A Genetic Instrumental Variables Analysis of the Effects of Prenatal Smoking on Birth Weight: Evidence from Two Samples

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Abstract

There is a large literature showing the detrimental effects of prenatal smoking on birth and childhood health outcomes. It is somewhat unclear, though, whether these effects are causal or reflect other characteristics and choices by mothers who choose to smoke that may also affect child health outcomes or biased reporting of smoking. In this paper, we use genetic markers that predict smoking behaviors as instruments in order to address the endogeneity of smoking choices in the production of birth and childhood health outcomes. Our results indicate that prenatal smoking produces more dramatic declines in birth weight than estimates that ignore the endogeneity of prenatal smoking, which is consistent with previous studies with non-genetic instruments. We use data from two distinct samples from Norway and the US with different measured instruments and find nearly identical results. The study provides a novel application that can be extended to study several behavioral impacts on health, social and economic outcomes.

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Keywords

Smoking; Birth Weight; Infant Health; Instrumental Variables; Genetic Instruments; Mendelian Randomization

I. Introduction

Maternal health behaviors at conception and during pregnancy are important determinants of fetal growth and child development. Maternal smoking is one of the most commonly studied behavioral risk factors that affect fetal/child development and is often considered the single most important, modifiable factor affecting birth outcomes (Kramer 1987). Prenatal and postnatal exposures to cigarette smoking are leading causes of child mortality and morbidity (DiFranza and Lew 1996; Ebrahim, Floyd, Merritt, et al. 2000). Prenatal smoking has also been linked to low fetal growth, low birth weight, premature births, and sudden infant death syndrome (Schoendorf and Kiely 1992), and has been shown to increase the risk of admission to neonatal intensive care, increasing healthcare costs of the birth by $700 (Adams et al. 2002).

Several observational studies have found that prenatal maternal smoking decreased birth weight by about 250 grams (Evans and Ringel 1999; Rosenzweig 1983). Low birth weight is an important predictor of child neurodevelopment and future health and socioeconomic status (Anderson and Doyle 2003; Boardman et al. 2002; Mervis et al. 1995; Saigal et al. 2001; Victora et al. 2008; Wolf, Smit, and de Groot 2001), suggesting that fetal exposure to smoking may reduce long term health and human capital through the impact of smoking on birth outcomes. Indeed, researchers have found that maternal smoking during pregnancy is associated with greater child's behavioral risks including developing behavioral problems later in childhood (Weitzman, Gortmaker, and Sobol 1992), participating in criminal behavior, and lifetime nicotine dependence (Buka, Shenassa, and Niaura 2003). Maternal smoking during pregnancy has also been associated with increased risks of language problems, hyperactivity, fearfulness, and not getting along with peers (Faden and Graubard 2000).

The prevalence of prenatal smoking has fallen over time but is still high with a substantial number of children exposed to tobacco pre and postnatally worldwide. For example, 13.8% of women smoked during pregnancy in 2005 in the US(Tong et al. 2009). In Norway, the rate of smoking during pregnancy was 11 % in 2004, compared to about 21% in 1994–1995 (Eriksson et al. 1998; Kvalvik, Skjaerven, and Haug 2008).

Discovering which behavioral factors have the greatest negative effect on fetal and child development will aid policymakers in the development of interventions to reduce these negative effects (Heckman 2000; Heckman 2008). Given that maternal health behaviors during the prenatal period are likely to influence multiple child physical and neurological outcomes (such as birth weight and neurological development), developing interventions that address these health behaviors is likely to have large returns in child and future health and to be more cost-effective in enhancing child health than specific interventions that target child developmental problems post occurrence.

The commonly reported harmful effects of prenatal smoking on fetal growth and child health may occur via various biological pathways, including cell damage and changes to the placenta and a reduction in oxygen availability (hypoxia) to the fetus (Walsh 1994). However, endogenous maternal selection into smoking and biased reporting of smoking behaviors complicate the estimation of the causal effects of smoking on birth

outcomes(Brachet 2005). Specifically, mothers who smoke during pregnancy are also likely to self-select into smoking based on their preferences for health and risk taking and their perceptions of fetal health endowments. These factors, typically unobserved in available data samples, are related to fetal health through other pathways besides smoking. For example, women who smoke during pregnancy may adopt other unhealthy behaviors that may also have adverse effects on the fetus (e.g. poorer nutrition or reduced prenatal care), but may also be less likely to have a family history of poor birth outcomes. Therefore, the actual contribution of smoking to child health, independently of the confounding pathways that correlate with both smoking and child health, and the direction of the potential net bias in estimating the effects of smoking on birth outcomes without accounting for non-random self-selection into smoking, is theoretically ambiguous and an open question.

Several papers have previously evaluated the effects of smoking on birth weight using a myriad of statistical and econometric methods. Most commonly, researchers employ statistical models that attempt to adjust directly for a variety of observable characteristics that may proxy for the relevant unobservable factors. These factors include other maternal behaviors besides smoking, measures of pregnancy wantedness and maternal health (Reichman et al. 2006). Others have used propensity score matching strategies that are also limited to observable characteristics and found similar results as more traditional specifications (Almond, Chay, and Lee 2005).

Several authors have used experimental or quasi-experimental designs to attempt to estimate causal effects of prenatal smoking on birth outcomes. Permutt and Hebel (1989) use a smoking cessation intervention to introduce random variation in smoking status and find large effects of smoking cessation on birth weight (15 grams per cigarette vs. 2 grams using OLS and an overall effect of 400 grams)(Permutt and Hebel 1989). Evans and Ringel (1999) use state level cigarette taxes in an instrumental variable (IV) strategy and find no statistically discernable difference between 2SLS and baseline estimates(Evans and Ringel 1999). However, the 2SLS effect estimate is 350–600 gram decrease in birth weight across several 2SLS models versus 230–250g across OLS models. Interestingly, the 2SLS estimates in both Permutt and Hebel and Evans and Ringel are larger than their OLS estimates. This is consistent with other studies that use IV estimation of smoking effects on birth weight, which also find generally *larger* adverse smoking effects using IV than those found with classical single-equation models (see also (Grossman and Joyce 1990; Lien 2005; Rosenzweig 1983)).

In this paper, we employ an IV model with genetic risk factors for smoking as instruments to shed more light on the causal link between maternal smoking during pregnancy and infant birth weight.[1] The goal is to identify the effects of smoking using a previously unexplored source of variation in smoking that is due to individual-level differences in genetic risk factors that predispose for smoking, in order to account for unobserved factors that are related to the choice of smoking and to birth outcomes. One strength of utilizing genetic variants as instruments is that these variants are inherited at conception and, therefore, cannot be reversely affected by smoking or other behaviors. Another advantage is that confounding factors for smoking and birth weight, such as state-level health measures, are unlikely to be correlated with genetic variants compared to other instruments, such as tax rates or smoking policies (Lawlor et al. 2008; Smith et al. 2007). Similar to other instruments, there are also challenges in using genetic instruments, which we describe in detail in the instrument validity section below.

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[1]The use of genetic instruments is sometimes referred to as "Mendelian Randomization" in epidemiology, but the approach is a standard instrumental variable application with genetic instruments (Wehby, Ohsfeldt, and Murray 2008).

Previous IV estimations of the effects of smoking have mainly utilized taxes or changes in smoking policies between states as instruments. One limitation in these analyses is that these are aggregate level measures that only utilize area-level variation in smoking and ignore within area variation due to individual-level factors. Our primary contribution is that variation in genetic markers occurs within the individual at the molecular level. Thus, the study uses a different source of variation to identify impacts. It is of interest to use different instrument sets in order to potentially estimate different local average treatment effects (LATE). We describe below how we select the genetic instruments for this analysis.

We focus our attention on birth weight as the measure of infant health, similar to most of the previous studies. Low birth weight is generally considered to be an important predictor of other health and human capital outcomes later in life. From a policy perspective, the study findings are important for developing health policies that target pharmacotherapy or raise awareness for smoking cessation and public taxation policies that aim at reducing the negative externalities of smoking, given that accurate estimation of the effects of smoking on child health is needed in order to assess the cost-effectiveness of such policies.

