
The Interplay between Maternal Smoking and Genes in Offspring Birth Weight

© ↗ ⓘ

Rita Dias Pereira
Cornelius A. Rietveld
Hans van Kippersluis

ABSTRACT

It is well established that birth weight is affected by the child's genetic endowments and maternal smoking during pregnancy. Here, we investigate whether an interaction between genetic endowments and maternal smoking on birth weight exists. We instrument the maternal smoking decision with a genetic variant (rs1051730) located in the nicotine receptor gene CHRNA3 and deal with the underreporting of maternal smoking by using a biomarker of nicotine collected during pregnancy. We confirm that genetic endowments and maternal smoking negatively affect the child's birth weight. However, we do not find evidence of meaningful interactions between genetic endowments and maternal smoking.

Rita Dias Pereira is affiliated with Erasmus School of Economics, Erasmus University Rotterdam, and Tinbergen Institute (diaspereira@ese.eur.nl). Cornelius A. Rietveld is affiliated with Erasmus School of Economics, Erasmus University Rotterdam, Tinbergen Institute, and Erasmus University Rotterdam Institute for Behavior and Biology, Erasmus University Rotterdam. Hans van Kippersluis is affiliated with Erasmus School of Economics, Erasmus University Rotterdam, and Tinbergen Institute. The authors thank Andrew Jones, Stefanie Schurer, and participants of internal seminars, the DIAL conference, the Mendelian Randomization conference, and the European Health Economics Association conference, and two anonymous reviewers for providing valuable comments on earlier versions of this study. The authors thank Rachel Freathy and Robin Beaumont for sharing the birth weight GWAS summary statistics depleted of ALSPAC and UK Biobank. Ethical approval for the study was obtained from the ALSPAC Ethics and Law Committee and the Local Research Ethics Committees. The authors are extremely grateful to all the families who took part in this study, the midwives for their help in recruiting them, and the whole ALSPAC team, which includes

(continued on next page)

[Submitted October 2020; accepted May 2022]; doi:10.3368/jhr.1020-11266R2

JEL Classification: I100, and I140

ISSN 0022-166X E-ISSN 1548-8004 © 2025 by the Board of Regents of the University of Wisconsin System

© Color version of this article is available online at: <https://jhr.uwpress.org>.

↗ Supplementary materials are available online at: <https://jhr.uwpress.org>.

ⓘ This open access article is distributed under the terms of the CC-BY-NC-ND license (<https://creativecommons.org/licenses/by-nc-nd/4.0>) and is freely available online at: <https://jhr.uwpress.org>.

Rita Dias Pereira <https://orcid.org/0000-0002-0514-2118>

I. Introduction

Early life experiences matter. The fetal origins literature has convincingly established that a wide range of prenatal exposures, including stress, pollution, maternal risky health behaviors, and nutrition, have long-term consequences (Currie 2009; Almond and Currie 2011; Almond, Currie, and Duque 2018). Likewise, the behavior genetics literature has established that all relevant life outcomes are partially heritable, with the vast majority of outcomes being influenced by many genetic variants, each with a tiny effect (Turkheimer 2000; Chabris et al. 2015; Polderman et al. 2015). The current consensus is therefore that both genes and the environment are important, and the traditional nature versus nurture debate is obsolete (Turkheimer 2000; Heckman 2007). However, whereas it is repeatedly argued that life outcomes result from a complex interplay between genes and environment (Rutter 2006; Almond, Currie, and Duque 2018), estimations of the actual interaction between genes and the environment remain rare.

We move beyond the nature versus nurture debate by investigating how birth weight is influenced by the interaction between genes and a critical prenatal environmental exposure: maternal smoking. Birth weight is an important predictor of newborn and infant survival and is associated with later life health and outcomes such as cognitive development, educational attainment, and earnings (Black, Devereux, and Salvanes 2007; Royer 2009; Figlio et al. 2014; Bharadwaj, Lundborg, and Rooth 2018; Trejo 2020). As a consequence, it also affects health and socioeconomic outcomes of the next generation (Currie and Moretti 2007). Birth weight is the most commonly used barometer among pregnancy outcomes (Conti et al. 2018), and it comes with the advantage (compared to later-life outcomes) that its value is easily attributed to genes and environmental exposures in a specific period, that is, the time in utero.

