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Maternal exposures in the National Birth Defects Prevention Study: time trends of selected exposures

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Abstract

Background—Our objective was to describe time trends in selected pregnancy exposures in the National Birth Defects Prevention Study (NBDPS).

Methods—We analyzed data from the NBDPS, a multi-site case-control study of major birth defects, for mothers of live-born infants without birth defects (controls), with an expected date of delivery (EDD) from 1998 –2011. Mothers from the 10 participating centers across the United States were interviewed by phone between six weeks and two years after the EDD. We focused on maternal race/ethnicity and five maternal risk factors: obesity, use of folic acid-containing multivitamins, opioid analgesics, selective serotonin reuptake inhibitors (SSRIs), and loratadine because of their prevalence of use and some reports of associations with major birth defects. Prevalence time trends were examined using the Kendall's τ_β test statistic.

Results—The exposure trend analysis included 11,724 control mothers with EDDs from 1998–2011. We observed a significant increase in obesity prevalence among control mothers, as well as use of SSRIs and loratadine. We also observed an increase in periconceptional use of folic acid-containing multivitamins. Some of the time trends varied by race/ethnicity. No remarkable trend in the overall use of opioid analgesics was observed. The racial/ethnic distribution of mothers changed slightly during the study period.

Conclusions—Long-term, population-based case-control studies continue to be an effective way to assess exposure-birth defects associations and provide guidance to health care providers.

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However, investigators examining rare outcomes covering many years of data collection need to be cognizant of time trends in exposures.

INTRODUCTION

The National Birth Defects Prevention Study (NBDPS, 1997–2011) was a multi-site, case-control study of major birth defects that collected data over a period of 14 birth years, which is an important strength of the study since it can be challenging to have an adequate study size for the investigation of birth defects. However, during this period there were some changes in the study protocol, such as revisions in the content of some of the telephone interview questions, as well as changes in the funded study centers resulting from open competitions for cooperative agreements. There were also changes outside of the control of the study, such as shifts in population demographics in a study area (Suro and Singer, 2002), Food and Drug Administration (FDA) warnings on the use of specific drugs during pregnancy, such as paroxetine (Food and Drug Administration, 2005), and recommendations by professional organizations on how to treat diseases in pregnancy, such as the American College of Obstetricians and Gynecologists (ACOG) guidelines on treating urinary tract infections (American College of Obstetricians and Gynecologists, 2011).

Because data are published throughout the course of a long-term study like the NBDPS, results from NBDPS publications could potentially affect the exposure prevalence in subsequent years of data collection. For example, the change in ACOG guidance for treating urinary tract infections during pregnancy cited a 2009 NBDPS publication in which researchers observed a significant association between some birth defects and first trimester use of nitrofurantoin or sulfonamides (Crider et al., 2009; American College of Obstetricians and Gynecologists, 2011). Papers published by other study groups during the study period, including those supporting or refuting NBDPS results, could also potentially impact exposure prevalence.

Because many internal and external factors may affect exposure prevalence, it is important for researchers involved in long-term studies to be aware of these factors and the potential impact on their analyses. In this paper, our objective was to examine time trends and review the published findings for maternal race-ethnicity and five selected risk factors – obesity; and use of folic acid-containing multivitamins, opioid analgesics, selective serotonin reuptake inhibitors (SSRIs), and loratadine.

METHODS

The NBDPS was a case-control study of birth defects that was a collaborative effort of the Centers for Birth Defects Research and Prevention in Arkansas, California, Georgia, Iowa, Massachusetts, New Jersey, New York, North Carolina, Texas, and Utah. Institutional Review Boards at each site approved the study. Methods for recruitment of participants and data collection have been described in detail elsewhere (Yoon et al., 2001; Rasmussen et al., 2003; Reefhuis et al., this issue). Cases included infants or fetuses with major birth defects identified through population-based surveillance systems at each site. Controls, i.e., live-

born infants without major birth defects, were randomly selected using birth certificates or birth hospital records from the same ascertainment area and time period as the cases.

Maternal Race-Ethnicity and Selected Risk Factors

We selected maternal race-ethnicity and five risk factors for an analysis of time trends and a discussion of their reported relationship with major birth defects in the NBDPS. Maternal race/ethnicity was selected and assessed because it is strongly associated with study site and might have been impacted by changes in the study sites and because it might be associated with other exposures of interest (Siega-Riz et al., 2009, Ma et al., 2010, Glidewell et al., 2014). Obesity was selected because it is one of the strongest and most consistent risk factors for many major birth defects, and obesity prevalence in the United States has increased over the time period of the study (Waller et al., 2007, Stothard et al., 2009, Flegal et al., 2012). Folic acid-containing multivitamins were selected for assessment because of the existing Public Health Service recommendation that all women capable of becoming pregnant consume at least 400 micrograms of folic acid daily (Houk et al., 1992). Medications are a strong focus of NBDPS because they provide an opportunity for safer medication use choices just before and during pregnancy, therefore we selected three medications of interest for the trend analysis either due to concerns about risk for major birth defects (opioids), rising use among reproductive aged women and some reports of fetal effects (SSRIs), and some reports of concern coupled with a transition from prescription to over-the-counter status (loratadine) (Centers for Disease Control and Prevention, 2004, Alwan et al., 2007, Gilboa et al., 2009, Broussard et al., 2011).