There is a broad range of scientific evidence that supports the use of genetic markers as instruments for smoking. Many twin and adoption studies have demonstrated that genetic heritability is at least 50% for both smoking initiation and smoking persistence (Carmelli et al. 1992; Heath and Martin 1993; Lessov et al. 2004; Maes et al. 2004; Sullivan and Kendler 1999). Researchers have also identified several variants in nicotine, detoxification, and neurotransmitter genes to be significantly correlated with smoking behaviors including through candidate gene, genome-wide association studies (GWAS), and meta-analyses(Berrettini et al. 2008; Beuten 2005; Caporaso et al. 2009; Freathy et al. 2009; Li et al. 2009; Liu et al. 2010; Tyndale 2003; Vink, Staphorsius, and Boomsma 2009). Specific genetic risk factors have also been related to quitting and intensity of smoking during pregnancy (Freathy et al. 2009). Further, several studies have shown that the success of a treatment for smoking cessation may vary by neurotransmitter and detoxification pathway genes(Kortmann et al. 2009). The genetic variants that are employed in this study and described below in detail are in candidate genes for smoking.

The remaining sections are designed as follows: Section II describes the data sources and the model used to identify the impact of prenatal smoking on birth weight, as well as a description of the study measures. Section III presents our empirical results. Section IV discusses the study findings and implications for public policy and future research studies.

II. Data and Methodology

A. Study Samples

The study uses two independent samples from Norway and the US and conducts all analyses separately for each sample. The goal is to compare the results between samples that differ in their populations, smoking rates, and the genetic instruments used to identify the effects of smoking in order to gauge the result sensitivity to these factors. The idea is that observing similar findings under these different factors suggests that the effect is generally insensitive to differences in these factors. We describe below each data source in detail.

A.1 Norwegian Sample—The Norwegian sample includes children born without birth defects who were enrolled as a control group in a study of oral clefts in Norway. The study is a joint collaboration between the National Institute for Environmental Health Sciences (NIEHS.) and researchers at the University of Bergen, and involved a population survey of infants born with oral clefts in Norway in 1996 through 2001 and their parents as well as a randomly selected control sample of infants born without oral clefts in the same period

(NIEHS. 2009), with a total sample of 574 cleft cases and 763 non-cleft cases recruited. The study goal is to identify behavioral, environmental and genetic risk factors for oral clefts, which are common and burdensome birth defects. DNA samples from parents and children and extensive data on maternal behaviors and household factors and socioeconomics were collected. Behavioral data were self-reported by the mothers through self-administered questionnaires, which were completed between 3–4 months on average post delivery. The DNA samples have been genotyped for a large list of single nucleotide polymorphisms (SNPs), which are DNA base-pair variants, including those in genes that are related to nicotine dependence and detoxification. The data has been used in several studies(Jugessur et al. 2009; Lie et al. 2008).[2]

Our study uses the sample of babies without oral clefts (control sample) to identify the effects of smoking on birth weight, using a set of SNPs that are involved in neurotransmitter or detoxification pathways and that are predictive of smoking in this sample. We limit the study to the control sample given that it represents a random sample of the population of births without oral clefts and in order to provide a more comparable sample to the Add Health sample, which is a general birth sample. We describe the SNP selection process below. The analytical sample includes 507 children with complete data on all the model variables, including genetic variants. Out of the 763 unaffected children, 592 samples had been genotyped (Jugessur et al. 2009).[3]

For the analyses using the Norway sample, we measure smoking by smoking participation and the number of cigarettes smoked per day during the first trimester.[4] We evaluate the effects of any smoking participation during pregnancy given that less than daily smoking exposure may still have adverse effects on fetal development.[5] We also study the number of cigarettes in order to evaluate the smoking intensity effects.

The Norway dataset provides data on several inputs and risk factors that are relevant for infant health production including behavioral inputs (alcohol drinking, multivitamin use, maternal calorie intake and BMI during pregnancy; pregnancy wantedness), and maternal socioeconomic and demographic characteristics. Table 1 presents the distribution of the study variables for the Norway sample with complete data on all model variables. Table A1 in the Appendix compares the distributions of study variables between the study samples and the excluded samples due to incomplete data. As can be seen, there is no systematic differences between the analytical and excluded samples, suggesting random data loss.

The average birth weight for the analytical Norway sample is 3647 grams. The mean population birth weight in Norway between 1999 and 2004 was around 3566 grams(Kvalvik, Skjaerven, and Haug 2008). The average rate of any first trimester smoking participation in the analytical sample is 31.7%. About 21% of the sample smoked 1 cigarette or more per day during the first trimester. Eriksson et al. (1998) reported that about 21% of pregnant women in Norway reported daily smoking around 18 weeks of pregnancy in 1994–1995 based on a multisite sample(Eriksson et al. 1998). Using data on the whole birth population, Kvalvik et al, (2008) reported that about 17.3% of pregnant women reported

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[2]See study website http://www.niehs.nih.gov/research/atniehs/labs/epi/studies/ncl/publications.cfm

[3]The genotyped sample did not include samples of 171 control children due to inadequate and/or low quality DNA samples. The analytical sample excludes 85 cases from the genotyping sample due to missing data on the study variables, including genotypic data. The data loss is not correlated with any characteristics that are related to smoking and birth weight as described below, and is therefore thought to be random and not systematic.

[4]The first trimester is a critical period for fetal development and maternal exposures during this period are likely to have large effects on fetal growth and birth weight. The majority (about 74%) of mothers who smoked at pregnancy continued to do so during the first trimester.

[5]In a sensitivity analysis, we estimated the impact of daily smoking (i.e. a minimum of 1 cigarette per day) during the first trimester on birth weight.

daily smoking at the end of the pregnancy in 1999–2001. The Norway sample includes births in 1995–2002. Therefore, the sample smoking participation rates are comparable to other study estimates for Norway.[6]

A2. US Sample—The US data sample is from the restricted version of the National Longitudinal Study of Adolescent Health (Add Health). Add health was initially designed as a school-based study of the health-related behaviors of a nationally representative sample of adolescents who were in grades 7 to 12 in 1994/5. A large number of these adolescents have subsequently been followed and interviewed two additional times in both 1995–6, and 2001–2. There are approximately 6,700 records of completed pregnancies by the time of the wave 3 survey, when the 15,000 respondents were on average 22 years old. Approximately 4,500 completed pregnancies are reported by females. Nearly 2,900 pregnancies resulted in a live birth, and nearly 2,100 pregnancies are a first birth.[7] Nearly 1,850 pregnancies were reported as the first pregnancy of the relationship. We have information on birth weight and child gender for approximately 1,700 of these births. Because the DNA sample currently includes only 2,500 of the original 15,000 respondents in Add Health, our sample size that has genetic marker information available is approximately 300 mothers.

For the analyses using the Add Health sample, we measure smoking by smoking participation during pregnancy.[8] Table 2 represents the distribution of the study variables used in the analytical sample of the Add Health sample. Table A2 in the Appendix compares the distributions of the model variables between the analytical and the overall sample. As can be seen, the analytical sample is representative of the overall sample and data loss is thought to be random.

The average birth weight in the Add Health sample is over 3200 grams (approximately 7.2 pounds). Seventeen percent of the sample reports smoking during pregnancy (2.5 cigarettes a day on average). Ebrahim et al. (2000) shows using the BRFSS survey that the prevalence of pregnant women who smoked between 1987 and 1996 fell from 16.3% to 11.8% (Ebrahim, Floyd, Merritt, et al. 2000). Ventura et al. (2003) shows using recent birth certificate data that the proportion of mothers who smoke prenatally is 15% for 15–17 year olds, 19% for 18–19 year olds and 16.8% for 20–24 year olds(Ventura et al. 2003). The CDC (2004) finds that approximately 11.4% of all US women report smoking during pregnancy in the early 1990s and 2000s(CDC 2004). Fewer than 40% of the births in the Add Health sample were reported to be wanted at the time of the pregnancy.

