Until then, more culturally tailored educational materials on the importance of preconception folic acid supplement use among Hispanic women of reproductive age, particularly those with diabetes, is needed to improve adherence.

The statistical significance of our finding might be limited but previous studies have shown the importance of preconception folic acid advice from a provider on adherence to preconception folic acid recommendations. Suggesting that providers or community health workers serving populations of Hispanic women of reproductive age across the nation should be encouraged to recommend preconception folic acid supplement use among this target population. A previous study evaluating the use of the promotora de salud model to promote the use multivitamin containing folic acid among Spanish-speaking Hispanic women in North Carolina found that among Hispanic women that had a previous pregnancy only 14% of them reported discussing pregnancy with a health provider prior to becoming pregnant (76). Research has shown that discussing pregnancy with a health provider and more importantly receiving appropriate care prior to pregnancy improves preconception behaviors among women. A study evaluating a pre-pregnancy care program for women with diabetes found that diabetic women who participate in pre-pregnancy care that encourages preconception folic acid use are more likely to take preconception folic acid (97%) compared to diabetic women who do not participate in pre-pregnancy care (58%) (77). Our study adds to the growing body of literature that suggests that more work needs to be done to improve folic acid supplement use among Hispanic women of reproductive age in the US. It is clear that improving culturally tailored pre-pregnancy care and preconception folic acid advice from a provider among Hispanic women is needed to improve recommended intake of preconception folic acid supplements. Besides improving preconception care and folic acid advice from providers, efforts such as those of the promotoras the salud, who are often more accessible to communities of Hispanic women in the US, should continue to expand to reach the maximum number of Hispanic women of reproductive age.

Future Directions

Future studies should aim to improve the quality and completeness of data for pre-pregnancy diabetes and pre-conception folic acid supplement use among all women of reproductive age, as well as Hispanic sub-populations. It would be ideal to have data collected prospectively to establish a temporal relation between pre-pregnancy diabetes and folic acid supplement use. Additionally, there is a need to increase the sample size of Hispanic women of reproductive age in the study populations to allow for the exploration of differences in this association across different Hispanic subpopulations in the US.

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