Previous studies have convincingly established that genetic endowments influence the risk of being born with low birth weight (Horikoshi et al. 2013, 2016; Warrington et al. 2019). In [Online Appendix A.4](#), we replicate the evidence by Trejo (2020) that these genetic endowments for birth weight also affect later-life physical and cognitive outcomes in our analysis sample, showing that genetic variation provides a relevant source of variation in birth weight. Likewise, a body of literature points at maternal smoking during pregnancy as a significant and important determinant of birth weight

interviewers, computer and laboratory technicians, clerical workers, research scientists, volunteers, managers, receptionists, and nurses. The authors gratefully acknowledge funding from NORFACE under the Dynamics of Inequality (DIAL) programme (462-16-100). Research reported in this publication was also supported by the National Institute on Aging of the National Institutes of Health (R56AG058726) and the European Research Council (GEPSI 946647). The UK Medical Research Council and Wellcome (Grant ref: 217065/Z/19/Z) and the University of Bristol provide core support for ALSPAC. A comprehensive list of grants funding is available on the ALSPAC website (<http://www.bristol.ac.uk/alspac/external/documents/grant-acknowledgements.pdf>). This publication is the work of the authors, and they will serve as guarantors for the contents of this paper. This research has been conducted using confidential data from the Avon Longitudinal Survey of Parents and Children (ALSPAC) and the UK Biobank Resource under Application Number 41382. The data can be obtained by filing a request directly to the University of Bristol (<https://proposals.epi.bristol.ac.uk/>). UKB data are available by application via the UKB Biobank website (<https://www.ukbiobank.ac.uk/>). The authors are willing to assist (diaspereira@ese.eur.nl).

(Sexton and Hebel 1984; Kramer 1987a,b; Hamilton 2001; Ringel and Evans 2001; Bharadwaj, Johnsen, and Løken 2014; Lien and Evans 2005; Banderali et al. 2015; Simon 2016; Yang, Millard, and Smith 2020).¹ Our innovation compared with this literature is to study the *interaction* between genetic endowments and maternal smoking during pregnancy in determining the child's birth weight.

Estimating gene-by-environment ($G \times E$) interplay first and arguably foremost represents an advance in the fundamental understanding of how nature and nurture interact in shaping life outcomes (Biroli et al. 2022).² Second, the study of $G \times E$ interplay may help to identify environments or policies that reduce genetic disadvantage. For example, Barcellos, Carvalho, and Turley (2018) show how an educational policy reform reduced obesity, particularly for those with a high genetic risk, and both Fletcher (2012) and Slob and Rietveld (2021) show how tobacco control policies moderate genetic effects on smoking. These studies illustrate how $G \times E$ interplay analyses provide valuable and previously hidden information on whether interventions are helping particular groups of disadvantaged individuals (Raffington, Mallard, and Harden 2020). Finally, $G \times E$ interplay can shed new empirical light on theoretical predictions. A key prediction from the theory of human capital formation is “dynamic complementarity,” where later-life investments are complementary to higher values of the stock of human capital (for example, Cunha and Heckman 2007). Since birth weight is arguably the first realization of one's human capital, studying whether investments during pregnancy (for example, not smoking) exacerbate or compensate for genetic advantages can uncover properties of the production function for human capital.

Our main analysis sample comes from the Avon Longitudinal Study of Parents and Children (ALSPAC), a UK cohort study of children born in the early 1990s. The data are uniquely suited to answer our research question since both the mothers and their children are genotyped, a nurse administered the child's birth weight, and maternal smoking was not just self-reported but additionally biochemically validated using biomarkers. The main limitation of the ALSPAC data is that the sample is relatively small, with around 5,000 mother-child pairs for whom we observe both genotypes, and only around 2,500 mother-child pairs for whom the nicotine biomarker is available. Therefore, we additionally exploit data from the much larger UK Biobank. In this sample, we have to rely on some proxy and self-reported variables, but its size (around 250,000 individuals) makes it appealing to replicate our key findings.

1. See Mejdoubi et al. (2014) for an exception, where despite a modest reduction in cigarette smoking during pregnancy in an intervention group, no effects on birth outcomes were found.