B. Empirical model

A well established empirical literature in economics has analyzed the effects of prenatal investments on birth outcomes. These studies generally estimate birth weight production functions and examine the impacts of various inputs including, pregnancy-specific behavioral investments such as parental smoking and prenatal care (Grossman and Joyce 1990; Rosenzweig 1983; Wehby et al. 2009). Following this analytical framework, the birth weight production function is specified as:

$$birthweight = \beta_0 + \beta_1 Smoke + \beta_2 X + \varepsilon \tag{1}$$

[6]The smoking rates in the Norway sample reported at the first prenatal visit at about 10.3 weeks of gestation on average (available through the Medical Birth Registry) were lower than first trimester smoking rates reported post delivery in the NCL survey, suggesting that smoking status later in pregnancy may not accurately reflect first trimester smoking due to quitting during pregnancy (Lie et al. 2008).

[7]We identify first births by examining whether the reported age of the mother at the time the pregnancy ended was the lowest age of all observations for that mother.

[8]The Add Health sample had no data on number of cigarettes smoked—only number of packs smoked.

where *Smoke* is an indicator of maternal smoking during pregnancy and *X* is a vector of other inputs to the production process.

It is well known that OLS estimation of equation (1) would yield biased estimates of β_1 since the mother's decision whether or not to smoke reflects behavioral choices which are likely based on her perceptions of fetal health risks and anticipations of child health outcomes, including birth weight.[9] Therefore, self-selection of risk behaviors is likely correlated with unobserved characteristics that also affect child health in equation (1).

To overcome the endogeneity problem we consider an instrumental variable (IV) analysis which exploits exogenous variation in smoking generated from a set of instruments to identify its impact on birth weight. Specifically, we use sets of genetic variants in candidate genes for smoking as the instruments.[10] These variants are statistically valid instruments if they are significantly correlated with smoking, and are otherwise unrelated to birth weight through unobserved characteristics.

We estimate the IV model using 2SLS, which estimates the following equation by OLS prior to equation (1), with *Z* representing a vector of the genetic instruments:

$$Smoke = \delta_0 + \delta_1 Z + \delta_2 X + \upsilon$$

(Ebrahim, Floyd, Merritt, et al.; Ebrahim, Floyd, Merritt II, et al. 2000)

The 2SLS model estimates the local average treatment effect of smoking on birth weight under well-known conditions(Angrist, Imbens, and Rubin 1996; Imbens and Angrist 1994). We conduct a Hausman test to determine if researchers should treat maternal smoking as endogenous (Hausman 1978). We describe below the genetic instruments.

B.1 Instrument selection in Norwegian Sample—In order to identify candidate genetic instruments, we evaluate 65 SNPs in neurotransmitter and detoxification genes that are considered to be candidate genes for nicotine dependence by the NICSNP Nicotine Project[11] and that have been genotyped in this sample[12]. We assess the SNP correlations

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[9]These expectations are based on maternal perceptions of the biologic and environmental risk factors that contribute to maternal and child's health (health. endowments). However, maternal risk perceptions and health endowments are inadequately measured in typically available datasets for birth outcomes studies, including the samples used in this study. The net bias in estimating the effects of smoking on birth weight by estimating equation (1) via OLS is a function of the average positive and negative biases in an available sample and cannot be signed a priori. For example, a potential mother may choose to smoke prior to pregnancy in part due to her perceptions of her health risks and how these risks might be affected by smoking. During pregnancy, the mother will decide to continue to smoke or not in part due to her perceptions of her health risks during pregnancy, of fetal health risks, and of the effect of smoking on these risks. Thus, a woman may decide to smoke during pregnancy in part because she considers herself to be healthy and considers that continuing to smoke will have no adverse effects on her and her child's health. In this case, unobservable indicators of health endowments that are positively correlated with both smoking and child health (such as no history of low birth weight in the family or in previous pregnancies, history of smoking without health problems in the family, and others) may result in an underestimation (positive bias) of the negative effects of smoking on birth weight. On the other hand, mothers who smoke are likely to have, on average, stronger preferences for current versus future consumption and are therefore more likely to engage in other unhealthy behaviors besides smoking, such as poor nutrition, lack of exercise, drug use, overall risk taking, and others. These factors likely have negative effects on birth weight. If some of the health behaviors correlated with smoking and birth weight are unobserved, as is typically the case in available datasets, the effects of smoking on birth weight may be overestimated (negative bias). The net bias in estimating the effects of smoking on birth weight is a function of the average positive and negative biases in an available sample and cannot be signed a priori.

[10]A few studies (Evans and Ringel 1999; Rosenzweig 1983) among others have used an IV strategy to account for self-selection into prenatal smoking. As we discuss above, the main contribution is to exploit a new source of variation generated by genetic instruments that vary at the individual level as opposed to group or state level instruments of tax rates.

[11]http://zork.wustl.edu/nida/Results/data1.html

[12]These were *GSTM1*, *UGT1A7*, *NAT1*, *NAT2*, *CYP2E1*, *CHRNA4*, *GSTT1*, *CYP2D6*, *GABBR2*, *GABRB3*, *DDC*, *GAD1*, and *KCNJ2*. We also consider SNPs in the gene *ACTN1* which has been identified in a recent GWA study of smoking and that have been genotyped in this sample (Caporaso et al. 2009).

with smoking using chi-square and ANOVA tests for smoking participation indicator and number of cigarettes, respectively.

SNPs in *NAT2*, *CYP2D6*, *GABBR2*, *GABRB3*, and *ACTH1* have a significant or marginally significant association with the smoking measures and are used as instruments.[13] Due to potential interactive effects between smoking and detoxification pathways genes on birth outcomes (Shi, Wehby, and Murray 2008), we estimate sensitivity analysis models that excluded *NAT2* and *CYP2D6* variants as instruments. The instruments include two binary indicators that represent the three genotypes of each of the relevant SNP in order to avoid any restrictive assumptions about the recessive or dominant effects of these genes and to allow for gene dosage effects.

B.2 Instrument selection in Add Health Sample—While the Norwegian data includes several candidate SNPS, the Add Health sample only contains six genetic markers that are in candidate genes for smoking, including the dopamine transporter (*DAT*), the dopamine D4 receptor (*DRD4*), the serotonin transporter (*5HTT*), monoamine oxidase A (*MAOA*), the dopamine D2 receptor (*DRD2*) and the cytochrome *P4502A6* (*CYP2A6*) gene. [14] Gene-gene interactions are likely important and a growing body of evidence is consistent with this notion. For example, Skowronek et al. (2006) suggest an interactive effect between *DRD4* and *5-HTTLPR* in predicting tobacco use(Skowronek et al. 2006). After examining the first stage properties of the genetic markers and consulting the medical literature, we use combinations between the *DRD2* and *MAOA*, the *DRD4* and *5HTT*, and the *MAOA* and *5HTT* genes as instruments for the analysis, which are described in Table 2.[15][16]

B.3 Instrument Validity and Alternative Estimations—Similar to other instruments, genetic instruments may suffer from certain limitations that should be acknowledged. One challenge in using genetic instruments is that they may correlate with other "physically near" genetic variants on the same chromosome that in turn are correlated with the unobserved confounders that impact the outcome (Lawlor et al. 2008).[17] However, we are aware of no such effects for the specific instruments employed in this study. Indeed, work by Fletcher and Lehrer (2009) find no evidence of linkage disequilibrium for the genetic variants used in our study. Another potential limitation is that genetic variants may also influence the study outcome through other pathways besides the endogenous variable due to

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[13]rs1041983 (*NAT2*), rs1930139 (*GABBR2*), rs1432007 (*GABRB3*), and rs4906908 (*GABRB3*) are correlated with smoking participation and are used as instruments. rs1041983 (*NAT2*), rs721398 (*NAT2*), rs1432007 (*GABRB3*), rs2059574 (*GABRB3*), rs5758589 (*CYP2D6*), rs2268973 (*ACTN1*) are correlated with the number of cigarettes and used as instruments. *NAT2* and *CYP2D6* are genes of detoxification pathways and have been implicated in several types of cancer including breast, prostate, bladder cancer, and others (Abdel-Rahman et al. 2000; Sanderson, Salanti, and Higgins 2007)) especially when combined with smoking and alcohol, though results are generally inconsistent across studies. Given that the study is limited to women of childbearing age and is focused on birth outcomes, it is unlikely that these variants affected the studied outcomes through their effect on cancer risks. *GABBR2* and *GABRB3* are genes that code receptors for the neurotransmitter GABA, which are involved in neurological inhibition. *GABBR2* has been implicated in smoking behaviors Previous studies of smoking genetics that included *GABRB3* did not report significant results t in coding for cytoskeletal proteins and has overall no well documented disease associations and functions, but a SNP in *ACTN1* has recently been found in a GWA study to be significantly related to a threshold indicator of number of cigarettes per day(Caporaso et al. 2009).

