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The Impact of Cigarette Quitting during Pregnancy on Other Prenatal Health Behaviors

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Abstract

Several economic studies have evaluated the effects of cigarette smoking and quitting on other health behaviors such as alcohol use and weight gain. However, there is little research that evaluates the effects of cigarette quitting during pregnancy on other health behaviors such as caloric intake, alcohol consumption, multivitamin use, and caffeine intake. In this paper, we evaluate these effects and employ a genetic variant that predicts cigarette quitting to aid in identification. We find some evidence that cigarette quitting during pregnancy may increase multivitamin use and caloric intake and reduce caffeine consumption.

Keywords

Cigarette quitting; smoking; pregnancy; maternal health; caloric intake; alcohol; prenatal behaviors; caffeine; multivitamins; genetic instruments; Mendelian randomization

1. Introduction

Maternal smoking during pregnancy has received a wide research attention for its implications for maternal and child health. Many studies have reported adverse effects of prenatal smoking on infant health outcomes such as birth weight (Kramer 1987; Evans and Ringel 1999; Lien 2005; Wehby et al. 2012) and neurodevelopment (Faden and Graubard 2000; Herrmann et al. 2008; Indredavik et al. 2007; Wehby et al. 2011a). Previous studies have also reported increases in birth weight with cigarette quitting during pregnancy (Permutt and Hebel 1989; Secker-Walker et al. 1998).

Advising pregnant mothers who are smokers to quit smoking is a standard prenatal care practice. However, not much is known about the effects of cigarette quitting during pregnancy on other health behaviors that are thought to be relevant for maternal and child health. Overall, there is little research that directly assesses the effects of cigarette quitting during pregnancy on other important prenatal health behaviors such as caloric intake,

multivitamin use, alcohol consumption and caffeine intake. Maternal caloric intake and weight gain affect maternal and infant health as well as childhood obesity (Crozier et al. 2010; Rooney et al. 2010; Torloni et al. 2009; Bhattacharya et al. 2007). Alcohol consumption may reduce intrauterine growth (Lien 2005; Okah et al. 2005), increase risk of stillbirth (Reddy et al. 2010), and cause fetal alcohol syndrome, which may have detrimental effects on child behavior and neurological development (CDC 2011). Multivitamin use may also improve birth weight, reduce preterm birth, and prevent certain birth defects (Wehby et al. 2009; Scholl et al. 1997). Caffeine consumption, especially high consumption, has been shown to increase the risk of fetal growth restriction (CARE 2008). Therefore, evaluating the effects of cigarette quitting on such prenatal behaviors is important for gaining further knowledge about the returns to maternal and child health from prenatal cigarette quitting.

Cigarette quitting during pregnancy may influence other prenatal behaviors as it may modify maternal preferences through either biologic or psychosocial pathways. The biologic effects may result from the effects of cigarette quitting on metabolism, appetite, and exercising capacity which in turn can affect caloric intake. Successful cigarette quitting may also encourage further maternal effort to quit other risk behaviors and adopt healthy behaviors by increasing self-motivation, empowerment, and knowledge for behavioral change. For example, individuals who successfully quit smoking may gain further motivation and learn skills that allow them to adopt healthier behaviors in order to improve their and their children's health. However, the psychosocial pathways linking behavioral changes are complex and may vary between individuals. For example, while some individuals may feel encouraged to reduce their drinking behavior after quitting cigarettes, others may compensate for a potential utility loss after reducing smoking by drinking more. Therefore, an empirical evaluation is needed to identify the average effects of quitting on other prenatal behaviors.

We study the effects of cigarette quitting during the first trimester of pregnancy among women who smoked before pregnancy on their caloric intake, alcohol consumption, multivitamin use, and caffeine intake also during the first trimester of pregnancy. We account for the endogeneity of quitting using a bivariate probit model and a genetic variant that influences quitting but is otherwise thought to be unrelated to the other prenatal behaviors of interest. We find that cigarette quitting during pregnancy may increase caloric intake and multivitamin use and decrease caffeine consumption, suggesting important behavioral changes with quitting.

2. Empirical Model

Empirically, identifying the causal effects of maternal cigarette quitting on other health behaviors during pregnancy is complicated by unobserved factors that are relevant to quitting as well as the other health behaviors of interest. These unobservables such as preferences for health, risk taking, and child health endowments influence the demand for both quitting and the other health behaviors. As we show below, women who quit cigarette smoking during pregnancy are very different on several observable characteristics from those who do not, suggesting differences between these two groups on unobservable characteristics. Another potential source of endogeneity is the reverse effect of the other health behaviors on cigarette quitting, such as the potential effect of body weight (and by extension dietary patterns) on smoking behaviors (Cawley et al. 2004; Rees and Sabia 2010). In other words, just as cigarette quitting may influence other behaviors, the choice to continue smoking or quit during pregnancy may in turn be affected by other behaviors.

Our approach for identifying the effects of cigarette quitting on other prenatal behaviors employs a simultaneous equation model with two equations, one for quitting and another for

other behaviors, one at a time. In the first equation, we model quitting as a function of maternal demographic and socioeconomic factors ($\mathbf{X}$) that may relate to maternal preferences over health behaviors including quitting and the extent of information about behavior effects on health in addition to a genetic variant (G) that influences quitting but is assumed to have no direct effects on the other health behaviors of interest and to only relate to these other behaviors indirectly through its effect on cigarette quitting:

$$Q_i = \alpha_0 + \beta G_i + \mathbf{X}_i \boldsymbol{\kappa} + u_i, \quad (1)$$

where for each individual i , β is the effect of the genetic variant on cigarette quitting, $\mathbf{K}$ is a vector of the effects of the control variables ($\mathbf{X}$) on quitting, α_0 is the intercept, and u is the error term.

The second equation is for a set of prenatal behaviors (B) that are modeled (one at a time) as a probit function of cigarette quitting (Q) and the same maternal demographic and socioeconomic factors ($\mathbf{X}$) as in equation (1):

$$B_i = \alpha_1 + \gamma Q_i + \mathbf{X}_i \boldsymbol{\delta} + v_i, \quad (2)$$

where γ represents the cigarette quitting effect on the prenatal behavior, $\boldsymbol{\delta}$ represents the effects of control variables, α_1 is the intercept, and e is the error term. Estimating equation (2) alone results in a biased estimate of γ if the error terms u and v of equations (1) and (2) are correlated.