2. We focus in our study on the impact of genes, that is, the sequence of molecules in the DNA, which does not change over the lifetime. There exists a related literature on how maternal smoking induces epigenetic expression in offspring (for example, Joubert et al. 2016). Epigenetics is the study of gene expression (active vs. inactive genes) that do not involve changes in the underlying DNA sequence. Epigenetic expression could be a mechanism through which the effect of maternal smoking arises, and additionally it provides a potential mechanism through which genes and the environment interact. However, because of possible behavioral adjustments of the mother or child during pregnancy, and because epigenetic expressions are often occurring at genetic loci that do not exhibit variation across humans, epigenetic expression alone is not a sufficient condition for the presence of gene-by-environment interactions in birth weight.

To proxy genetic endowments, we construct a polygenic score for birth weight using the results of the latest genome-wide association study (GWAS) on birth weight (Warrington et al. 2019). This polygenic score represents the best linear genetic predictor for birth weight and can be interpreted as one's genetic predisposition for high or low birth weight. In empirically establishing how the effect of maternal smoking differs by the child's genetic endowments, we have to address two commonly discussed issues with regards to smoking. First, relying on self-reported data about smoking is problematic given the stigma associated with this behavior. Especially during a pregnancy, it is likely that women misreport their smoking habits in surveys. To tackle this issue, we compare the self-reported measures of smoking with a measure of cotinine, a biomarker of nicotine, collected from the mothers while they were pregnant. This approach has been used before to determine actual smoking during pregnancy (Tappin, Ford, and Schluter 1997; Lindqvist et al. 2002) and to study the impact of smoking on newborns' health (Li et al. 1993; Wang et al. 1997). In our data, the prevalence of self-reported smoking is 22 percent, while 31 percent of the mothers had enough cotinine in their urine during their pregnancy to be considered active smokers. We show that in our data misreporting leads to overestimation of the effect of smoking, which suggests that mothers who smoke and report smoking are different from the ones who smoke but do not report smoking.

Second, smoking mothers are likely to be different from the nonsmoking mothers in many ways that we cannot account and correct for in a regular regression framework (for example, Bradford 2003). Possible factors include how careful they are during their pregnancy, if their pregnancy was planned, and how acquainted they are with the available prenatal care. All these factors are typically unobserved in survey data, and hence their omission from the regression model will bias the estimation of the effect of maternal smoking on children's outcomes. Some studies tackle this issue by exploiting variation in cigarette taxes across states (Evans and Ringel 1999), the introduction of smoking bans (Bharadwaj, Johnsen, and Løken 2014), or randomized nurse visits (Mejdoubi et al. 2014) as exogenous factors impacting smoking behavior during pregnancy. In this study, we instrument the number of cigarettes smoked during pregnancy with a genetic instrumental variable (IV): the genetic variant rs1051730 located in the nicotine receptor gene *CHRNA3* (Tyrrell et al. 2012; Wehby et al. 2012; Van Kippersluis and Rietveld 2018a; Yang, Millard, and Smith 2020). This so-called single nucleotide polymorphism ("SNP," pronounced "snip") has consistently been associated with the number of cigarettes smoked per day, also during pregnancy (Bierut 2010; Furberg et al. 2010; Liu et al. 2010), and its biological function is well understood. We find that this SNP is independent of maternal and paternal characteristics and that it consistently reduces offspring birth weight among mothers who smoke, but that it is unrelated to the child's birth weight among nonsmoking or former-smoking mothers. Together, these tests are consistent with the *intensity* of smoking being the single channel through which the IV affects the outcome.

Our IV analyses show that, on average, an extra cigarette per day during pregnancy reduces birth weight by 20–40 grams. These point estimates are considerably larger than the reduction of 9–14 grams we find in ordinary least squares (OLS) regressions. While our IV estimates could be biased upwards by the underreporting of smoking in the first stage (the effect of SNP rs1051730 on smoking), auxiliary

analyses suggest that even under extreme underreporting, the point estimates in the IV regression are still larger than in the OLS regression. Another explanation of why IV estimates could be larger than OLS estimates lies in the restrictive assumption that our IV (SNP rs1051730) exclusively influences smoking *during pregnancy*. While we present evidence that smoking during pregnancy is plausibly the dominant channel through which our IV influences birth weight, we cannot rule out that the IV also influences birth weight through smoking-induced health problems or assortative mating pre-pregnancy. This provides an alternative explanation for why the IV estimates are somewhat larger than our OLS estimates and also warrants a prudent interpretation of our findings as the effect of *prenatal* smoking as opposed to smoking during pregnancy only. Nevertheless, our estimates corroborate earlier findings that prenatal maternal smoking reduces birth weight and go beyond earlier findings in carefully assessing the sign and magnitude of the bias due to the misreporting of smoking.