[14]All of these genes except for DRD4 are considered to be candidate genes for smoking by the NICSNP Nicotine Project. However, DRD4 have been linked in previous studies to smoking behaviors (Laucht et al, 2008; Hutchison et al. 2002). Comings et al. (1996) find an association between *DRD2* and smoking behavior, while Jin et al. (2006) find an association between *MAOA* and smoking behaviors, and Gerra et al. (2005) find an association between *5-HTT* and smoking behaviors(Comings 1996; Gerra et al. 2005).

[15]There is no consistent evidence in the literature for interactive effects between the genetic variants used as instruments in the analysis of the Norway sample. Therefore, we do not include interaction terms between these variants in the Norway sample analysis. Using binary indicators as instruments for the main effects of these genetic variants as done in the Norway data model is suboptimal as these indicators have insignificant effects, which weakens the first stage.

[16]Four new SNPs have recently been added to the Add Health data, but they were weaker predictors of smoking behaviors of pregnant women in our sample than those we use in this paper.

[17]This may occur due to the correlations between alleles that are tightly linked within a certain genomic area on a certain chromosome (referred to as linkage-disequilibrium).

the multi-functionality of certain genes and alleles(Lawlor et al. 2008). For example, it is possible that one or more of the employed instruments may impact birth weight through impacting unobserved behaviors or risk factors that are also related to birth weight. However, there is no current evidence that the specific employed instruments in this study are related to birth weight through such unobserved pathways.

There is no way to fully test that instruments, of any type, are truly exogenous due to the role of unobservables(Wooldridge 2002). Therefore, it is important to appeal to the theoretical strengths and genetics literature that motivate our use of genetic variants as instrumental variables. However, in order to further validate the extent to which the set of genetic instruments fit the IV assumptions, we employ the standard over-identification statistical test, which is a partial test of the extent to which instruments are truly excludable from the birth weight function. We also describe the sensitivity of our results to alternative instruments specifications as described above.[18]

One limitation that may be common with genetic instruments and that is relevant for our study is that instruments may have "weak" statistically significant effects on behaviors do to the complex etiology of behaviors that may involve multiple genetic and non-genetic risk factors. Instruments are generally considered to be weak if they have a joint F-statistic in equation (Ebrahim, Floyd, Merritt, et al.) less than 10 (Staiger and Stock 1997). In our analysis the F-statistics range from 3.3 to 4.4. In this case, weak-instrument robust confidence bounds are needed for accurate inference. Therefore, in addition to standard inference using the usual asymptotic standard errors, we estimate 95% confidence bounds that are robust for weak instruments using the conditional likelihood ratio (CLR) statistic, which has more statistical power than other tests (Finaly and Magnusson 2009; Andrews, Moreira, and Stock 2006). Furthermore, we also re-estimate the IV model using limited information maximum likelihood (LIML), which has been suggested to provide less biased estimates with weak-instruments compared to 2SLS (Stock, Wright, and Yogo 2002). Assuming that the instruments are exogenous (unrelated to unobserved confounders), weak-instruments tend to over-reject the over-identification restrictions (Hahn and Hausman 2003). Therefore, failing to reject the over-identification restrictions if instruments are exogenous is unlikely to be a result of weak instruments.

III. Results

A. Norway Sample

Table 3 below reports the OLS and the 2SLS coefficients of the birth weight production function in the Norway Sample.[19] Under OLS, smoking participation in the first trimester reduces birth weight by about 162 grams. The number of cigarettes smoked reduces birth weight by about 12.7 grams per cigarette (marginally significant).

Under 2SLS, smoking participation has a marginally significant and larger effect (in absolute value) on birth weight than under the OLS model. Smoking participation reduces birth weight by about 523 grams (p=0.075). However, the effect is not significant based on the 95% weak-instrument robust confidence bounds. A larger smoking effect (in absolute value) is observed under LIML, with a 614 gram decrease in birth weight (p=0.098), but the effect is insignificant based on the weak-instrument robust confidence bounds.[20]

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[18]See Fletcher and Lehrer (2009), Ding et al. (2006, 2009) and Norton and Han (2008) for other applications that use genetic markers as instruments. These studies use a similar approach to evaluate the instrument validity (Ding 2006; Ding et al. 2009; Fletcher and Lehrer 2009; Norton and Han 2008).

[19]Table A3 in the Appendix reports the full regression results along with the tests of the IV assumption and Table A4 reports the coefficients of the first stages of the 2SLS models.

[20]The exogeneity of smoking participation is not rejected based on a Hausman test (0.189)

Similar to smoking participation, the number of cigarettes has a larger and significant effect under 2SLS, reducing birth weight by about 46 grams (p=0.04).[21] The effect is significant based on the weak-instrument robust confidence bounds. The LIML cigarette effect is slightly larger than the 2SLS estimate, with a 52 gram birth weight decrease per cigarette (p=0.053), and the effect is significant using the weak-instrument robust confidence bounds.

The instruments have significant F statistics of 3.3 for smoking participation and 3.99 for the number of cigarettes. Over-identification tests fail to reject the validity of the instruments, with p values ranging from 0.5 to 0.8.

Table A5 in the Appendix reports the sensitivity analysis models in the Norway sample described above. The 2SLS estimates of smoking participation and cigarette effects on birth weight are larger (in absolute value) when the detoxification gene instruments are excluded. The same pattern of differences between OLS and 2SLS estimates is observed when daily smoking participation (smoking at least one cigarette per day) is used as the smoking measure, with a decrease of 612 grams in birth weight under the 2SLS model (p=0.056). The over-identification restrictions cannot be rejected under these sensitivity analyses.

B. Add Health Sample

Table 3 presents the OLS and 2SLS estimates of the effects of smoking in the Add Health sample.[22] Under OLS, mother's report of smoking during pregnancy reduces birth weight by over 150 grams. The 2SLS results suggest larger effects of smoking on birth weight than those indicated in our baseline specifications. Maternal prenatal smoking reduces birth weight by 587 grams (p-value<0.15).[23] The instruments have a first stage F-statistic of 4.4, and the over-identification test does not reject the excludability of the instruments from the birth weight function (p-value < 0.63).[24] A larger smoking effect (in absolute value) is observed under LIML, with a 617 gram decrease in birth weight (p=0.162) and an over-identification test of p=0.632.

VI. Discussion and Conclusion

The study provides the first empirical estimation of the effects of prenatal smoking on birth weight using a source of variation in smoking that is due to individual-level genetic instruments, unlike previous studies which mostly utilize area-level instruments. The findings suggest that standard OLS estimates may significantly underestimate the harmful effects of maternal smoking during pregnancy on birth weight. Specifically, smoking may reduce birth weight by as much as three times more than what is estimated using OLS.

It is important to acknowledge that the instruments are considered "weak" which complicates IV inference. However, the significant weak-instrument robust confidence bounds for cigarettes in the Norway sample and the similarity of the IV smoking participation effects between the two study samples even with different populations, smoking rates, and genetic instruments, provides support for the study results. Also, it is important to acknowledge that even if the instruments satisfy the over-identification tests at

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[21]The exogeneity of cigarettes is not rejected based on a Hausman test (p=0.107).

[22]Table A6 reports the full OLS and 2SLS regression results.

[23]The Add Health Wave IV data have recently been released. At a reviewer's request, we attempted to increase our sample by including the births that occurred between the two waves of data. While we were able to double our sample, the instruments were somewhat weaker in the larger sample, (F-stat <2). The point estimates were nearly identical to those in the tables (−570 in the large sample vs. −586 in this paper). The reason for the weaker instruments in the large sample are unknown but could be related to the composition of the new births, which are from older, more advantaged mothers. It appears that these genetic variants play a smaller role in the smoking decisions of these mothers.