The study population for the time trend analysis was limited to mothers of control infants with an expected date of delivery (EDD) from January 1, 1998 through December 31, 2011. Mothers of control infants with an EDD between October 1, 1997 and December 31, 1997 were excluded from this analysis due to the small sample size in 1997. Participants from New Jersey included mothers with EDDs from 1998–2002; North Carolina and Utah participants included mothers with EDDs after January 1, 2003. The maternal interviews of case-infants were excluded from this analysis because the association between certain exposures and birth defects outcomes might affect the exposure prevalence and trends.

Mothers participated in a computer-assisted telephone interview (CATI), which included questions regarding pregnancy history, demographics, and exposures that occurred from three months before conception through the end of the pregnancy. Mothers were interviewed in English or Spanish between six weeks and 24 months after their EDD, with a mean of approximately 9.5 months. In 2005, the CATI underwent a major revision to the content and order of the questions; the post-2005 CATI was implemented for births that occurred on or after January 1, 2006. For example, in the post-2005 CATI a new section on stress was added and two questions were added to the section on maternal high blood pressure to better distinguish pregnancy-related and chronic hypertension. Other questions, such as questions on the use and source of water, were substantially reduced and reformatted. Minor changes in wording or interviewer prompts were made throughout the study period. During the entire study period the interview participation rate was approximately 64% for control mothers. Participation rates for control mothers fluctuated over time, ranging from a high of 76% for

2000 EDDs to a low of 59% for 2010 EDDs; participation rates for 2011 EDDs were slightly lower (54%) due to a shorter time for follow-up, as the final interviews were conducted in March 2013.

For this analysis, obesity was defined as a pre-pregnancy body mass index (BMI) of ≥ 30 kg/m^2 (National Heart Lung and Blood Institute, 2000). Mothers reported height and weight and then BMI was later calculated from her responses. In the first several years of data collection, participants were only able to report height in feet and inches; if a mother was only able to report her height in centimeters, this was noted by the interviewer in the comments, and was then extracted and included in the BMI calculation (Razzaghi et al., submitted). Mothers with a calculated BMI of < 10 or > 70 kg/m2 were considered "out of range" and set to missing.

The NBDPS collected data on the frequency, duration, and timing of medication use for the exposure window of three months prior to pregnancy through the end of pregnancy. Mothers were asked about specific medical conditions and their treatment, as well as a specific list of medications, and about the use of fertility treatments. Mothers could also report use of any other medication that she was not explicitly asked about. Several medications were added to the specific list of medications in the post-2005 CATI, for example Claritin® (loratadine) and Celexa® (citalopram). For this analysis, we examined use of opioid-, SSRI-, and loratadine-containing medications at any time in pregnancy, which was defined as any self-reported use from the month prior to conception through the end of the pregnancy. We also examined use of specific opioids (codeine, hydrocodone) and SSRIs (citalopram, fluoxetine, paroxetine, sertraline). The month prior to the pregnancy is included in our exposure window because of the difficulty in determining the exact date of conception and the likely errors in recall of specific dates of exposure, as well as the possibility of longer half-lives of some of the exposures possibly resulting in pregnancy exposures. In this analysis, folic acid-containing multivitamin use was defined as any reported use of prenatal vitamins, supplements containing vitamin B complex, or any supplement with folic acid as a component during the month before pregnancy. This exposure window was chosen based on the Public Health Service recommendations for preconceptional use of folic acid for the prevention of neural tube defects.

The questions regarding maternal race/ethnicity were modified for the post-2005 CATI to be consistent with the National Center for Health Statistics' categorization (Ingram et al., 2003). In the earlier version of the CATI, mothers were asked "what is your race/ethnic group?" and were given the options to choose a single race/ethnicity or "other." In the post-2005 CATI, in addition to asking the mothers their race/ethnic group, they received an interviewer prompt that they were able to select more than one category: American Indian or Alaska Native; Asian; Black or African American; Hispanic or Latina; Native Hawaiian or Other Pacific Islander; and White. For the time trend analysis of maternal race/ethnicity, we categorized this variable as non-Hispanic white, non-Hispanic black, Hispanic, and other/mixed race/ethnicity, with non-Hispanic white mothers as the reference group.