Despite the robust negative relationship between maternal smoking and birth weight, we do not find evidence of significant heterogeneity in the effect of maternal smoking on birth weight by the child's genetic predisposition for birth weight. While in ALSPAC the confidence interval of the interaction term does not rule out sizable heterogeneity, our replication analysis in the UK Biobank provides a rather precisely estimated zero for the interaction effect. Our results therefore suggest that maternal smoking as well as genetic endowments influence birth weight in an additive fashion, and there is no meaningful moderation effect of one on the other. In other words, even a strong genetic predisposition for high birth weight does not cushion the negative effects that maternal smoking during pregnancy bring about.

Our study contributes to at least two streams of literature. First, it contributes to the literature on the effects of maternal smoking on offspring birth weight (for example, England et al. 2001; Tappin et al. 2015). Low birth weight is strongly associated with worse later-life health and socioeconomic outcomes, and maternal smoking has been identified as the most significant modifiable risk factor for the incidence of low birth weight in developed countries (Kramer 1987a,b; Almond, Chay, and Lee 2015). We contribute to this literature by exploiting the unique features of the ALSPAC data that enable us to simultaneously address the underreporting and endogeneity of maternal smoking. In doing so, we obtain a more reliable estimate of the average reduction in birth weight as a result of maternal smoking. Moreover, we are the first to investigate treatment effect heterogeneity related to the child's genetic predisposition for low birth weight.³ Heterogeneity of treatment effects by genotype is not merely important to better understand differential responses to maternal smoking, but additionally has important intergenerational implications. If the effect of maternal smoking consistently affects certain groups with a specific genetic predisposition more,

3. There is, however, one study analyzing heterogeneity in the effect of maternal smoking on the child's birth weight by *maternal* genotype (Wang et al. 2002), but this study focuses on maternal rather the offspring genotype, relies on specific maternal candidate genes rather than a polygenic score, and does not take into account the endogeneity of maternal smoking decisions. Moreover, Trejo (2020) analyzes interactions between the *child's* polygenic score for birth weight and maternal socioeconomic status and BMI, but does not take into account the endogeneity of these maternal characteristics.

then these effects will propagate through generations, potentially increasing inequalities in future generations.

A second literature to which we contribute is a still small but emerging literature analyzing $G \times E$ interactions by exploiting exogenous environmental exposures (Biroli et al. 2022). Whereas $G \times E$ studies have been around for a long time in the medical and social sciences, estimating meaningful interactions is often prohibited since genes and the environment tend to be correlated. For example, individuals with certain genetic predisposition may self-select into certain environments, and parental genes are not just transmitted to children but additionally shape the rearing environment for their children (Kong et al. 2018). These sources of so-called gene–environment correlation pose a threat to the identification of $G \times E$ and can only be tackled using exogenous variation in environmental exposures. Here we instrument the environmental exposure maternal smoking by a maternal genetic variant, and we show that this genetic variant is independent of the child's genetic predisposition for birth weight. As such, by exploiting exogenous variation in the environmental exposure, we contribute to the literature seeking to improve our understanding of the interplay between genes and the environment in shaping life outcomes (for example, Schmitz and Conley 2017; Barcellos, Carvalho, and Turley 2018).

The remainder of our study is organized as follows. The next section describes our main data set, ALSPAC, and the variables we utilize from it. In Section III, we detail our identification strategy. In Section IV, we present our main empirical results, including a number of sensitivity analyses. Section V present the results of our replication study in the UK Biobank. The final section discusses our findings and concludes.

II. Data

In this section, we introduce our main data set, and we define and operationalize the variables used in our analyses.