[24]First-stage results are available in Appendix Table A7.

relatively high p-values, which provide statistical support excluding the instruments from the birth weight function, it is still possible that the instruments may be related to birth weight through other unobserved factors. If so, the IV estimates would be biased as they would be reflecting the effects of other factors besides smoking. However, there are some safeguards that provide assurance against a major potential bias. First, there is no apriori consistent evidence in the literature that the instruments we employ in the Norwegian data are not exogenous and that they affect birth weight through unobserved pathways. Second, we control for several behavioral and human capital factors that are expected to serve as good proxies for potential unobserved behavioral effects on birth weight that are related to the instrument. Third, we re-estimate the Add Health model adjusting for alcohol use during pregnancy and ADHD status, which have been associated with the instruments we employ in Add Health, and find no qualitative difference in our findings (results available upon request). Fourth, we also re-estimate the Add Health model adjusting for twin-birth status, given that the Add Health sample includes a higher-than-average proportion of twins. Both the OLS and 2SLS smoking effects are virtually unaffected by this adjustment[25]. Finally, the result insensitivity to alternative smoking measures and instrument specifications that are described above also provides support for the stability of the 2SLS estimates. Therefore, while it is still possible that the study findings are biased due to weak-instruments and the potential of the instruments may be related to birth weight through other factors besides smoking, the set of results as a whole provides are quite suggestive. As further knowledge becomes available on the functions of the genes that play a role in smoking, future studies become feasible to further evaluate these issues in selecting the instruments for smoking.

There is currently limited knowledge of what constitutes a causal genetic variant for smoking and several efforts are currently underway to identify causal variants. This study uses existing genotypic data which provides a cost-effective approach to study the smoking effects on birth weight using genetic instruments but imposes the limitation of being restricted to a certain set of candidate instruments. As discussed above, we select the instruments from variants in several genes that are commonly considered to be candidate genes for smoking, and some of which have been reported in more than one study to be associated with smoking (e.g. *GABBR2*). However, we are unable to evaluate other genes and variants as candidate instruments. Identifying causal variants for smoking behaviors will enable future studies to evaluate their utility as instruments for studying the effects of smoking on health outcomes. Further, this emphasizes the importance of replicating our study in future studies that use different samples and/or different variants.

The underestimation of OLS smoking effects is consistent with most previous IV studies that also find larger harmful smoking effects on birth weight under IV estimation (Evans and Ringel 1999; Grossman and Joyce 1990; Lien 2005; Permutt and Hebel 1989; Rosenzweig 1983). This may result from "favorable" self-selection into smoking based on unobservable factors that also affect birth weight. For example, a favorable history of pregnancy outcomes and infant health in the immediate and extended family of the mother may increase the propensity of the mother to smoke during pregnancy with the study infant, ceteris paribus, but may also improve the infant's birth weight through correlated unobserved genetic or social health endowments. Moreover, mothers whose parents smoked and had favorable health and pregnancy outcomes may be more likely to smoke themselves during pregnancy than mothers whose parents smoked and had unfavorable health and pregnancy outcomes. It is expected that the unobserved genetic or social endowments that contribute to better health and pregnancy outcomes in the first group of families may also contribute to improving the

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[25]In the Add Health models that adjust for twin-birth status, the smoking coefficient is −144 (marginally significant), −551 and −571 under OLS, 2SLS and LIML, respectively. The instrument effects on smoking are also virtually unaffected (F-statistic = 4.22). Further detailed results are available upon request.

birth weight of infants of mothers in this group compared to the second group. Unobserved maternal health characteristics may also contribute to favorable selection into smoking, conditional on the other determinants of smoking. Specifically, healthier mothers may be more likely to smoke during pregnancy compared to less healthy mothers due to their perceptions of low health risks. The underestimation of smoking effects on birth weight in OLS is similar to the underestimation of prenatal care effectiveness due to adverse maternal self-selection into prenatal care (Rosenzweig 1983; Wehby et al. 2009).

Biased maternal reporting of prenatal smoking status post delivery based on observed infant health and birth weight may also contribute to underestimation of the adverse smoking effects on birth weight. Specifically, mothers of infants with poorer birth outcomes may underreport their prenatal smoking status due to feelings of guilt, which would result in a positive bias in the OLS smoking effects. In both the Norway and Add Health samples, mothers reported their prenatal smoking status after delivery. However in the Norway sample, all mothers who report smoking at the time of their first prenatal visit also report smoking during the first trimester in the post-delivery survey (Lie et al. 2008). This provides some assurance against significant underreporting of smoking in the Norway sample based on observed birth weight.[26]

Other unobserved health factors such as maternal preferences for child health and risk taking which result in correlations between several maternal health and risk behaviors may result in a positive bias in OLS smoking effects. For instance, smoking mothers may also adopt less healthy behaviors during pregnancy (drug use, poor nutrition, less exercise, more stress). The net OLS bias is a function of the contribution of all unobserved factors, which may contribute differently to this bias, as described above. The study results suggest that conditional on the observed maternal behaviors and other production inputs that may influence the infant's birth weight, the net effect of unobservable factors results in a positive bias in OLS estimates.

We must also be aware of the issues of population stratification in studies that use genetic variants as instruments. While the Norwegian population is quite homogenous, the Add Health data comes from a representative sample of the US. In order to attempt to control for issues of population stratification, we adjusted the analyses for racial/ethnic group membership. Our sample size in the Add Health is far too small to report separate estimates for each racial group (65 blacks and 57 Hispanics), so we conducted auxiliary analyses for the sample of Caucasian mothers in our sample. The estimates were somewhat larger (−660 grams), statistically significant at the 10% level and had a first stage F-statistic of 5.2. Therefore, we place more weight on the results for Caucasian mothers in both samples and exercise caution in extrapolating the results to other populations until further evidence is available.

The used instruments represent variants in genes that are candidates for contributing to the etiology of smoking. Other genetic variants have been identified that also contribute to smoking behaviors. Unfortunately, many of these have not been measured yet in the available data samples for this study. In the future, we hope to replicate this study with other genetic instruments for smoking when they are measured. Studies using genetic instruments in other samples are also needed in order to gauge the sensitivity of the results to alternative samples and genetic specifications. The study supports the utility of employing genetic

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[26]The rates of smoking reported post delivery in the Norway sample were higher than those reported during the first prenatal visit. This may be due to some mothers stopping smoking before their first prenatal visit (around 10 weeks of pregnancy on average in this sample) or due to underreporting of smoking during prenatal visits) (Lie et al. 2008). Therefore, biased reporting of smoking cannot be completely ruled out as a potential contributor to underestimation of smoking effects by OLS in the Norway sample.

instruments to identify the effects of maternal smoking on infant health. Other maternal risk behaviors and health characteristics including alcohol use and obesity are also influenced by genetic factors, and previous studies have identified specific genetic variants that may contribute to their etiology. Therefore, genotyping these genetic variants in relevant data samples with maternal DNA is a major research priority in order evaluate the utility of these variants as instruments for maternal alcohol use and weight and in order to obtain accurate estimates of the effects of these risk behaviors on infant health outcomes.

The study results have major implications for developing public health policies to reduce the negative externalities of maternal smoking on child health. The study highlights the need for further public health efforts to increase the awareness of women of childbearing age about the harmful effects of smoking, which the current study suggests exceed previous findings. Further, the study suggests that taxation rates and smoking ban policies need to take into account a larger negative effect of smoking on child health that may also be carried into larger health risks and poorer socioeconomic outcomes during adulthood. Finally, the study supports the development of additional policy interventions that enhance early life investments in health beginning at conception and reduce maternal risk behaviors as these may have large individual and social health and economic returns.