Exposure Trend Analysis

For the selected exposures, we examined the prevalence over time for all control mothers collectively, and stratified by race/ethnicity. Results were reported in two-year intervals, due to the small sample size of exposed mothers for some exposures, and to improve the stability of the estimates. For the time trend analysis, we used the non-parametric test statistic Kendall's τ_β, which evaluates monotonic trends in bivariate relationships (Kendall, 1948). We used exact procedures when cell counts were less than five. Because of the addition of the specific loratadine question in 2006, we also conducted a sub-analysis of the loratadine trend stratified by the CATI version (pre-2006 EDDs as compared to EDDs 2006 and later). All analyses were conducted using SAS version 9.3 (Cary, NC).

To put our results in context, we also reviewed all NBDPS manuscripts that examined one of these six variables, published through December 2014, and created a matrix summarizing the findings for the exposures of interest by categorizing them as all positive (dark red, vertical lines), some positive (light red, vertical lines), some negative (light blue, horizontal lines), all negative (dark blue, horizontal lines), or null (yellow, no lines) associations, or blank if the exposure-birth defects combination had not been published on yet.

RESULTS

There were 11,724 control mothers with EDDs from 1998–2011 who participated in the maternal interview. The mean maternal age at delivery was approximately 27 years. The interview was conducted in Spanish for 8.8% of interviewed mothers (n=1,032). The average time to interview was approximately 9.5 months.

The racial/ethnic distribution changed slightly during the study period, during which we observed a significant monotonic increase in the proportion of Hispanic mothers (20.7% to 21.6%; $p<0.01$) and mothers reporting other/mixed race/ethnicity (4.1% to 13.7%; $p<0.01$), compared to non-Hispanic white mothers (Table 1). No significant monotonic time trend was noted for non-Hispanic black mothers.

Overall, approximately 18% of control mothers self-reported a pre-pregnancy height and weight that classified them as obese (Table 1). We observed a significant increase in the proportion of obese mothers over time, from 14% in 1998–1999 to 22% in 2010–2011 ($p<0.01$). This trend was observed for each of the race/ethnicity categories ($p<0.01$). Among non-Hispanic white mothers, the proportion of obese mothers increased marginally from 14% in 1998–1999 to 19% in 2010–2011 (Figure 1a). The increase was greatest among non-Hispanic black mothers, for whom the obesity prevalence increased from approximately 20% in 1998–1999 to more than 33% by the end of the study period. The proportion of obese mothers increased 12 percentage points for Hispanic mothers and mothers of other/mixed race/ethnicity.

Approximately 32.5% of all control mothers reported use of a folic acid-containing multivitamin during the month preceding conception, with a slight increase observed over time (27.1% in 1998–1999 to 38.9% in 2010–2011; $p<0.01$) (Table 1). Use of folic acid-

containing multivitamins increased approximately 5–17% for mothers of most race/ethnicities. We observed some variability for non-Hispanic black mothers (Figure 1b).

Overall, we did not observe a significant monotonic trend in the use of opioid analgesics during the study period (p=0.93) (Table 1). The only statistically significant monotonic trend in the use of opioids was an increase among mothers of other/mixed race/ethnicity between 1998–1999 and 2010–2011 (p=0.03). However, we observed a spike in the prevalence of opioid use in 2004–2005 for non-Hispanic white mothers and non-Hispanic black mothers (Figure 1c). The increase in use in 2004–2005 was observed for use of hydrocodone-containing medications, some of the most widely used opioids in this cohort, but was not observed for use of codeine-containing medications.

We observed an overall increase in the prevalence of use of SSRIs from 1998 to 2011 (Table 1). This trend appears to be largely driven by the increase in the prevalence of use among non-Hispanic white mothers ($p<0.01$) and mothers of other/mixed race/ethnicity ($p<0.01$); there was no significant monotonic change in the prevalence of use among non-Hispanic black or Hispanic mothers (p=0.84 and p=0.56, respectively) (Figure 1d). The prevalence of use of sertraline increased slightly during the study period (1.0% in 1998–1999 to 2.8% in 2010–2011). For citalopram there also appears to be an increase, albeit not statistically significant. For fluoxetine and paroxetine no clear trend was observed.

The prevalence of use of loratadine among all control mothers appears to have roughly doubled during the study period, from 3.6% in 1998–1999 to 6.3% in 2010–2011 ($p<0.01$) (Table 1). The overall increase in prevalence was observed for all mothers except for Hispanic mothers (Figure 1e). However, in sub-analyses stratifying by the CATI version significant trends were no longer observed.