A. *The Avon Longitudinal Study of Parents and Children*

The Avon Longitudinal Study of Parents and Children (ALSPAC) is a prospective and longitudinal study of children and parents (Boyd et al. 2013; Fraser et al. 2013). The data collection started during pregnancy with the aim to monitor children from fetal life through infancy into adolescence and young adulthood. All mothers residing in Bristol, Avon, United Kingdom, with an expected delivery date between April 1, 1991 and December 31, 1992, were eligible to take part in ALSPAC. The mothers and their partners were recruited for the study soon after the confirmation of the pregnancy. Details of their social background, attitudes towards healthcare, and psychological well-being were obtained by self-completion questionnaires. The clinical course of pregnancy and childbirth were recorded from medical case notes. A total of 14,541 eligible pregnant women were enrolled at baseline. From these pregnancies, 13,988 children were alive at 12 months of age. Maternal blood and urine were collected during pregnancy, and the same samples were later collected from their

children. Finally, both mothers and their children were genotyped. The data set comprises 9,115 genotyped mothers and 9,048 genotyped children. Fraser et al. (2013) provide more details about this study.⁴

Our analysis of the average treatment effect of maternal smoking is restricted to a baseline sample of 7,598 mother–child pairs, which corresponds to pairs with information about the maternal genotypes, as well as about the outcome and main explanatory variable (the number of cigarettes smoked per day). We call this Baseline Sample 1. To study the heterogeneous effects of maternal smoking we further restrict Baseline Sample 1 to mother–child pairs with nonmissing child genotypes, which leaves us with 5,006 mother–child pairs. This constitutes Baseline Sample 2. Additional analyses further restrict the sample to mother–child pairs for which the mother supplied a urine sample. Cotinine measurements in this subsample are used to correct smoking misreporting.

B. Variables

1. Outcome variable

The main outcome of interest in our study is birth weight of the child. The weight was obtained from routine hospital birth records. We restricted our analyses to children alive at one year of age, which corresponds in our sample to the exclusion of babies with a birth weight of less than 640 grams. Table 1 shows that for the 7,598 children in our first baseline sample the mean birth weight is 3,406 grams.

2. Main explanatory variables

The main environmental explanatory variables are measures for maternal smoking. We use a binary indicator for regularly smoking during pregnancy, as well a continuous variable reflecting the intensity of smoking in terms of the average number of cigarettes smoked per day during pregnancy. Given that our proposed instrumental variable is more closely associated with the number of cigarettes per day rather than the binary indicator of smoking (see Section III below), most of our analyses will be based on the intensive margin (that is, the number of cigarettes smoked per day). Both variables are self-reported. However, we correct for self-reporting by considering the levels of cotinine in urine collected from the mothers when they were pregnant.

Smoking regularly: At 18 weeks of gestation women were asked to report whether they smoked regularly or not during the first three months of their pregnancy. Table 1 shows that 22 percent of mothers classified themselves as regular smokers.

Number of cigarettes smoked per day: During their pregnancy, women were asked to report the number of cigarettes per day they smoke presently. The timing varied from as early as eight to 42 weeks of gestation. Table 1 shows that the average number of cigarettes smoked per day is 2.02. This number reflects both smokers and nonsmokers. The average number of cigarettes smoked per day among smokers is 10.80 (not shown).

4. ALSPAC's study website contains details of all the available data through a fully searchable data dictionary and variable search tool; see <http://www.bristol.ac.uk/alspac/researchers/our-data/> (accessed September 12, 2024).

Table 1
Descriptive Statistics of the Main Analysis Sample (ALSPAC)

	Mean	SD	Min.	Max.	<i>N</i>
Outcome Variable					
Birth weight (grams)	3,406.24	556.60	703	5,600	7,598
Main Explanatory Variables					
Smoking regularly	0.22	0.42	0	1	7,417
Smoking regularly (adjusted)	0.31	0.46	0	1	2,777
Number of cigarettes smoked per day	2.02	5.09	0	51	7,598
Number of cigarettes smoked per day (adjusted)	4.96	6.64	0	51	3,784
Cotinine (ng/mL)	743.76	1,923.57	0	24,674	2,844
Birth weight PGS (child)	0.00	1.00	-3	3	5,006
Instrumental Variable					
rs1051730	0.67	0.67	0	2	7,598
Control Variables					
Mother's birth weight (grams)	3,269.01	601.43	909	6,108	4,541
Mother's age (years)	28.47	4.66	15	44	7,598
Mother's marital status (married = 1)	0.78	0.41	0	1	7,540
Mother's education (categories)	3.65	1.61	0	6	5,484
Mother's social class (categories)	2.85	1.07	1	6	6,141
Grandmother's education (categories)	2.45	1.29	1	5	4,267

Notes: SD, standard deviation; Min., minimum; Max., maximum; PGS, polygenic score.