We estimate this simultaneous equation model using conditional maximum likelihood bivariate probit (Wooldridge 2002).¹ Testing the significance of the correlation between the error terms of the two equations provides a test of the exogeneity of cigarette quitting. The bivariate probit model utilizes both nonlinearity restrictions by assuming bivariate normal distributions as well as the exclusion restriction of the genetic variant for identification. To gauge the extent to which the distributional assumptions versus the exclusion restriction contribute to identification, we re-estimate the bivariate probit model excluding the genetic variant from equation (2) and compare to the main model including this variant. As a reference, we also estimate equation (1) using standard probit assuming exogenous cigarette quitting.

The genetic variant we employ is SNP rs10985765 in the gamma-aminobutyric acid type B receptor subunit 2 (*GABBR2*) gene on chromosome 9. We find that this variant is correlated with quitting but not with relevant socioeconomic and behavioral background characteristics that are correlated with cigarette quitting. The specific genetic variable we employ is an indicator for the minor allele of this SNP, which is associated with a reduction in the probability of quitting in this sample. We do this since both the homozygote and heterozygote minor allele forms have negative effects on cigarette quitting and because of the low frequency of the minor allele homozygote genotype (2.5%).

¹The bivariate normal density function for the error terms can be denoted as follows:

$$\varphi_2(u, v, \rho) = \frac{\exp(-(1/2)(u^2 + v^2 - 2\rho uv)/(1 - \rho^2))}{2\pi \sqrt{(1 - \rho^2)}},$$

where ρ is their covariance (Greene, 2002).

Two previous studies have found variants in *GABBR2* to be significantly related to smoking behaviors (Beuten 2005; Li et al. 2009).² *GABBR2* codes for a protein that is part of one of the GABA-B receptors which are involved in neurotransmitter release. Further support for a role of *GABBR2* in smoking comes from observing that nicotine exposure in rats changes messenger RNA and protein levels of *GABBR2* in the brain (Sun et al., 2007). *GABBR2* is considered a candidate gene for smoking behaviors (The NICSNP Nicotine Project, 2007). The empirical evidence from previous studies finding association of *GABBR2* with smoking, the information about the gene function, and association that we find in our study with cigarette quitting as described below supports the involvement of this gene in smoking.³

The use of molecular genetic information is becoming increasingly of interest in social science applications aimed at identifying health or behavioral effects (Norton and Han 2008; Ding et al. 2009; Fletcher and Lehrer 2009; von Hinke Kessler Scholder et al. 2011; Wehby et al. 2011b; Wehby et al. 2011c; Wehby et al. 2012). The premise is that children inherit their genetic variants randomly from their parents.⁴ This does not mean that everyone has the same chance of inheriting a certain variant, but it means that within each family, parents that have heterozygote form of a certain genetic variant have a 50/50 percent chance of passing either of the two alleles to their child. Therefore, it is expected that variables that are not causally related to a certain genetic variant (either directly or indirectly) should not be correlated with that variant, which is empirically supported (Smith et al. 2007; Wehby and von Hinke Kessler Scholder 2012). However, the theoretical advantage of genetic variants for satisfying exclusion restrictions does not come without challenges. A main challenge is that some genes may have multiple effects on several behaviors, which may violate the exclusion restrictions. Given that not all the functions a gene can have (including *GABBR2*) may be currently known, there is some chance that the exclusion restriction might not be valid due to the gene influencing other unobservable relevant variables. Therefore, it is important to recognize and evaluate this threat for the genetic variants of interest.⁵

²Li et al. (2009) employed the same data source as Beuten et al. (2005) but included a larger sample. Smoking involves a complex etiology of several genetic and socioeconomic contributors (Tyndale 2003; Li 2006), with at least 50% genetic heritability (Carmelli et al. 1992; Heath and Martin 1993; Lessov et al. 2004; Maes et al. 2004). Several neurotransmitter and detoxification genes have been identified over the past few years to be implicated in smoking. Some of the main candidate genes for smoking behaviors are *CHRNA3*, *CHRNA5*, *DRD2*, *DBH*, *CCK*, *TPH*, *GABBR2*, *CYP2A6*, *GABBR2*, *GABRA4*, *GABRA2* and *GABRE*, *MAOA* and *ACTN1* (Comings DE 1996; Noble EP 1994; Spitz et al. 1998; McKinney et al. 2000; Ma et al. 2005; Yu et al. 2006; Comings et al. 2001; Lerman et al. 2001; Sullivan 2001; Agrawal et al. 2009; Beuten 2005; Kramer et al. 2005; Thorgeirsson et al. 2008; Pianezza et al. 1998; Sellers et al. 2000; Agrawal et al. 2008; Berrettini et al. 2008; Caporaso et al. 2009; J. Z. Liu et al. 2010; Berrettini et al. 2008; Caporaso et al. 2009; The Tobacco and Genetics Consortium 2010).

³One candidate-gene study did not find *GABBR2* to be significantly related to nicotine dependence (Agrawal et al. 2008). The inability to replicate genetic effects for genetically complex phenotypes is common and can be due to several factors including genetic/allelic heterogeneity and gene-gene interactions which may vary between samples, differences in phenotypic measures, and statistical designs (Wehby et al. 2012). The candidate-gene study that found no significant association of *GABBR2* with smoking used a different sample, design and nicotine dependence measure from the two studies that found a significant association.³ Similarly, recent genome-wide association studies (GWAS) did not report *GABBR2* to be significantly related to smoking (Liu et al. 2010; Berrettini et al. 2008; Caporaso et al. 2009; The Tobacco and Genetics Consortium 2010). However, the demographics and health characteristics of the samples included in these studies vary from our sample. For example, these studies include significantly older individuals on average than our study; mean age in the samples of the Tobacco and Genetics Consortium (2010) study ranges from 39.6 to 72.3 years. Genetic effects may be modified by environmental, demographic, and human capital characteristics. Pregnant women face additional incentives to quit smoking in order to avoid adverse health risks to their infants compared to the general population. This may modify the influence of certain genetic factors on smoking during pregnancy compared to a more ordinary time. Therefore, it is possible that these differences in sample characteristics may partially contribute to why GWAS have not identified *GABBR2* to be significantly related to smoking behaviors. Also, GWAS impose very low thresholds for statistical significance due to correcting for testing of a very large number of SNPs (typically more than 500,000) which may result in missing some real genetic effects that may not reach the p-value cutoff.