The six exposures selected for the trend analysis have been studied in association with 58 birth defects categories by NBDPS collaborators to date. The results from the analyses are summarized (Figure 2). For BMI, 19 of the 40 birth defects categories examined were noted to have a significant positive association with pre-pregnancy obesity. Gastroschisis was significantly associated with a low BMI. There were eight birth defects categories (of 33) with significant positive associations with use of opioids and three defect groups (of 24) significantly associated with use of SSRIs. There were 23 significant negative associations (some with overlapping case groups) between birth defects and use of folic acid-containing multivitamins. Results for use of loratadine and maternal race/ethnicity were inconsistent, with both significant positive and negative associations reported.

DISCUSSION

The NBDPS has made a major contribution to our understanding of the risk associated with a broad range of maternal exposures in early pregnancy. Some of these exposures have experienced changes over the course of the study that heighten the significance of their potential role in birth defects etiology. Over the 14 year period of NBDPS interviews, the prevalence of obesity among control mothers increased significantly as did the use of folic acid-containing multivitamins, SSRIs, and loratadine. No remarkable monotonic change in

the reported use of opioid medications was observed. The proportion of Hispanic mothers and mothers of other/mixed race/ethnicity increased during the study period; the proportion of non-Hispanic white mothers decreased during the study period.

The exposure prevalence trends we observed may be partly explained by factors external to the study, such as changing demographic characteristics of the source populations, or internal factors, such as changes to the CATI. The racial/ethnic distribution of NBDPS control mothers was similar to the distribution of pregnant women who participated in the National Health and Nutrition Examination Survey (NHANES) from 2001–2006, which was comprised of 55.9% non-Hispanic white women, 16.9% non-Hispanic black, 17.0% Mexican American, and 10.2% women who reported other race/ethnicity (Mirel et al., 2009). However, comparing the racial/ethnic distribution in the NBDPS with NHANES is somewhat limited by the oversampling of pregnant women in NHANES, which resulted in a slightly higher proportion of Mexican American women and a lower proportion of non-Hispanic white women in the pregnant cohort than was observed in the non-pregnant cohort. Based on birth certificate data, the trends in race and ethnicity distribution we observed in the NBDPS were comparable to national trends during this time period (Martin et al., 2015). In 2011, approximately 76.4% of infants in the United States were born to white mothers as compared to 79.2% in 1997; 23.2% of infants were born to Hispanic mothers in 2011 as compared to 18.3% in 1997. The obesity trend we observed was also similar to national estimates of an increase in the prevalence of pre-pregnancy obesity from 17.6% in 2003 to 20.5% in 2009, using data from the Pregnancy Risk Assessment Monitoring System (Fisher et al., 2013). Similarly, the trend in use of SSRIs that we observed appears to reflect the overall increase in use of antidepressants during pregnancy in the United States and in Europe, which has been partly attributed to the increase in use for conditions other than depression (Cooper et al., 2007; Andrade et al., 2008; Harman et al., 2009). A decrease in use of paroxetine, however, has been noted in the United States following the release of the FDA warnings (Meunier et al., 2013). The observed trend in use of folic acid-containing multivitamins also appears to mirror the overall slight increase in use of folic acid-containing supplements among women of childbearing age in the United States, which has been partly attributed to the increase in national interest in prevention of neural tube defects (Centers for Disease Control and Prevention, 2008). We did not observe a clear pattern in use of opioid analgesics during pregnancy. There does not appear to be a consistent trend in use in other studies, as some studies have reported an increase in the prevalence of opioid use among pregnant women while others have observed a decrease in use (Bateman et al., 2014; Maeda et al., 2014). The interview participation rate among control mothers generally declined during the study period, which could affect the exposure prevalence trends and potentially be a source of bias. In a 2009 study of control mothers (1997–2003 EDDs), researchers found that NBDPS control mothers were generally representative of their base population, but the difference in distributions for certain characteristics, such as maternal race/ethnicity, was associated with participation (Cogswell et al., 2009).

Some observed changes in exposure are possible artifacts of the study protocol. For example, the trend in use of loratadine appears to be at least partially related to the addition of a question in the CATI explicitly asking about use of the medication. Although NBDPS exposure data are limited by maternal self-report and are potentially subject to recall bias,

prior studies have indicated that asking mothers about specific medications may help with maternal recall of medication use during pregnancy (Mitchell et al., 2011). In addition, loratadine moved from prescription to over-the-counter status in 2002, which might have impacted use (Food and Drug Administration, 2002). Investigators who want to assess the relationship between loratadine and birth defects should consider stratifying their analyses by year of EDD.

With changes in the NBDPS Centers over the 14 year period, some changes in catchment areas within the study sites, and the change in the race/ethnicity questions, we anticipated a noticeable change in the racial/ethnic distribution during the study period. Although these are possible explanations for the changes that were observed, overall, there was not a dramatic shift in this distribution. This provided some reassurance that the change in study sites did not have as much of an impact on the maternal race/ethnicity distribution as was anticipated.