Cotinine: During the first three months of pregnancy, a urine sample was collected and tested for cotinine. Cotinine is the predominant metabolite of nicotine (Langone, Gjika, and Van Vunakis 1973) and is used as a biomarker for exposure to tobacco smoke. While nicotine has a half-life of about two to three hours—meaning that two hours after ingestion, half of the nicotine disappears from one's body—cotinine has a half-life of approximately 12–20 hours (Kim 2016). This implies that cotinine remains in the body for a much longer period than nicotine, which is the typical test substance in standard tobacco tests. However, there is no consensus on the most appropriate threshold for identifying active smokers from cotinine data. We choose to reclassify women with high cotinine levels during pregnancy as active smokers using a reasonable yet conservative threshold of 100 ng/mL. In [Online Appendix A.1](#), we provide an in-depth discussion about cotinine thresholds.

Smoking regularly (adjusted): This variable is created by recoding the *Smoking regularly* measure. Mothers are reclassified as smokers if they have more

than 100 ng/mL of cotinine in their urine. Compared to the self-reported measure, we classify 31 percent instead of 22 percent of the mothers as smokers (see Table 1).⁵

Number of cigarettes smoked per day (adjusted): This variable is created by (i) assuming that people who reported a positive number of cigarettes during pregnancy reported their smoking behavior truthfully (this assumption is relaxed in Section IV), (ii) running a simple OLS regression between the number of cigarettes and the value of cotinine in urine for those who reported to have smoked a positive number of cigarettes, and (iii) predicting the number of cigarettes based on that regression for the ones who claimed to have smoked zero cigarettes but had a cotinine value higher than 100 ng/mL. According to this adjustment, the mean number of cigarettes smoked per day is 4.96 instead of 2.02 (Table 1). Again, this number reflects the number of cigarettes smoked by smokers and nonsmokers. The average adjusted number of cigarettes smoked per day among smokers is 10.55.

Polygenic score for birth weight: The other main explanatory variable of interest—the variable that we use to interact with the maternal smoking variables—is the child’s polygenic score (PGS) for birth weight. Recent advances in genetics, such as the completion of the Human Genome Project in the early 2000s and the advent of inexpensive genotyping chips, have made it possible to identify linkages between a person’s genetic endowments and important life outcomes, such as health and socioeconomic status (Beauchamp et al. 2011; Visscher et al. 2017). Due to these advances, it is now possible to construct credible measures of “nature” for many traits; those measures are called polygenic scores.

The human genome consists of more than 3.2 billion nucleotides located on 23 pairs of chromosomes (Lehrer and Ding 2017). These nucleotides come in four varieties: adenine (A), guanine (G), cytosine (C), and thymine (T). Approximately 99.6 percent of the nucleotides are identical between two randomly selected individuals (Kidd et al. 2008). However, there are particular positions in the genome where individuals can have different nucleotides. The most common type of such genetic variation is called a single nucleotide polymorphism (SNP), and SNPs constitute the main source of genetic differences between individuals. At each SNP location there can be two different nucleotides. It is common to measure SNPs by counting the number of minor alleles (the nucleotide that occurs least frequently in the population) that an individual carries. Hence, a SNP can take the values 0, 1, or 2. Taking the minor or major allele as reference is to some extent arbitrary but does not affect downstream analyses. However, summing up the number of reference alleles is common because virtually all genetic variants contribute additively to genetically influenced traits (Pazokitoroudi et al. 2021). There are approximately 85 million SNPs in the human genome with a minor allele frequency >1 percent (1000 Genomes Project Consortium 2015). In some rare cases, a difference at a specific locus on a chromosome can single-handedly lead to a disease; Huntington’s disease is an example. However, the vast majority of human (behavioral) traits are polygenic, meaning they are influenced by multiple genetic polymorphisms with each having a tiny effect

5. The self-reported smoking prevalence in the subsample for which we have cotinine measurements is 20 percent.

(Chabris et al. 2015). A polygenic score is constructed by adding up the individual SNPs, where each SNP is weighted by the strength of the association between the SNP and the outcome variables as estimated in a GWAS (Dudbridge 2013). The underlying rationale is that based on GWAS results, you can assign weights of relative importance to each SNP. Then, with a polygenic score (PGS), one can exploit the joint predictive power of multiple SNPs for a particular outcome.