Acknowledgments

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APPENDIX

Table A1

Distribution of study variables in the NCL analytical and excluded samples due to incomplete data

Variable	Mean (SD)	
	Analytical sample	Excluded Sample[e]
Birth weight	3646.64[**] (589.76)	3540.04 (585.64)
Smoking	0.32 (0.47)	0.32 (0.47)
Daily smoking	0.27 (0.44)	0.29 (0.45)
Cigarettes	1.83 (3.79)	2.36 (4.61)
Binge drinking in the first trimester[a]	0.05 (0.21)	0.06 (0.23)
Moderate drinking in the first trimester[a]	0.09 (0.29)	0.09 (0.28)
Low drinking in the first trimester[a]	0.18 (0.39)	0.14 (0.34)
Binge drinking before pregnancy[a]	0.38 (0.49)	0.4 (0.49)
Moderate drinking before pregnancy[a]	0.4 (0.49)	0.41 (0.49)
Low drinking before pregnancy[a]	0.13[*] (0.34)	0.09 (0.29)
Multivitamin use	0.38 (0.49)	0.34 (0.47)
Underweight[b]	0.03 (0.17)	0.05 (0.22)
Overweight[b]	0.19 (0.39)	0.18 (0.38)
Obese[b]	0.07 (0.25)	0.08 (0.26)
Calories	2281.19 (751.15)	2300.01 (928.38)
Maternal age	29.43 (4.7)	28.84 (4.91)
Married	0.53 (0.5)	0.53 (0.5)
Less than high school[c]	0.09[***] (0.28)	0.17 (0.37)
High school[c]	0.27 (0.44)	0.3 (0.46)
Technical college[c]	0.2 (0.4)	0.21 (0.41)
University[c]	0.07 (0.26)	0.04 (0.2)
Maternal employment	0.86 (0.35)	0.83 (0.37)
Very low maternal income[d]	0.34[*] (0.47)	0.41 (0.49)
Moderate maternal income[d]	0.25 (0.43)	0.2 (0.4)

Variable	Mean (SD)	
	Analytical sample	Excluded Sample[e]
High maternal income[d]	0.15 (0.35)	0.13 (0.34)
Pregnancy planning	0.74 (0.44)	0.71 (0.45)
rs1041983_ C/T	0.43 (0.5)	0.45 (0.5)
rs1041983_ C/C	0.49 (0.5)	0.36 (0.49)
rs1930139_ A/G	0.32 (0.47)	0.26 (0.44)
rs1930139_ G/G	0.05 (0.21)	0.11 (0.31)
rs721398_C/T	0.39 (0.49)	0.49 (0.51)
rs721398_C/C	0.07 (0.26)	0.07 (0.26)
rs5758589_A/G	0.49 (0.5)	0.5 (0.51)
rs5758589_G/G	0.25 (0.44)	0.24 (0.43)
rs1432007_A/G	0.52 (0.5)	0.56 (0.5)
rs1432007_G/G	0.26 (0.44)	0.24 (0.43)
rs2059574_A/T	0.47 (0.5)	0.52 (0.51)
rs2059574_T/T	0.34 (0.47)	0.36 (0.49)
rs2268973_A/G	0.4 (0.49)	0.36 (0.48)
rs2268973_G/G	0.52 (0.5)	0.48 (0.51)

[a] The reference category is no drinking.

[b] The reference category is normal weight (18.5≤BMI<25).

[c] The reference category is 2–4 years of college.

[d] The reference category is 151,000–200,000 kr.

[e] The distribution in the excluded sample for a certain variable is based on the observations that had data for that variable (these observations did not have complete data on all study variables). In the Norway sample, About 250 observations had data on non-genetic variables except for calories (about 200 observations). About 40–45 observations had data on the genetic instruments.

*, **, and *** indicate significant differences between the analytical and excluded

samples at p<0.1, 0.05 and 0.01 respectively.

Table A2

Distribution of study variables in the Add Health analytical and excluded samples due to incomplete data

Variable	Mean (SD)	
	Analytical sample	Excluded Sample[a]
Birth weight (grams)	3246 (556)	3260 (568)
Smoke During Pregnancy	0.17 (0.38)	0.17 (0.38)
Age (wave 1)	17.43 (1.64)	17.43 (1.6)
Male baby	0.51 (0.5)	0.52 (0.5)
Married at Birth	0.28 (0.45)	0.26 (0.44)
Black	0.21 (0.41)	0.3 (0.46)
Hispanic	0.19 (0.39)	0.16 (0.37)
Family Income (during adolescence)	36.0 (30.78)	35.58 (33.62)

Variable	Mean (SD)	
	Analytical sample	Excluded Sample[a]
Grandmother Education	12.45 (2.04)	12.56 (2.01)
No Health Insurance (wave 3)	0.25 (0.44)	0.22 (0.41)
Medicaid (wave 3)	0.26 (0.44)	0.26 (0.44)
Want Child Before Pregnancy	0.38 (0.49)	0.37 (0.48)

[a]N = 1691.

Table A3

Birth Weight Function Coefficients in Norway Sample

	OLS Smoking	OLS Cigarettes	2SLS Smoking	2SLS Cigarettes
Smoking	−161.7 ** (63.74)		−522.5 * (293.4)	
Cigarettes		−12.66 (8.256)		−46.21 ** (22.85)
Binge drinking in the first trimester	59.55 (137.2)	47.33 (137.8)	117.5 (147.7)	83.72 (148.8)
Moderate drinking in the first trimester	126.8 (91.89)	111.4 (91.35)	221.1 ** (112.8)	182.7 * (103.2)
Low drinking in the first trimester	96.64 (73.96)	84.51 (75.52)	156.3 * (89.16)	123.3 (80.79)
Binge drinking before pregnancy	−176.4 (112.3)	−210.0 * (111.8)	−71.88 (128.0)	−174.7 (112.6)
Moderate drinking before pregnancy	−69.72 (108.4)	−92.46 (108.9)	−34.73 (108.2)	−111.2 (111.1)
Low drinking before pregnancy	99.63 (119.3)	79.95 (119.6)	117.1 (117.4)	48.52 (122.3)
Multivitamin use	−90.13 * (53.56)	−91.43 * (53.74)	−101.5 * (55.86)	−108.4 ** (54.57)
Underweight	−257.6 ** (101.6)	−284.3 *** (100.6)	−197.5 (123.4)	−283.9 *** (103.8)
Overweight	107.9 * (61.65)	107.2 * (62.10)	116.5 * (61.90)	115.7 * (60.94)
Obese	77.52 (131.2)	67.65 (129.4)	108.3 (139.5)	77.98 (129.2)
Calories	0.0115 (0.0358)	0.00693 (0.0352)	0.0273 (0.0394)	0.0136 (0.0352)
Maternal age	10.65 (6.572)	10.35 (6.549)	12.28 * (6.787)	11.47 * (6.557)
Married	−68.63 (57.55)	−68.58 (57.38)	−93.70 (62.87)	−98.21 (62.44)
Less than high school	−2.996 (101.7)	−12.19 (103.7)	87.71 (129.6)	71.16 (122.6)
High school	62.46 (68.28)	50.23 (68.10)	105.6 (72.63)	69.02 (66.82)
Technical college	−92.98 (78.27)	−104.0 (78.33)	−38.16 (92.93)	−68.29 (81.38)
University	0.125 (105.9)	14.41 (107.9)	−9.110 (107.3)	41.32 (116.4)
Maternal employment	4.716 (81.44)	16.67 (81.98)	−49.57 (93.47)	−16.11 (85.36)
Very low maternal income	98.28 (69.89)	96.38 (69.72)	110.1 (71.17)	105.4 (69.56)
Moderate maternal income	−48.59 (79.60)	−49.23 (79.42)	−30.41 (78.32)	−29.36 (77.50)
High maternal income	−86.23 (101.5)	−83.38 (103.0)	−94.69 (102.9)	−85.87 (105.2)
Pregnancy planning	56.70 (61.52)	58.24 (62.15)	40.61 (61.70)	43.21 (61.58)
Constant	3408.6 *** (263.5)	3424.8 *** (263.9)	3394.8 *** (265.9)	3451.1 *** (261.2)
Instrument F statistic [df]			3.33 *** [8, 476]	3.99 *** [12, 472]
Over-identification Chisquare [df]			6.0 [7]	8.66 [11]
Wu-Hausman F Statistic [df]			1.66 [1, 482]	2.53 [1, 482]

Heteroscedasticity-robust asymptotic standard errors are in parentheses.