NBDPS authors have published several papers examining the relationship birth defects and the exposures selected for this analysis. Several analyses investigating a spectrum of potential risk factors for specific birth defects have included race/ethnicity. In a 2007 study of factors associated with hypospadias, using NBDPS data from 1997–2000, researchers found sons of Hispanic mothers were at less risk of hypospadias than those of non-Hispanic white mothers (Carmichael et al., 2007). In a more recent follow-up to this study (1997–2009 EDDs), researchers observed a decreased risk of second-degree hypospadias among sons of mothers of Hispanic or Asian/Pacific Islander race/ethnicity, but an increased risk of third-degree hypospadias among offspring of mothers of Asian/Pacific Islander or non-Hispanic black race/ethnicity (Groen in ‘t Woud et al., 2014). Infants born to mothers of non-Hispanic black race/ethnicity have also been observed to be at increased risk of biliary atresia (1997–2002 EDDs) but a decreased risk of gastroschisis (1997–2003 EDDs) (The et al., 2007; Bird et al., 2009). No significant association with maternal race/ethnicity was observed in a 2010 spectrum analysis of factors associated with non-syndromic holoprosencephaly (Miller et al., 2010).

Studies examining the relationship between pre-pregnancy BMI and birth defects have mostly focused on the potential role of obesity. In 2007, using NBDPS data from 1997–2002, Waller et al. found a significant association between maternal obesity and spina bifida, heart defects (all phenotypes combined), anorectal atresia, hypospadias, limb reduction defects, diaphragmatic hernia, and omphalocele; the odds ratio for the association between obesity and gastroschisis was below unity (Waller et al., 2007). In a 2008 study (1997–2003 EDDs) focusing on bilateral renal agenesis/hypoplasia, researchers observed a significant association with maternal obesity (Slickers et al., 2008). In a follow-up to the Waller et al. study, using data from 1997–2003, researchers examined the relationship between BMI and gastroschisis combined with the effect of maternal age, finding gastroschisis to be associated with low maternal age and low pre-pregnancy BMI (Siega-Riz et al., 2009). Although not statistically significant, a slightly elevated odds ratio was observed for the association between obesity and craniosynostosis (1997–2005 EDDs) (Boulet et al., 2010). Offspring of overweight and obese mothers have also been observed to be at increased risk of specific heart defects, including tetralogy of Fallot, total anomalous

pulmonary venous return, hypoplastic left heart syndrome, pulmonary valve stenosis, and secundum atrial septal defect, using NBDPS data from 1997–2004 (Gilboa et al., 2010).

In 2009, researchers used NBDPS data from 1998–2003 to examine rates of neural tube defects among pregnancies conceived after folic acid fortification of the food supply (Mosley et al., 2009). The researchers found little evidence of an association between folic acid supplement use and neural tube defects. In a study that examined the joint effects of maternal obesity and folic acid intake in association with microtia (1997–2005 EDDs), researchers found a decreased risk of microtia in non-obese women that reported periconceptional intake of folic acid-containing supplements (Ma et al., 2010). Similarly, in a study on the association of birth defects with folic acid supplementation and diabetes, using data from 1997–2004, researchers concluded that the lack of supplementation may be associated with an excess risk of birth defects in diabetic mothers (Correa et al., 2012).

As of December 1, 2014, investigators have published 42 articles using NBDPS data to examine associations between medication use in pregnancy and birth defects. In one of the earliest publications, there was no evidence of an increased risk of second- or third-degree hypospadias in association with use of loratadine (Centers for Disease Control and Prevention, 2004). In a study using NBDPS data from 1997–2003, researchers observed a significant positive association between loratadine and transverse limb deficiency, as well as a significant negative association with orofacial clefts (Gilboa et al., 2009). In a 2007 study of the association between SSRI use and birth defects, which used NBDPS data from 1997–2002, researchers found significant associations between SSRIs and anencephaly, craniosynostosis, and omphalocele (Alwan et al., 2007). Also in 2011, researchers found use of opioid analgesics to be associated with an increased risk of several heart defects, including atrioventricular septal defects, and hypoplastic left heart syndrome, as well as spina bifida and gastroschisis (Broussard et al., 2011).

NBDPS reports have contributed substantially to the understanding of the birth defects risk of a broad range of exposures. Investigating risk factors and possible protective factors for birth defects remains of public health importance, as birth defects are the leading cause of infant mortality in the United States, and the etiology of most birth defects remains unclear (Nelson and Holmes, 1989; Petrini et al., 2002, Mathews et al., 2013). Long-term, population-based case-control studies continue to be an effective way to assess these associations and provide guidance to healthcare providers and the women they are treating. However, researchers involved in these studies should consider the internal and external factors that influence exposure prevalence over the course of a long-term study and consider updating early analyses after additional data are collected.