⁴This prompted referring to the use of genetic variants as instruments as “Mendelian Randomization” in the epidemiological literature, which is a standard instrumental variables approach but with genetic variants as the exclusion restrictions (Wehby et al. 2008).

⁵Another limitation related to population stratification by ancestry (Lawlor et al. 2008) is not relevant to this study which employs a racially homogenous sample as described below.

There is no consistent evidence from the literature that *GABBR2* or the particular SNP that we use is related to any of the other prenatal behaviors other than through smoking, which supports the exclusion restriction. A few studies have reported differences in the protein-levels of GABA(B) receptor 2 units in the brain between patients with autism and other mental health disorders such as schizophrenia, depression and bipolar disorder and unaffected individuals (Fatemi et al, 2009, 2011). However, these studies include very small samples and their results do not necessarily suggest that *GABBR2* affects these disorders. Also, given that our sample only includes pregnant women, it is highly unlikely that this gene or the specific SNP we employ affects the behaviors that we evaluate through such disorders. Nonetheless, it is theoretically possible that the gene may relate to the study behaviors through unobserved pathways. To evaluate this possibility, we test the correlations between the genetic variant and observable background characteristics several of which are significantly related to quitting. We find that this variant is not related to any of these characteristics as described below. These results and the current knowledge of the gene's effects provide some assurance against this bias.

An alternative approach to the bivariate probit model is to employ an instrumental variables (IV) model such as two-stage least squares (2SLS). Unlike the bivariate probit model, 2SLS only uses variation in quitting that is predicted by the genetic variant and cannot be identified without the instrument based on distributional assumptions. One drawback of 2SLS is that it is less efficient than the bivariate probit model and may be seriously biased with binary endogenous variables and outcomes (Terza et al, 2008). On the other hand, the identification in the bivariate probit model would also be biased if the distributional assumptions are not valid. Therefore, for comparison purposes, we provide IV estimates using both the simple Wald IV estimator (without adjusting for any covariates $\mathbf{X}$) as well as the adjusted 2SLS estimator.

3. Data

Our data come from a population-based study of infants born in 1996–2001 in Norway that included infants with oral clefts and unaffected infants (Lie et al. 2008; NIEHS. 2009). The study enrolled the majority of the Norwegian infants born with oral clefts during this period (about 88%) and a random sample of live born infants in the same period, who were included as controls. Mothers completed questionnaires about their prenatal behaviors, health, and socioeconomic and demographic characteristics 3–4 months after delivery and provided DNA samples.⁶

Since we focus on studying the effects of cigarette quitting during pregnancy, we limit the sample to the women who smoked within 12 months before pregnancy and have data on the genetic variant and model variables. The study sample ranges between 470 and 499 women depending on the behavioral outcome. Performing a power calculation for the bivariate probit model is challenging, and we are not aware of any direct way to calculate the power in this model. Calculating the statistical power for models with exclusion restrictions and IV models depends on several parameters, some of which can only be partially evaluated.⁷ Published power simulations indicate that the small sample size in our study provides low power.⁸ Therefore, we view this as a preliminary study that highlights the need for future

⁶A description of the study and the study questionnaires can be found at the following links: <http://www.niehs.nih.gov/research/atniehs/labs/epi/studies/ncl/index.cfm> and <http://www.niehs.nih.gov/research/atniehs/labs/epi/studies/ncl/question.cfm>.

⁷These include the strength of association between the exclusion restriction (i.e. genetic variant) and the endogenous variable (i.e. cigarette quitting), the validity of the exclusion restriction (i.e. the genetic variant is unrelated to the other behaviors except through its effects on cigarette quitting and is not related to unobservable confounders), the size of the effect of the endogenous variable on the outcome, and other parameters (Small and Rosenbaum, 2008). The validity of the exclusion restriction can only be partially evaluated, which complicates the power calculation.

replication studies with larger samples, and our results should be interpreted with this caveat. However, to our knowledge, this is one of the few datasets with readily available information on both behavioral and genetic variables to evaluate the study question.

We study the effects of cigarette quitting during the first trimester of pregnancy on caloric intake, alcohol drinking, multivitamin use, and caffeine consumption also during the first semester. These behaviors are not measured beyond the first trimester in the dataset we employ. However, the first trimester is a highly relevant and sensitive period for fetal development since all major organs are developing during this period and changes in fetal environment and maternal behaviors can have major effects on fetal growth and development. Fetal exposures to risk factors during this period can result in extreme developmental abnormalities such as congenital defects. Therefore, studying these behaviors during the first trimester is relevant in terms of their implications for fetal growth and development.

The data on the study behaviors were reported by the mothers a few months after delivery. This suggests potential measurement errors due to recall and report biases. Random recall error is expected to inflate the variance estimates but should not bias the coefficient estimates. Non-random report errors can obviously bias the coefficient estimates. The extent of measurement error likely varies between the behaviors.

Cigarette quitting is measured by reporting not smoking in the first trimester among women who reported that they smoked during the 12 months before pregnancy. In addition to the self-report data after delivery that we use, data on smoking were collected prospectively and independently of this survey during the first prenatal visit. The prospective (pre-delivery) smoking report at the prenatal visit was compared with the retrospectively (after delivery) reported data (Lie et al, 2008). Only one woman who had reported smoking during the first prenatal visit reported not smoking in the retrospective survey. About 55% of those who reported not smoking during the prenatal visit reported smoking in the retrospective survey. This suggests no systematic bias towards not reporting smoking based on observed infant health post-delivery or social acceptance. Furthermore, the genetic exclusion restriction helps to account for some of the measurement error in quitting.