The predictive power of PGSs increases with the sample size of the underlying GWAS (Dudbridge 2013). Therefore, meta-analysis techniques are used to make GWASs as large as possible (Visscher et al. 2017). However, to avoid overfitting in PGS analyses, it is necessary to exclude the prediction sample from the GWAS meta-analysis used to construct the PGS. Therefore, in our study, we used the summary statistics of Warrington et al. (2019) to retrieve the relevant SNPs and their weights. Importantly, ALSPAC was excluded from this meta-analysis. The weights were subsequently corrected for linkage disequilibrium (LD; structural correlation across SNPs in the genome) using the software LDpred (Vilhjálmsón et al. 2015). The resulting PGS is a continuous measure that represents the propensity to be born with a high birth weight as determined by the child's genotypes. This measure was standardized in such a way that the mean is zero and the standard deviation is one in the analysis sample. [Online Appendix A.2](#) and [Online Appendix A.3](#) present more details about the genotyping procedure and construction of the PGS. Importantly, SNP rs1051730 (and SNPs in the same genetic region) were excluded from the polygenic score because we use this SNP as our instrumental variable (see Section 3 and [Online Appendix A.7](#)).

Figure 1 shows that, despite a lot of individual variation, the PGS for birth weight predicts actual birth weight in our sample. This figure also suggests that a linear relationship between the variables provides a reasonable fit with the data. The difference between the bottom and top decile of the PGS is around 400 grams in birth weight, and we can explain around 4.8 percent of the variation in birth weight with the PGS.

3. Instrumental variable

As we will elaborate on in the next section, we instrument the number of cigarettes smoked per day with a SNP of the mother, namely SNP rs1051730, which is located in the nicotinic receptor gene *CHRNA3*. This genomic region located in the chromosome 15 cluster of virtually adjacent nicotinic receptor genes (*CHRNA3*, *CHRNA5*, and *CHRNA4*) was identified in all genome-wide association studies of smoking as a risk factor for the intensity of smoking defined by the number of cigarettes smoked per day (for example, Furberg et al. 2010; Liu et al. 2019). Both the *CHRNA3* and *CHRNA5* genes are expressed in regions of the human brain involved in, among others, reward and emotion (Berrettini 2013). Our variable rs1051730 is equal to zero if the mother carries no adenine (A) nucleotide for SNP rs1051730, one if the mother carries one A nucleotide, and two if the mother carries two A nucleotides. The adenine nucleotide of rs1051730 has consistently been associated with an increased number of cigarettes consumed per day. In our baseline sample, 45 percent

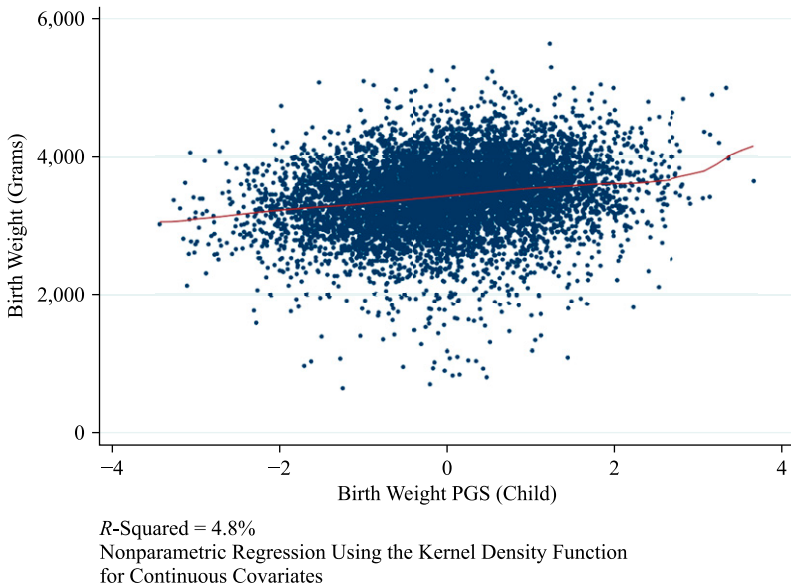


Figure 1

Relationship between Birth Weight and the Polygenic Score (PGS) for Birth Weight in ALSPAC