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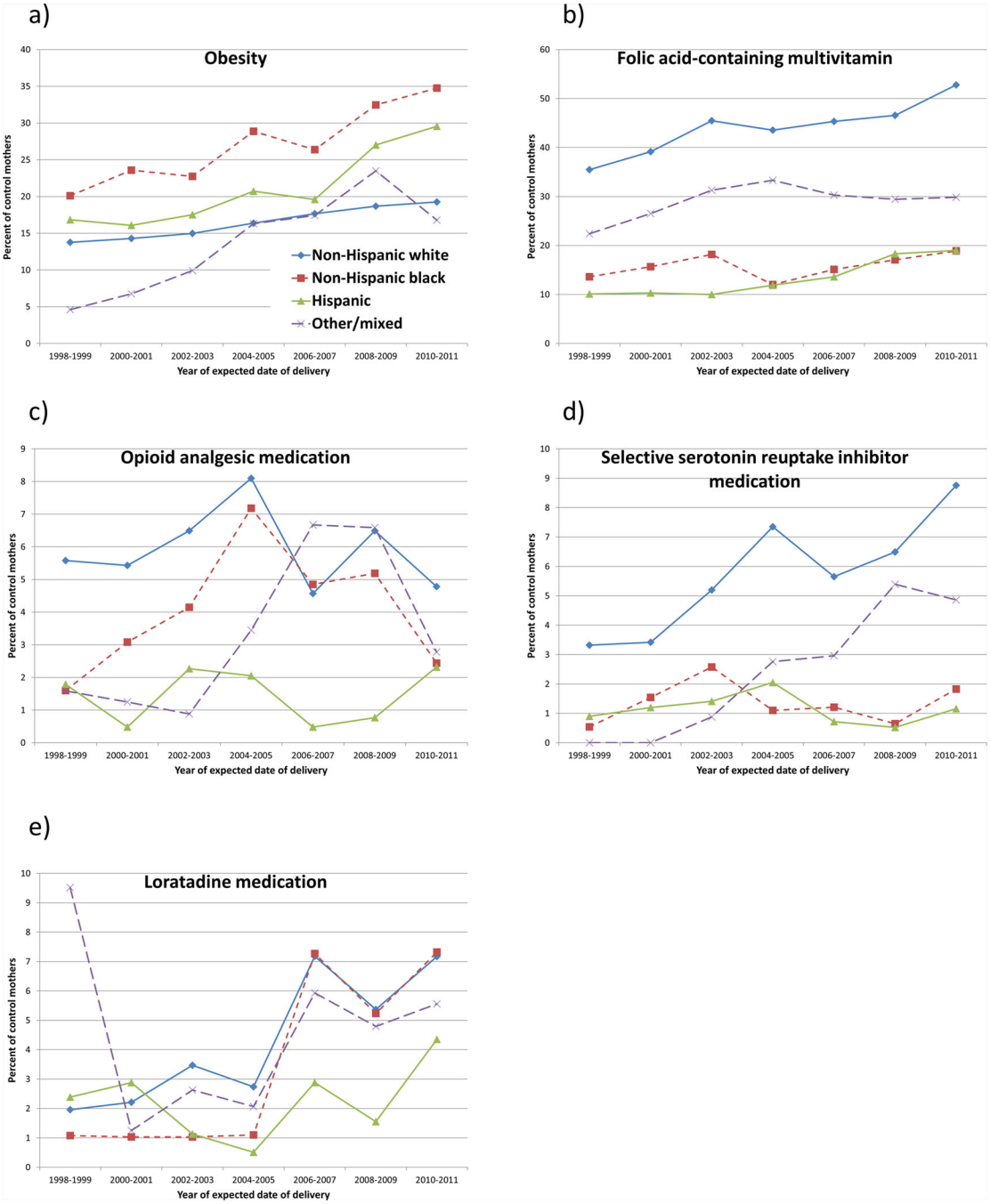

Figure 1.

Trends in selected maternal pregnancy exposures, stratified by race/ethnicity among control mothers in the National Birth Defects Prevention Study, 1998–2011. a) obesity; b) use of folic acid-containing multivitamins during the month prior to pregnancy; c) use of opioid analgesic medication during the month prior to pregnancy through the end of pregnancy; d) use of selective serotonin reuptake inhibitor medications during the month prior to pregnancy through the end of pregnancy; e) use of loratadine during the month prior to pregnancy through the end of pregnancy