Average daily caloric intake is estimated from a standardized questionnaire on food consumption for the Norwegian population. Women were asked in the post-delivery survey to describe their diet approximately one year earlier, during the first trimester of pregnancy (Wilcox et al. 2007). Therefore, the data on diet and derived caloric intake are considered crude measures. Due to the skewed distribution of total calories (to the right) and in order to account for outliers, we evaluate the effects of cigarette quitting on caloric intake above the median, which is 2,189 calories.⁹ This helps to mitigate the measurement error in calculated caloric intake by reducing the influence of outliers and extreme observations. Calorie need varies by age, physical activity and BMI. The USDA estimates calorie needs of about 2,000–2,200 calories for women age 19–30 with moderate activity levels (USDA 2005). While some weight gain is recommended during pregnancy, the Institute of Medicine (IOM) recommends no increase in caloric consumption during the first trimester of pregnancy

⁸Small and Rosenbaum (2008) evaluate power in a general IV framework under different assumptions. With moderate effect sizes of an endogenous binary variable on the outcome (an effect of $\frac{1}{2}$ standard deviation) and fairly moderate association between the instrument and the endogenous variable, an IV model has a power of about 80% in sample of 2000 individuals (Small and Rosenbaum, 2008). The power deteriorates significantly under this scenario if the instrument does not fit the exclusion restriction and is related to the outcome through unobserved factors.

⁹An alternative approach would be to apply instrumental variable quantile regression. However, applying this model for caloric intake does not result in stable estimates.

(Fowles 2006). Therefore, the above-median caloric threshold in our dataset may be interpreted as consumption above recommended levels.

We measure alcohol consumption in the first trimester from the report of any consumption in this period in the post-delivery survey. Again, it is possible that this variable is affected by recall and report errors. Unlike for smoking, we are unable to verify the extent of such errors by comparing to pre-delivery data. However, the fact that smoking was not underreported post-delivery compared to the first prenatal visit provides some assurance against a strong bias in alcohol reporting.

We measure multivitamin use based on reporting of any use of multivitamins during the first trimester. The self-report data on vitamins are generally considered to be of good quality because they were validated for folic acid supplements by comparing self-reports to product names and pillbox labels provided by the women; use of folic acid supplements was confirmed for the majority (99%) of women reporting this use (Wilcox et al, 2007).

Caffeine intake during the first trimester is measured by an indicator for consuming 2 or more caffeinated drinks per day (based on reported number of cups/glasses), including coffee with caffeine and other caffeinated beverages such as coke or diet coke. We do not evaluate any caffeine consumption since the majority of the sample (about 90%) had some caffeine in the first trimester. We focus instead on more intensive use which is more clinically relevant. Similar to the food intake data, this measure may be limited by recall and report biases. However, given that caffeine use is a fairly common and habitual behavior and unlike smoking is well socially accepted, it is unlikely that it suffers from a major report bias.

Finally, our model controls for several maternal variables including age, marital status, schooling, income, and employment in the first trimester.¹⁰ We control for employment because it is both theoretically and empirically relevant for quitting and the other prenatal behaviors. Employed mothers have different time costs than unemployed ones and may experience different stressors. Also, employment has significant effects on quitting and the other behaviors in this sample. However, employment choice may be endogenous to the same unobservables as the other study behaviors. Therefore, we estimate an additional specification that excludes employment to test the sensitivity of the cigarette quitting effects to controlling for employment. Table 1 lists the study variables and their distributions.

4. Results

4.1 Characteristics of Quitters

We first evaluate the differences between cigarette quitters and non-quitters on the control variables described above, and report these in Table 2. We also compare these two groups on other background characteristics including whether the pregnancy was planned, BMI before pregnancy, and alcohol and caffeine consumption before pregnancy. We do not control for these variables in the main specification as they are likely endogenous.

About 22% of the women who smoked in the year before pregnancy quit smoking during the first pregnancy trimester. Quitters have more favorable characteristics for maternal and child health than non-quitters. Specifically, quitters are more educated, have higher incomes, and are more likely to have been employed and to have planned their pregnancy than non-

¹⁰We do not control for the other maternal characteristics shown in Table 2 when comparing quitters and non-quitters including pregnancy planning, alcohol and caffeine consumption before pregnancy, and BMI because they are clearly endogenous to maternal health status and health behaviors and may be driven by the same unobservable preferences that confound the relationships between cigarette quitting and the other prenatal behaviors of interest.

quitters. Also, quitters have consumed less caffeine during the past 12 months before pregnancy. Regressing cigarette quitting on all the control and background variables shows that they are highly jointly significant ($p=4.5\times 10^{-8}$). These results suggest that quitters may be different from non-quitters on unobservable characteristics such as maternal preferences and child health endowments. These unobservables may also correlate with the other prenatal behaviors and therefore confound the estimation of the cigarette quitting effects on these behaviors if ignored.

4.2 Exogeneity of the Genetic Variant

We compare the control variables and other observable background characteristics between two groups defined by the genetic variant: carries of the minor allele versus those carrying only the major allele; we report this comparison in Table 3. As expected, there are no significant differences in any of these variables between the two groups. Furthermore, when regressing the genetic variant on all these variables, we find that they are jointly insignificant ($p=0.968$). This provides some support for the hypothesis that the genetic variant satisfies the exclusion restriction.

4.3 Quitting Regression

Next we regress quitting on the genetic variant and all control variables first using probit then OLS (to calculate the F-statistic). Table 4 reports the incremental/marginal effects on cigarette quitting from the probit and OLS functions.¹¹ The genetic variant is significantly related to quitting; those with the minor allele are about 8 percentage-points less likely to quit. The marginal effects are similar between the probit and OLS function. The F-statistic for the effect of the genetic variant is 4.3 and its adjusted R^2 is 0.009. This genetic variant would be considered a weak instrument following common rules of thumb for the linear IV (2SLS) models (such as $F\text{-statistic} > 10$, Staiger and Stock, 1997). However, such rules are not directly applicable to and may even be restrictive for the bivariate probit model, which is more efficient than the linear IV model. Furthermore, what might be considered a low R^2 is consistent with what is expected for complex phenotypes such as smoking which has multiple contributing genetic factors (most of which are yet to be identified). A single genetic variant typically explains a very small percent of the total variation in a complex trait. Therefore, this result is consistent with the multifactorial and complex etiology of smoking and supports the validity of the observed genetic effect. Similar to the regression excluding the genetic variant, higher educated and employed mothers are more likely to quit smoking.