*
p< 0.1,

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Table A4

First Stage Regression Estimates in the Norway sample

	Smoking	Cigarettes
Binge drinking in the first trimester	0.172[*] (0.0960)	0.983 (0.776)
Moderate drinking in the first trimester	0.258[***] (0.0691)	2.320[***] (0.562)
Low drinking in the first trimester	0.171[***] (0.0529)	1.233[***] (0.426)
Binge drinking before pregnancy	0.300[***] (0.0767)	1.122[*] (0.620)
Moderate drinking before pregnancy	0.101 (0.0757)	−0.773 (0.614)
Low drinking before pregnancy	0.0192 (0.0860)	−1.204[*] (0.694)
Multivitamin use	−0.0424 (0.0402)	−0.605[*] (0.324)
Underweight	0.164 (0.114)	0.138 (0.922)
Overweight	0.00861 (0.0496)	0.214 (0.401)
Obese	0.0749 (0.0782)	0.271 (0.632)
Calories	0.00004 (0.00003)	0.0001 (0.0002)
Maternal age	0.00504 (0.00459)	0.0516 (0.0373)
Married	−0.0661 (0.0413)	−0.891[***] (0.334)
Less than high school	0.216[***] (0.0786)	2.172[***] (0.636)
High school	0.109[**] (0.0521)	0.507 (0.418)
Technical college	0.133[**] (0.0589)	0.953[**] (0.473)
University	−0.0235 (0.0842)	0.862 (0.681)
Maternal employment	−0.142[**] (0.0624)	−0.915[*] (0.506)
Very low maternal income	0.0410 (0.0524)	0.466 (0.425)
Moderate maternal income	0.0326 (0.0570)	0.342 (0.462)
High maternal income	−0.0245 (0.0709)	−0.166 (0.570)
Pregnancy planning	−0.0517 (0.0458)	−0.388 (0.371)
rs1041983_C/T	−0.109 (0.0717)	−1.029 (1.355)
rs1041983_C/C	−0.00760 (0.0713)	0.312 (1.499)
rs1930139_A/G	0.0782[*] (0.0415)	
rs1930139_G/G	0.0839 (0.0908)	
rs1432007_A/G	−0.0973[*] (0.0497)	−0.955[**] (0.404)
rs1432007_G/G	−0.0738 (0.0565)	−0.469 (0.463)
rs2268973_A/G	−0.157[**] (0.0746)	−0.563 (0.607)
rs2268973_G/G	−0.204[***] (0.0725)	−1.507[**] (0.591)
rs721398_C/T		1.077 (0.737)
rs721398_C/C		1.136 (1.593)
rs5758589_A/G		−0.116 (0.383)
rs5758589_G/G		−0.962[**] (0.436)
rs2059574_A/T		0.703[*] (0.414)
rs2059574_T/T		−0.618 (0.433)
Constant	0.226 (0.207)	2.164 (2.112)

Heteroscedasticity-robust asymptotic standard errors are in parentheses.

*
 p< 0.1,

Table A5

Sensitivity Analysis Models in the Norway sample

	Smoking 2SLS[a]	Cigarettes 2SLS[a]	Daily smoking 2LS[b]	Daily smoking OLS[b]
Smoking	−676.3* (358.0)			
Cigarettes		−57.45** (28.85)		
Daily smoking			−107.1 (68.07)	−612.2* (320.5)
Binge drinking in the first trimester	142.2 (159.9)	95.91 (156.2)	45.53 (136.1)	101.8 (150.0)
Moderate drinking in the first trimester	261.4** (126.0)	206.5* (110.0)	109.0 (92.90)	224.6** (112.5)
Low drinking in the first trimester	181.8* (96.85)	136.2 (84.30)	86.44 (76.24)	164.5* (91.70)
Binge drinking before pregnancy	−27.30 (142.9)	−162.9 (116.0)	−199.2* (112.1)	−85.61 (121.6)
Moderate drinking before pregnancy	−19.81 (112.2)	−117.5 (113.5)	−82.87 (108.1)	−70.96 (107.3)
Low drinking before pregnancy	124.5 (119.8)	37.98 (125.5)	91.85 (119.2)	92.06 (118.3)
Multivitamin use	−106.4* (57.86)	−114.1** (56.65)	−86.88 (54.01)	−95.63* (57.28)
Underweight	−171.9 (135.6)	−283.7*** (106.4)	−275.1*** (101.3)	−231.1* (124.3)
Overweight	120.2* (64.43)	118.5* (61.75)	104.4* (61.94)	106.2* (62.30)
Obese	121.4 (145.7)	81.44 (130.6)	72.68 (130.2)	114.8 (143.5)
Calories	0.0341 (0.0416)	0.0159 (0.0355)	0.00818 (0.0354)	0.0260 (0.0394)
Maternal age	12.97* (7.008)	11.85* (6.621)	9.970 (6.604)	10.18 (6.861)
Married	−104.4 (66.40)	−108.1* (65.53)	−66.77 (57.59)	−111.0 (68.41)
Less than high school	126.4 (144.2)	99.09 (132.7)	−17.47 (102.5)	106.0 (136.9)
High school	124.0 (77.86)	75.31 (67.78)	51.10 (68.48)	88.63 (73.30)
Technical college	−14.79 (101.2)	−56.31 (85.20)	−97.79 (79.61)	−4.656 (103.6)
University	−13.05 (111.2)	50.33 (122.0)	1.775 (106.2)	−9.955 (108.7)
Maternal employment	−72.71 (101.2)	−27.09 (88.11)	15.68 (81.90)	−47.34 (93.51)
Very low maternal	115.2 (75.38)	108.4 (70.80)	92.13 (69.99)	88.13 (74.23)
Moderate maternal	−22.66 (81.51)	−22.69 (78.59)	−53.50 (79.90)	−38.26 (80.82)
High maternal income	−98.30 (105.1)	−86.70 (107.3)	−88.63 (102.4)	−117.8 (112.3)
Pregnancy planning	33.75 (63.02)	38.17 (62.87)	59.28 (61.87)	37.43 (63.83)
Constant	3388.9*** (274.0)	3459.9*** (265.3)	3429.7*** (265.0)	3500.0*** (278.6)
F statistic [df]	2.88*** [6, 478]	4.52*** [6, 478]		3.18*** [8, 478]
Over-identification Chisquare [df]	4.59 [5]	7.1 [5]		4.74 [7]
Wu-Hausman F Statistic [df]	2.3 [1, 482]	2.98 [1, 482]		2.76* [1, 482]

Heteroscedasticity-robust asymptotic standard errors are in parentheses.

*
p< 0.1,
**
p< 0.05,
***
p< 0.01

[a] The detoxification gene (*NAT2* and *CYP2D6*) instruments are excluded.

[b] Women who smoked less than one cigarette per day on average are considered non-smokers (daily smoking defined as smoking 1 cigarette per day or more).

Table A6

Birth Weight Function Coefficients in Add Health Sample

	OLS	2SLS
Smoke During Pregnancy	−154.907 * (88.511)	−586.857 (409.118)
Age (wave 1)	0.035 (22.339)	3.286 (22.230)
Male Baby	120.112 * (65.475)	114.881 * (65.743)
Married at Time of Birth	67.252 (76.857)	7.854 (97.790)
Black	−81.584 (80.032)	−206.224 (126.365)
Hispanic	96.933 (103.675)	−8.166 (136.918)
Family Income	2.221 *** (0.730)	2.176 *** (0.669)
Maternal Education	3.820 (22.537)	−1.340 (23.379)
No Health Insurance (wave 3)	105.727 (74.230)	148.051 * (83.208)
Medicaid (wave 3)	31.645 (90.822)	58.944 (92.977)
Want Child	−34.866 (70.966)	−48.549 (71.466)
Constant	3,040.608 *** (572.485)	3,184.209 *** (636.250)
Observations	307	302
F-statistic [df]		4.353 *** [3, 301]
Over-identification Chisquare [df]		0.926 [3]
Wu-Hausman F Statistic [df]		0.82 [1, 289]

Heteroscedasticity-robust asymptotic standard errors are in parentheses.

***
$p < 0.01$

**
$p < 0.05$

*
$p < 0.1$

Table A7

First Stage Regression Estimations in the Add Health sample

Age	−0.012 (0.013)
Male Baby	−0.005 (0.042)
Married at Time of Birth	−0.119 ** (0.049)
Black	−0.233 *** (0.046)
Hispanic	−0.238 *** (0.048)
Family Income ($1000s)	0.002 (0.007)
Maternal Education	−0.017 * (0.010)
No Health Insurance (wave 3)	0.097 * (0.056)
Medicaid (wave 3)	0.078 (0.052)
Want Child	−0.016 (0.044)
$A1A2 \times MAOA4R1$	−0.101 ** (0.048)
$SL \times DRD4R1$	0.138 * (0.070)
$SL \times MAOAR2$	−0.150 *** (0.053)
Constant	0.713 ** (0.280)

Heteroscedasticity-robust asymptotic standard errors are in parentheses.