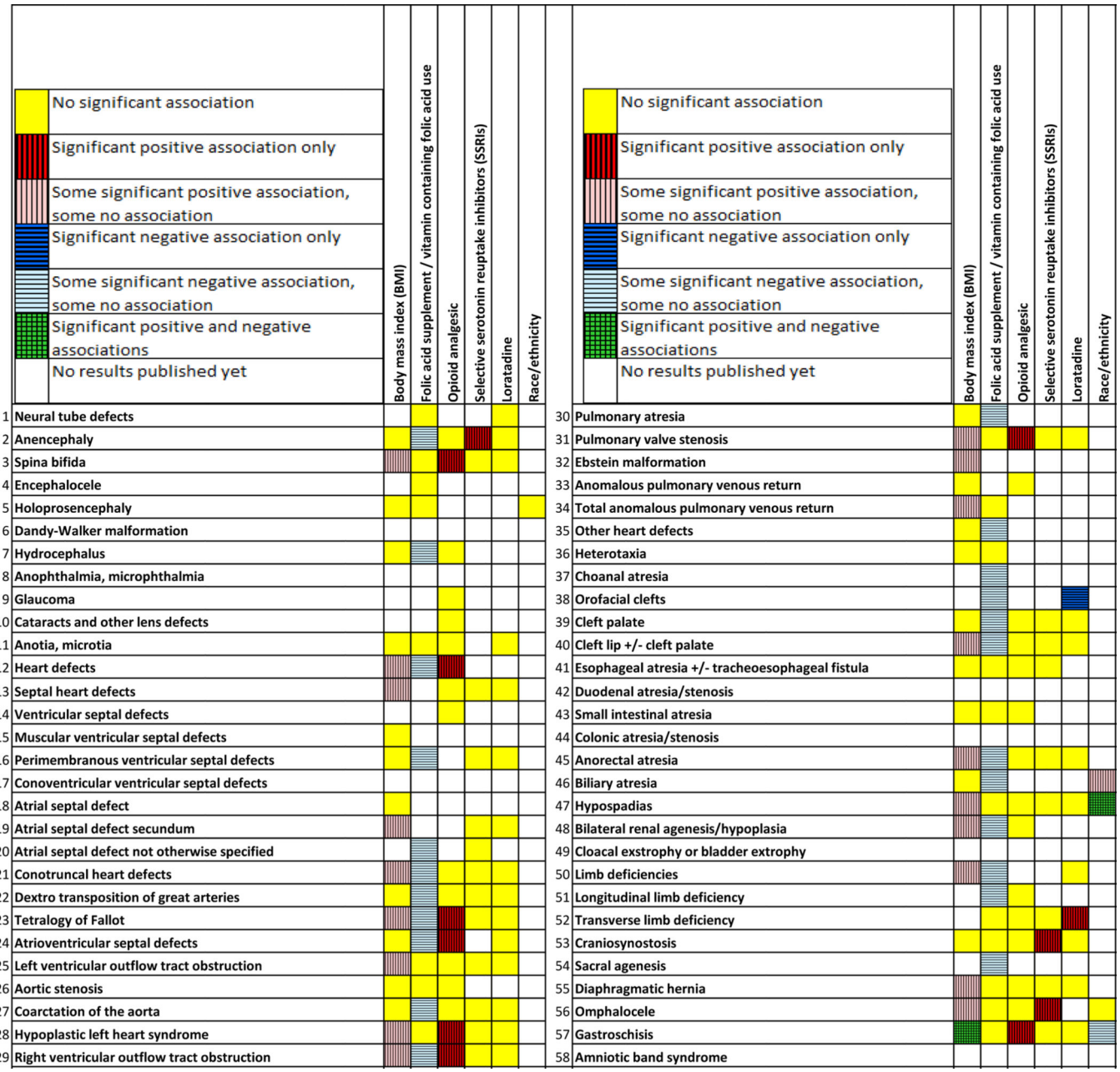

Figure 2.

Graphical summary of published results from the National Birth Defects Prevention Study, published 2004 – December, 2014, for associations between a spectrum of birth defects and selected maternal demographic characteristics and pregnancy exposures, including maternal pre-pregnancy body mass index (Waller et al., 2007; Slickers et al., 2008; Siega-Riz et al., 2009; Boulet et al., 2010; Gilboa et al., 2010), use of folic acid-containing multivitamins (Mosley et al., 2009; Ma et al., 2010; Correa et al., 2012), opioid analgesics (Broussard et al., 2011), selective serotonin reuptake inhibitors (Alwan et al., 2007), loratadine (Centers for Disease Control and Prevention, 2004; Gilboa et al., 2009), and race/ethnicity

(Carmichael et al., 2007; The et al., 2007; Bird et al., 2009; Miller et al., 2010; Groen in 't Woud et al., 2014).