4.4 Effects of Cigarette Quitting on Other Prenatal Health Behaviors

We report the incremental/marginal effects of cigarette quitting on the other prenatal health behaviors including caloric intake, alcohol consumption, multivitamin use, and caffeine intake from both the standard and bivariate probit models in Table 5.¹² Also reported are the tests for the significance of the correlation between the errors terms of the bivariate probit model equations.

Beginning with caloric intake, cigarette quitting has a small and insignificant negative effect on above-median caloric intake in the standard probit model. However, under the bivariate probit model, the cigarette quitting effect becomes positive and marginally significant. Quitting increases the probability of above-median caloric intake by 42 percentage-points.

¹¹Similar results to standard probit function are observed in the bivariate probit models.

¹²The incremental effect we estimate is: $\Pr(B=1|Q=1,Z) - \Pr(B=1|Q=0,Z)$, where B is the outcome, Q is the quitting, and Z are the exogenous variables.

However, the exogeneity of quitting based on the significance of the correlation between the error terms of the caloric intake and quitting equations cannot be rejected ($p=0.6$).

Turning next to the effect of cigarette quitting on alcohol consumption, we find a significant decrease in the probability of alcohol drinking by about 28 percentage-points with quitting in the standard probit model. However, the effect is of opposite sign in the bivariate probit model and is insignificant. Again, the exogeneity of cigarette quitting in the alcohol consumption model is not rejected (0.4).

Cigarette quitting has an insignificant negative effect on multivitamin use in the standard probit model, but has a significant and large positive effect in the bivariate probit model, increasing the probability of multivitamin use by 49 percentage-points. However, similar to the previous two behaviors, the exogeneity of cigarette quitting is not rejected for multivitamin use ($p=0.132$).

Finally, cigarette quitting has a significant negative effect on caffeine intake in both the standard and bivariate probit models; the effect is larger in the latter model. The probability of having two or more caffeinated/coffee drinks per day decreases by 33 percentage-points in the standard probit model, and by 54 percentage-points in the bivariate probit model. Similar to the other behaviors, the exogeneity of cigarette quitting cannot be rejected for caffeine intake ($p=0.383$).

Next, we investigate the relative importance of the exclusion restriction of the genetic variant versus the non-linearity restrictions for identifying the quitting effect in the bivariate model. We do so by re-estimating this model excluding the genetic variant (the effects of cigarette quitting are in Appendix Table A1). The genetic variant plays an important role in identifying the cigarette quitting effect for the behaviors for which there are noticeable differences between the probit and bivariate probit estimates including for caloric intake, alcohol drinking, and multivitamin use. The estimate of the cigarette quitting effect on above-median caloric intake decreases by half when excluding the genetic variant and becomes insignificant. The effect on alcohol drinking is negative and significant similar to the standard probit model but opposite to the bivariate probit model including the genetic variant.¹³ The model for multivitamin use has serious convergence problems when excluding the genetic variant, rendering the estimates inappropriate.¹⁴ The quitting effect on the caffeine use measure without the genetic exclusion restriction is close to that when including the genetic variant, which is expected given that the standard probit and bivariate probit estimates for caffeine intake are close.

As mentioned above, we evaluate the sensitivity of the cigarette quitting effects to controlling for employment which is potentially endogenous by re-estimating the bivariate and standard probit models excluding employment. We find that quitting has overall similar effects when excluding employment (results are in Appendix Table A2). One exception is the quitting effect on alcohol drinking in the bivariate probit model, which becomes much larger and significant. However, the difference between the standard and bivariate probit models remains insignificant ($p=0.11$). Also, the exogeneity of quitting is rejected in the multivitamin use model when excluding employment. Overall, these results indicate that including or excluding employment has no remarkable effect on the main results.

We re-estimate the cigarette quitting effects on the other prenatal behaviors using a linear IV model (2SLS) first not adjusting for any control variables (which is equivalent to the simple

¹³The effect is twice as large in absolute value as the standard probit estimate.

¹⁴The first eight iterations of the multivitamin model are not concave; the estimate of the quitting effect is smaller than the one including the genetic variant and is only marginally significant.

Wald IV estimator) and then adjusting for all control variables. We provide these estimates in Appendix Table A3, along with OLS (linear probability) models for comparison purposes. The signs are similar between the IV effects and those from the bivariate probit model. Furthermore, the difference in signs between the OLS and IV effects is similar to that between the standard and bivariate probit models. Similar to the probit models, none of the differences between the OLS and IV models are significant except for above-median caloric intake which is marginally significant ($p=0.08$). The cigarette quitting effects are close in magnitude between the IV and bivariate models for multivitamin use and for caffeine intake but are different for caloric intake and alcohol consumption. However, none of the IV effects are significant. This may be in part due to the lower power of the IV model compared to the bivariate probit model (assuming the distributional assumptions are met) for the binary measures of quitting and other prenatal behaviors. In addition to its inefficiency disadvantage, the linear IV estimator may result in biased estimates in the case of binary endogenous variables and outcomes as mentioned above (Terza et al, 2008). Also, 2SLS estimates the local average treatment effect (LATE), which only applies to those whose cigarette quitting depends on the genetic variant (i.e. those who would quit if they have the major allele but would not quit if they had the minor allele), while the bivariate probit model estimates an average treatment effect.¹⁵ Therefore, technically, the two models do not estimate the same effect.¹⁶

4.5 Implications for Infant Health

As mentioned above, previous studies have found that the prenatal behaviors that we observe to change with cigarette quitting including caloric intake, multivitamin use, and caffeine consumption may have important effects on infant health. Therefore, a natural question is whether these behaviors affect infant health in this sample and whether their effects partly explain the effects of cigarette quitting. However, we are unable to comprehensively evaluate this question due to the lack of instruments for these other behaviors. Also, we only observe immediate birth outcomes such as birth weight and do not observe longer-term child development outcomes that may also be influenced by these behaviors. Furthermore, even though we observe a positive effect of quitting on birth weight using OLS, we do not find a beneficial effect on birth weight when instrumenting for quitting using the genetic variant.¹⁷ This does not mean that quitting is not beneficial for the mother and the infant since as we cannot evaluate several other important child outcomes that are affected by maternal smoking such as child neurological development (Wehby et al, 2011).