*
$p < 0.1$,

**
p< 0.05,
***
p< 0.01

Table 1

Distribution of Study Variables in the Norway sample (N=507)

Variable	Definition	Mean (SD)
Birth weight	Infant's birth weight in grams	3646.64 (589.76)
Smoking	Binary (0,1) indicator for smoking in the first trimester	0.32 (0.47)
Daily smoking	Binary (0,1) indicator for daily smoking in the first trimester	0.27 (0.44)
Cigarettes	Number of cigarettes per day smoked in the first trimester	1.83 (3.79)
Binge drinking in the first trimester[a]	Binary (0,1) indicator for ≥ 4 drinks per drinking occasion in the first trimester	0.05 (0.21)
Moderate drinking in the first trimester[a]	Binary (0,1) indicator for 2–3 drinks per occasion in the first trimester	0.09 (0.29)
Low drinking in the first trimester[a]	Binary (0,1) indicator for 1 drink per occasion in the first trimester	0.18 (0.39)
Binge drinking before pregnancy[a]	Binary (0,1) indicator for ≥ 4 drinks per drinking occasion in the last few years before pregnancy	0.38 (0.49)
Moderate drinking before pregnancy[a]	Binary (0,1) indicator for having 2–3 drinks per occasion in the last few years before pregnancy	0.4 (0.49)
Low drinking before pregnancy[a]	Binary (0,1) indicator for having 1 drink per occasion in the last few years before pregnancy	0.13 (0.34)
Multivitamin use	Binary (0,1) indicator for using multivitamins before and during the first two months of pregnancy	0.38 (0.49)
Underweight[b]	Binary (0,1) indicator for maternal BMI prior to pregnancy of less than 18.5	0.03 (0.17)
Overweight[b]	Binary (0,1) indicator for maternal BMI prior to pregnancy between 25 and 29.9 inclusive	0.19 (0.39)
Obese[b]	Binary (0,1) indicator for maternal BMI prior to pregnancy of greater than 29.9	0.07 (0.25)
Calories	Average daily calorie intake during the first trimester	2281.19 (751.15)
Maternal age	Maternal age in years	29.43 (4.7)
Married	Binary (0,1) indicator for married mothers	0.53 (0.5)
Less than high school[c]	Binary (0,1) indicator for maternal education of less than completed high school	0.09 (0.28)
High school[c]	Binary (0,1) indicator for maternal education of completed high school	0.27 (0.44)
Technical college[c]	Binary (0,1) indicator for mother attending technical college	0.2 (0.4)
University[c]	Binary (0,1) indicator for mother completing university education	0.07 (0.26)
Maternal employment	Binary (0,1) indicator for maternal employment in the first trimester	0.86 (0.35)
Very low maternal income[d]	Binary (0,1) indicator for current gross maternal yearly income of less than 150,000 kr	0.34 (0.47)
Moderate maternal income[d]	Binary (0,1) indicator for current gross maternal yearly income between 201,000 and 250,000 kr inclusive	0.25 (0.43)
High maternal income[d]	Binary (0,1) indicator for current gross maternal yearly income of 251,000 kr or more	0.15 (0.35)
Pregnancy planning	Binary (0,1) indicator for mothers who were planning to become pregnant	0.74 (0.44)
rs1041983_C/T	Binary (0,1) indicator of C/T genotype of rs1041983	0.43 (0.5)
rs1041983_C/C	Binary (0,1) indicator of C/C genotype of rs1041983	0.49 (0.5)
rs1930139_A/G	Binary (0,1) indicator of A/G genotype of rs1930139	0.32 (0.47)
rs1930139_G/G	Binary (0,1) indicator of G/G genotype of rs1930139	0.05 (0.21)

Variable	Definition	Mean (SD)
rs721398_C/T	Binary (0,1) indicator of C/T genotype ofrs721398	0.39 (0.49)
rs721398_C/C	Binary (0,1) indicator of C/C genotype of rs721398	0.07 (0.26)
rs5758589_A/G	Binary (0,1) indicator of AB genotype of rs5758589	0.49 (0.5)
rs5758589_G/G	Binary (0,1) indicator of BB genotype of rs5758589	0.25 (0.44)
rs1432007_A/G	Binary (0,1) indicator of AB genotype of rs1432007	0.52 (0.5)
rs1432007_G/G	Binary (0,1) indicator of BB genotype of rs1432007	0.26 (0.44)
rs2059574_A/T	Binary (0,1) indicator of A/T genotype of rs2059574	0.47 (0.5)
rs2059574_T/T	Binary (0,1) indicator of T/T genotype of rs2059574	0.34 (0.47)
rs2268973_A/G	Binary (0,1) indicator of A/G genotype of rs2268973	0.4 (0.49)
rs2268973_G/G	Binary (0,1) indicator of G/G genotype of rs2268973	0.52 (0.5)

[a] The reference category is no drinking;

[b] The reference category is normal weight (18.5≤BMI<25);

[c] The reference category is 2–4 years of college;

[d] The reference category is 151,000–200,000 kr.

Table 2

Distribution of Study Variables in the Add Health sample(N=307)

Variable	Definition	Mean (SD)
Birth weight	Infant's birth weight in grams	3246 (556)
Smoke During Pregnancy	Binary (0,1) indicator for smoking during the pregnancy	0.17 (0.38)
Age	Maternal age in years at wave 1 of the survey	17.43 (1.64)
Male baby	Binary (0,1) indicator for male gender of baby	0.51 (0.5)
Married at Birth	Binary (0,1) indicator for whether the mother was married at the time of birth	0.28 (0.45)
Black	Binary (0,1) indicator for whether the mother was black	0.21 (0.41)
Hispanic	Binary (0,1) indicator for whether the mother was Hispanic	0.19 (0.39)
Family Income	Income is $1000s of the mother's family during adolescence (wave 1 of the survey)	36.0 (30.78)
Grandmother Education	Years of completed schooling by the mother's mother reported at wave 1 of the survey	12.45 (2.04)
No Health Insurance (wave 3)	Binary (0,1) indicator for whether the mother reported having no health insurance at the time of birth	0.25 (0.44)
Medicaid (wave 3)	Binary (0,1) indicator for whether the mother reported Medicaid status at the time of birth	0.26 (0.44)
Want Child Before Pregnancy	Binary (0,1) indicator for whether the mother reported wanting to have a child at the time of the pregnancy	0.38 (0.49)
A1A2 × MAOA4R1	Binary (0,1) indicator for having the combination of heterozygous *DRD2* gene (43%) and one, 4-repeats of the *MAOA* gene (41%)	0.2 (0.4)
SL × DRD4R1	Binary (0,1) indicator for having the combination of short/long allele of the 5-*HTTLPR* gene (43%)and one, 7-repeats of the *DRD4* gene (38%)	0.14 (0.35)
SL × MAOAR2	Binary (0,1) indicator for having the combination of short/long allele of the 5-*HTTLPR*(43%)and two, 4- repeats of the *MAOA* gene (36%)	0.18 (0.38)

Table 3

Effects of Smoking on Birth Weight

Smoking Indicator	OLS	2SLS	LIML
		Norway Sample	
Smoking participation	−161.7 ** (63.74)	−522.5 * (293.4) [−1641.4, 228.1]	−614.4 * (371.5) [−1634.95, 219.5]
Number of cigarettes	−12.66 (8.26)	−46.21 ** (22.85) [−110.4, −5.0]	−52.3 * (27.02) [−110.5, −5.27]
		Add Health Sample	
Smoking participation	−154.907 * (88.511)	−586.857 (409.118) [−2134, 215]	−616.7 (440.255) [−2129, 191]

Heteroscedasticity-robust asymptotic standard errors are in parentheses. 95% weak-instrument robust confidence bounds for 2SLS and LIML are in brackets.

Each set of rows is from a separate regression

*
p< 0.1,

**
p< 0.05.