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Table 1

Prevalence and time trends of selected maternal periconceptional exposures and demographic characteristics among control mothers in the National Birth Defects Prevention Study, 1998–2011

		Year of expected date of delivery							
Maternal Characteristic	**Overall**	**1998–1999**	**2000–2001**	**2002–2003**	**2004–2005**	**2006–2007**	**2008–2009**	**2010–2011**	**p-value for trend[a]**
Number of control mothers	11,724	1,630	1,699	1,605	1,782	1,720	1,605	1,612	
Obesity[b]									<0.01
Yes	2,063 (17.6)	231 (14.2)	252 (14.8)	246 (11.9)	315 (17.7)	309 (18.0)	353 (21.1)	357 (22.2)	
No	9,112 (77.7)	1,340 (82.2)	1,373 (80.8)	1,282 (79.9)	1,382 (77.6)	1,320 (76.7)	1,237 (73.8)	1,178 (73.1)	
Missing	549 (4.7)	59 (3.6)	74 (4.4)	77 (4.8)	85 (4.8)	91 (5.3)	86 (5.1)	77 (4.8)	
Use of folic acid-containing multivitamin[c]									<0.01
Yes	3,804 (32.5)	442 (27.1)	487 (28.7)	532 (33.2)	572 (32.1)	562 (32.7)	582 (34.7)	627 (38.9)	
No	7,715 (65.8)	1,167 (71.6)	1,202 (70.8)	1,053 (65.6)	1,171 (65.7)	1,112 (64.7)	1,064 (63.5)	946 (58.7)	
Missing	205 (1.8)	21 (1.3)	10 (0.6)	20 (1.3)	39 (2.2)	46 (2.7)	30 (1.8)	39 (2.4)	
Use of opioid analgesic[d]									0.93
Yes	515 (4.4)	66 (4.1)	63 (3.7)	77 (4.8)	107 (6.0)	62 (3.6)	81 (4.8)	59 (3.7)	
No	10,997 (93.8)	1,542 (94.6)	1,624 (95.6)	1,508 (94.0)	1,636 (91.8)	1,610 (93.6)	1,566 (93.4)	1,511 (93.7)	
Missing	212 (1.8)	22 (1.4)	12 (0.7)	20 (1.2)	39 (2.2)	48 (2.8)	29 (1.7)	42 (2.6)	
Use of selective serotonin reuptake inhibitor[d]									<0.01
Yes	456 (3.9)	38 (2.3)	42 (2.5)	59 (3.7)	89 (5.0)	64 (3.7)	70 (4.2)	94 (5.8)	
No	11,056 (94.3)	1,570 (96.3)	1,645 (96.8)	1,527 (95.1)	1,650 (92.6)	1,611 (93.7)	1,576 (94.0)	1,477 (91.6)	
Missing	212 (1.8)	22 (1.4)	12 (0.7)	19 (1.2)	43 (2.4)	45 (2.6)	30 (1.8)	41 (2.5)	
Use of loratadine[d]									<0.01
Yes	420 (3.6)	36 (2.2)	37 (2.2)	41 (2.6)	35 (2.0)	98 (5.7)	72 (4.3)	101 (6.3)	
No	11,085 (94.6)	1,570 (96.3)	1,651 (97.2)	1,543 (96.1)	1,705 (95.7)	1,572 (91.4)	1,574 (93.9)	1,470 (91.2)	
Missing	219 (1.9)	24 (1.5)	11 (0.7)	21 (1.3)	42 (2.4)	50 (2.9)	30 (1.8)	41 (2.5)	
Maternal race/ethnicity									
Non-Hispanic white	6,739 (57.5)	1,034 (63.4)	999 (58.8)	932 (58.1)	1,038 (58.3)	953 (55.4)	904 (53.9)	879 (54.5)	Reference
Non-Hispanic black	1,278 (10.9)	191 (11.7)	198 (11.7)	198 (12.3)	191 (10.7)	172 (10.0)	164 (9.8)	164 (10.2)	0.48

		Year of expected date of delivery							
Maternal Characteristic	**Overall**	**1998–1999**	**2000–2001**	**2002–2003**	**2004–2005**	**2006–2007**	**2008–2009**	**2010–2011**	**p-value for trend[a]**
Hispanic	2,742 (23.4)	338 (20.7)	419 (24.7)	360 (22.4)	405 (22.7)	450 (26.2)	422 (25.2)	348 (21.6)	<0.01
Other/mixed	955 (8.2)	67 (4.1)	83 (4.9)	115 (7.2)	147 (8.3)	142 (8.3)	180 (10.7)	221 (13.7)	<0.01
Missing	10 (0.1)	0 (0)	0 (0)	0 (0)	1 (0.1)	3 (0.2)	6 (0.4)	0 (0.0)	

Results presented as number of mothers (percentage of mothers out of the total number of mothers)

[a] Kendall's $\tau\beta$ test was used to assess the trend of proportions over time, for race each of the other race/ethnicities was compared to non-Hispanic white

[b] Obesity defined as body mass index of >=30 kg/m^2; reference=body mass index <30 kg/m^2

[c] Exposure defined as any use the month prior to pregnancy

[d] Exposure defined as any use between the month prior to pregnancy through the end of pregnancy