As an alternative, we are able to descriptively evaluate the relationship between the prenatal behaviors that are found to significantly vary with quitting and birth weight and low birth weight ($< 2,500$ grams). We do so by regressing birth weight and low birth weight on these behaviors adjusting for the model covariates (using OLS and probit regression, respectively). Table 6 reports the incremental/marginal effects of the prenatal behaviors in these regressions. Having two or more caffeinated drinks per day is associated with a 133-gram decrease in birth weight. Also, multivitamin use is associated with a decrease in LBW risk. Both of these findings are consistent with previous studies (CARE 2008; Wehby et al.

¹⁵Wooldridge (2002), section 18.5.1, pages 636–637.

¹⁶As mentioned above, our bivariate probit estimates of the quitting effects are largely dependent on the exclusion restriction of the genetic variant and not just the non-linearity restrictions. Therefore, these estimates are only generalizable to the extent that the variation in quitting due to the genetic variant that is used in identifying the quitting effect is not specific to a group of individuals who are different from the rest of sample (and population).

¹⁷Quitting is associated with a 159-gram increase in birth weight ($p=0.017$) using OLS. However, the effect is negative and large (but statistically insignificant) when using 2SLS (–1413 grams).

2009; Scholl et al. 1997). While descriptive, these findings suggest that the observed prenatal behavior changes with cigarette quitting have positive effects on infant health.

5. Conclusions

The study findings indicate that cigarette quitting during pregnancy may influence other prenatal behaviors. Specifically, cigarette quitting may increase caloric intake and multivitamin use and reduce caffeine consumption in the first trimester. Such effects may occur through biologic or psychosocial pathways. The increase in caloric intake may be a response in order to offset the disutility of cigarette quitting, suggesting that eating is a substitute for smoking. This effect is consistent with some previous studies reporting an increase in body weight with higher cigarette costs (e.g. Chou et al., 2004) but not with others finding an opposite effect (e.g. Wehby and Courtemanche, 2012; Wehby et al. 2012). This result is consistent with mice-based studies finding evidence of appetite loss with nicotine exposure (Chen et al. 2005; Chen et al. 2008), suggesting that the increased caloric intake may also be due to appetite increase with cigarette quitting. On the other hand, the increase in multivitamin use and reduction in caffeine consumption may be due to cigarette quitting encouraging further healthy behavior by increasing personal interest and confidence in one's ability to adopt such behaviors. Our study also suggests that smoking and caffeine consumption are complements. In contrast, our results are mixed on alcohol consumption. Prior research results are also mixed on whether alcohol and cigarettes are complements or substitutes (Decker and Schwartz 2000; Goel and Morey 1995; Gohlmann et al. 2008; Picone and Sloan 2003). The results suggest a bias in the effects of cigarette quitting using classical models that assume exogenous quitting. While we cannot formally reject the estimates assuming exogenous quitting in most specifications, this test likely has low power with the small sample size.

As mentioned above, these behavioral changes may have consequences for both maternal and child health. Increasing high caloric intake in the first trimester may have unfavorable effects on maternal and child health including a higher risk of child obesity later in life. Therefore, counseling women of childbearing age and pregnant women who smoke and are considering quitting about controlling their caloric intake may be important for overcoming any offsetting effect due to increased caloric intake and maximizing the returns from cigarette quitting during pregnancy to maternal and child health. In contrast, both multivitamin use and decreased caffeine consumption are expected to have positive effects on maternal and child health. Therefore, informing women of childbearing age and pregnant women who smoke about the potential improvement in these behaviors after cigarette quitting may increase their motivation to quit.

The study has some caveats that should be considered when interpreting the results including a modest sample size, limited generalizability, and lack of a replication sample. Also, we have no data on other genetic variants that influence cigarette quitting and can improve the identification.¹⁸ These limitations highlight the importance of replicating this study in richer and larger datasets. Another limitation is that both cigarette quitting and the other health behaviors are only measured in the first trimester, resulting in a short period for observing the quitting effects, which may vary over time (either accumulate or attenuate). Therefore, evaluating the longer-term effects of cigarette quitting is needed in future studies.

¹⁸Despite the current knowledge supporting the premise that the employed genetic variant is unlikely to affect the studied prenatal behaviors other than through cigarette quitting, it remains a possibility that the gene affects some of the other studied prenatal behaviors either directly or through behavioral pathways other than through quitting, especially since *GABBR2* is a neurotransmitter pathway gene which increases the possibility that it may be involved in multiple behaviors (Cawley et al. 2011) and its role has not yet been fully characterized. Therefore, it is important that future studies evaluate alternative exclusion restrictions with other variants involved in cigarette smoking and quitting such as variants in *CHRNA3* and *CHRNA5*.

Related to that is the potential reverse effect of the other prenatal behaviors of interest on cigarette quitting in the bivariate probit model.¹⁹ This may bias the quitting effect in the same direction as in the standard probit model and can be better addressed with longitudinal data. There is also the possibility of measurement error due to report biases and recall errors since the women were asked to recall prenatal behaviors after delivery. Finally, we lack data that can be used to explain the observed effects of quitting on the other prenatal behaviors. We leave this to future studies with more reliable and detailed measures of the study prenatal behaviors as well as intermediate ones that link them to cigarette quitting.

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¹⁹The IV (2SLS) model accounts for the reverse effect.

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Appendix

Table A1

Incremental/Marginal Effects of Cigarette Quitting on Health Behaviors from The Bivariate Probit Model Excluding the Genetic Variant

Caloric intake above median	0.242 (0.584)
Any alcohol drinking	−0.521 *** (0.022)
Taking multivitamins	0.424 * [†] (0.256)
Two or more caffeinated drinks per day	−0.584 *** (0.124)

Note: The table presents the incremental cigarette quitting effects on the probabilities of the binary health behaviors.

* and *** indicate significance at p<0.1 and p<0.01, respectively.

[†] The model has convergence problems.

Table A2

Incremental/Marginal Effects of Cigarette Quitting on Other Health Behaviors Excluding Employment Status from the Model

	Standard Probit	Bivariate Probit	Exogeneity Test Chi-square [p]
Caloric intake above median	−0.028 (0.056)	0.472 *** (0.075)	1.431 [0.232]
Any alcohol drinking	−0.280 *** (0.044)	0.354 ** (0.163)	2.504 [0.1136]
Taking multivitamins	−0.013 (0.051)	0.519 *** (0.085)	4.157 ** [0.042]
Two or more caffeinated drinks per day	−0.32 *** (0.052)	−0.486 ** (0.235)	0.332 [0.564]

Note: The table presents the incremental/marginal cigarette quitting effects on the probabilities of the binary health behaviors without controlling for employment status.

* and *** indicate significance at p<0.1 and p<0.01, respectively. The chi-square of the exogeneity test based on the correlation between the error terms of the two bivariate probit model equations is also reported with the p value in brackets. The sample sizes are the same as those in Table 5.

Table A3

Effects of Cigarette Quitting on Other Health Behaviors in Linear Probability Models

	OLS		2SLS				
	Unadjusted	Adjusted	Unadjusted	Adjusted	F statistic	Partial R ²	Hausman exogeneity F statistic
	Coefficient (SE)	Coefficient (SE)	Coefficient (SE)	Coefficient (SE)			
Caloric intake above median	−0.017 (0.055)	−0.011 (0.057)	0.14 (0.544)	0.146 (0.548)	5.15 **	0.011	0.082
Any alcohol drinking	−0.232 *** (0.053)	−0.279 *** (0.053)	0.609 (0.663)	0.618 (0.678)	4.71 **	0.010	2.723*
Taking multivitamins	0.037 (0.052)	−0.008 (0.053)	0.579 (0.614)	0.540 (0.614)	4.33 **	0.009	0.958
Two or more caffeinated drinks per day	−0.345 *** (0.051)	−0.335 *** (0.052)	−0.472 (0.556)	−0.423 (0.543)	4.41 **	0.009	0.026

Note: Standard errors are in parentheses. The unadjusted models only include cigarette quitting. The adjusted models include the covariates from Table 1. Unadjusted 2SLS provides the simple Wald IV estimator. The partial F statistic of the genetic instrument is in brackets. In order to more easily compare the estimates between the unadjusted and adjusted models, these models are estimated for the same sample that includes observations with complete data on all model covariates and the genetic instrument. The sample sizes are the same as those in Table 5.

** and *** indicate $p < 0.05$ and $p < 0.01$, respectively.

Table 1

Description of Study Variables

Variable	Description	Mean	Std. Dev.
Caloric intake above median	0/1 indicator for above median caloric intake in the first trimester (more than 2189 calories)	0.499	0.501
Any alcohol drinking	0/1 indicator for any alcohol drinking in the first trimester	0.410	0.492
Alcohol drinking before pregnancy *	0/1 indicator for any alcohol drinking in the past few years before pregnancy	0.969	0.175
Two or more caffeinated drinks per day	0/1 indicator for 2 or more caffeinated drinks per day during the first pregnancy trimester	0.595	0.491
Two or more caffeinated drinks per day before pregnancy *	0/1 indicator for 2 or more caffeinated drinks per day during the 12 months before pregnancy	0.765	0.424
Cigarette quitting	0/1 indicator for smokers quitting cigarettes during the first trimester	0.217	0.413
Age	Age in years	28.654	4.695
Married	0/1 indicator for married mothers	0.385	0.487
Less than high school ^a	0/1 indicator for maternal education of less than completed high school	0.174	0.379
High school ^a	0/1 indicator for maternal education of completed high school	0.263	0.441
Technical college ^a	0/1 indicator for mother attending technical college	0.248	0.433
University ^a	0/1 indicator for mother completing university education	0.037	0.190
Very low income ^b	0/1 indicator for current gross maternal yearly income of less than 150,000 kr	0.402	0.491
Moderate income ^b	0/1 indicator for current gross maternal yearly income between 201,000 and 250,000 kr inclusive	0.224	0.417
High income ^b	0/1 indicator for current gross maternal yearly income of 251,000 kr or more	0.108	0.310
Employed	0/1 indicator for the mother being employed in the first trimester	0.810	0.393
BMI *	Maternal body mass index before pregnancy	23.444	3.874
rs1930139_C	0/1 indicator for the C/C or T/C genotype relative to T/T genotype	0.329	0.470

Notes:

^aThe reference is 2–4 years of college;^bThe reference is 151,000–200,000 kr.

Descriptive statistics are based on the 483 women included in the caloric intake analysis. Alcohol consumption statistics are for 478 women from that group, respectively (5 women did not have data on alcohol consumption). Caffeine statistics are for 482 mothers from that group (1 woman did not have data on caffeine intake).

* indicates a variable that is only used in evaluating the exogeneity of cigarette quitting and the genetic variant and not as a control variable in the model estimating the effect of cigarette quitting on the other prenatal behaviors.

Table 2

Characteristics of Quitters and non-Quitters

	Quitters (N=105)	Non-quitters (N=382)	Quitting Regression Coefficient (SE)
Age	28.4 (4.7)	28.7 (4.8)	-0.004 (0.004)
Married	40.0	38.0	-0.002 (0.040)
Less than high school ^b	8.6	20.7	-0.112 [*] (0.060)
High school	21.0	27.8	-0.109 ^{**} (0.052)
Technical college	24.8	24.6	-0.035 (0.054)
University ^b	7.6	2.4	0.195 [*] (0.104)
Very low income ^b	25.7	44.0	-0.047 (0.048)
Moderate income ^d	29.5	20.7	0.012 (0.054)
High income ^c	16.2	9.2	0.004 (0.073)
Employed ^a	94.3	77.0	0.123 ^{**} (0.052)
Alcohol drinking before pregnancy ^d	99.1	95.6	0.026 (0.097)
Two or more caffeinated drinks per day before pregnancy ^a	59.1	81.4	-0.211 ^{***} (0.044)
Planned pregnancy ^b	77.1	64.4	0.073 [*] (0.041)
BMI	23.2 (3.5)	23.6 (4.1)	-0.002 (0.005)
Constant			0.449 ^{**} (0.202)
F-statistic			4.70 [p=4.5×10 ⁻⁸]

Note: The Table reports the distribution of observable relevant characteristics including percentages for categorical variables and means (standard deviations) for continuous variables between cigarette quitters and non-quitters. The descriptive statistics are based on 487 women with complete data on all the background variables, cigarette quitting, and the genetic variant. Chi-square tests of independence and tests of means are used to test differences in categorical and continuous variables by quitting status, respectively.

a, b, c, and d. indicate that the differences between cigarette quitters and non-quitters are significant at $p < 0.0005$, $p < 0.01$, $p < 0.05$, and $p < 0.1$, respectively. Also reported are coefficients (with standard errors in parentheses) from the OLS regression of quitting on all these variables simultaneously and the F-statistic for their joint significance.

^{*}, ^{**} and ^{***} indicate $p < 0.1$, $p < 0.05$, and $p < 0.01$, respectively.

Table 3

Characteristics of Groups Defined by the Genetic Instrument

Variable	C/C or T/C genotype (N=163)	T/T genotype (N=324)	rs1930139_C Regression Coefficient (SE) (N=487)
Age	28.7 (4.6)	28.7 (4.8)	-0.002 (0.005)
Married	39.9	37.7	0.032 (0.048)
Less than high school	19.0	17.6	0.030 (0.073)
High school	27.0	25.9	0.029 (0.064)
Technical college	24.5	24.7	0.005 (0.066)
University	3.7	3.4	0.063 (0.127)
Very low income	38.7	40.7	-0.055 (0.058)
Moderate income	23.3	22.2	-0.011 (0.066)
High income	9.2	11.4	-0.063 (0.089)
Employed	80.4	80.9	-0.001 (0.063)
Alcohol drinking before pregnancy	94.5	97.2	-0.172 (0.119)
Two or more caffeinated drinks per day before pregnancy	79.1	75.3	0.042 (0.053)
Planned pregnancy	66.3	67.6	-0.024 (0.049)
BMI	23.7 (3.8)	23.4 (4.0)	0.005 (0.006)
Constant			0.447* (0.246)
F-statistic			0.42 [p=0.968]

Note: The Table reports the distribution of observable relevant characteristics including percentages for categorical variables and means (standard deviations) for continuous variables by the genetic variant (rs1930139_C). The descriptive statistics are based on 487 women with complete data on all the background variables, cigarette quitting, and the genetic variant. Chi-square tests of independence and tests of means are used to evaluate differences in the categorical and continuous variables by the genetic variant, respectively. Also reported are coefficients (with standard errors in parentheses) from the OLS regression of rs1930139_C on all these variables simultaneously and the F-statistic for their joint significance.

* indicates $p < 0.1$.

Table 4

Incremental/Marginal Effects on Cigarette Quitting

	Probit	OLS
rs1930139_C	-0.081 ** (0.036)	-0.079 ** (0.038)
Age	-0.007* (0.004)	-0.008* (0.004)
Married	0.002 (0.038)	0.004 (0.039)
Less than high school	-0.119 ** (0.047)	-0.129 ** (0.060)
High school	-0.096 ** (0.045)	-0.108 ** (0.053)
Technical college	-0.049 (0.047)	-0.057 (0.054)
University	0.182 (0.119)	0.208 ** (0.103)
Very low income	-0.047 (0.046)	-0.051 (0.048)
Moderate income	-0.002 (0.051)	0.005 (0.055)
High income	0.018 (0.071)	0.030 (0.073)
Employed	0.154 *** (0.04)	0.136 *** (0.051)
F-statistic for rs1930139_C		4.33 **
Partial R ² for rs1930139_C		0.009
Observations	499	499

Note: The table represents the incremental/marginal effects of the model variables on cigarette quitting as estimated from standard probit regression. Standard errors are in parentheses.

and * indicate $p < 0.05$ and $p < 0.01$, respectively. The regression is based on the sample of 499 with complete data on all these variables.

Table 5

Incremental/Marginal Effects of Cigarette Quitting on Other Health Behaviors

	Standard Probit	Bivariate Probit	Exogeneity Test Chi-square [p]	Sample Size
Caloric intake above median	−0.011 (0.056)	0.417 * (0.226)	0.644 [0.643]	483
Any alcohol drinking	−0.277 *** (0.045)	0.014 (0.369)	0.686 [0.407]	493
Taking multivitamins	−0.010 (0.052)	0.492 *** (0.135)	2.274 [0.132]	499
Two or more caffeinated drinks per day	−0.333 *** (0.051)	−0.540 *** (0.166)	0.762 [0.383]	497

Note: The table presents the incremental/marginal effects of cigarette quitting on the probabilities of the binary health behaviors.

* and *** indicate significance at $p < 0.1$ and $p < 0.01$, respectively. The chi-square of the exogeneity test based on the correlation between the error terms of the two bivariate model equations is also reported with the p value in brackets.

Table 6

Incremental/Marginal Effects of Health Behaviors on Birth weight

	Birth weight - OLS	Low birth weight – Probit
Caloric intake above median	90.044 (56.961)	−0.017 (0.022)
Taking multivitamins	−28.644 (61.263)	−0.046 * (0.026)
Two or more caffeinated drinks per day	−133.377 ** (58.855)	0.014 (0.023)

Note: Standard errors are in parentheses. Effects of control variables are suppressed for brevity.

* and ** indicate $p < 0.1$ and $p < 0.05$, respectively.