Notes: Estimated using a nonparametric regression with a kernel density function for continuous covariates.

of mothers do not carry any A nucleotides for this SNP, 44 percent have one A nucleotide, and the remaining 11 percent of the mother carry two reference alleles.

4. Control variables

Although we exploit random-like and exogenous variation that only influences the number of cigarettes smoked by the mother, we include some control variables for three reasons. First, we would like to compare our IV results to the results of an ordinary OLS regression with control variables. Second, the control variables act as a sensitivity analysis for our IV regression. Since an instrumental variable should not be correlated with the control variables, including the control variables should not change the coefficient of interest. Third, including control variables that explain some of the variation in the outcome could help to increase precision. The control variables only involve characteristics of mother and grandmother, as these are the only variables possibly preceding offspring genetic endowments and birth weight. They include maternal birth weight, maternal age, maternal marital status, maternal education, maternal social class, and grandmother's education (see [Online Appendix A.6](#) for definitions and Table 1 for descriptive statistics). All control variables are included as (and when necessary transformed into) categorical variables with a dummy for each category, including a category for missing values (see [Online Appendix A.6](#) for details). Finally, the first four principal components of the mother's genetic relationship matrix are included to

control for subtle forms of “population stratification,” that is, systematic relationships between the prevalence of genetic variants and environments in subpopulations (Price et al. 2006; Rietveld et al. 2014). We also included the offspring sex in our analyses as a sensitivity analysis, and the results were very similar.⁶

III. Identification Strategy

Our interest is in the effect of the number of cigarettes smoked per day during pregnancy (C_M) on the child’s birth weight (B_C). Note that we use the subscript C to denote the child’s variables and the subscript M to denote those of the mothers. A conventional OLS regression of the form

$$(1) \quad B_C = \alpha + \beta C_M + X'_C \lambda_C + X'_M \lambda_M + \varepsilon$$

where X_C and X_M represent the child’s and maternal control variables as defined in Section II, respectively, is unlikely to produce an unbiased coefficient β . As already touched on, the number of cigarettes smoked per day C_M is subject to endogeneity concerns as a result of measurement error and omitted variables. To address the endogeneity of maternal smoking during pregnancy arising from omitted variables, we resort to an instrumental variable (IV) approach. In particular, we instrument the average number of cigarettes smoked per day C_M with SNP rs1051730, which has been consistently linked with smoking intensity (for example, Furberg et al. 2010; Liu et al. 2019) while being plausibly exogenous to offspring birth weight. The application of genetic instrumental variables is often referred to as Mendelian Randomization (Smith 2003; Von Hinke et al. 2016).

In terms of equations, our identification strategy is therefore as follows. We use the following two equations:

$$(2) \quad B_C = \alpha + \beta \hat{C}_M + X'_C \lambda_C + X'_M \lambda_M + \varepsilon$$

$$(3) \quad C_M = \gamma + \delta Z_M + X'_C \psi_C + X'_M \psi_M + \eta$$

where Z_M denotes maternal SNP rs1051730 used as instrumental variable, and ε and η denote the error terms. A causal interpretation of the resulting two-stage least squares (2SLS, or Mendelian randomization) estimates relies on three critical assumptions (see for example, Von Hinke et al. 2016), which we discuss in detail below.

First, our instrumental variable should have a strong effect on the endogenous variable of interest: $\delta \neq 0$. Several GWAS studies have robustly replicated the association between SNP rs1051730 and smoking intensity (Furberg et al. 2010; Liu et al. 2010, 2019). This SNP is known colloquially among researchers as “Mr. Big” because of its consistently estimated large effect size.⁷ In our sample, as we will show below, the first-stage estimate is positive and statistically significant, with the effective F -statistic values consistently in the range 15–25. Therefore, the relevance

6. Results are available upon request.

7. Sometimes, SNP rs16969968 is used instead of SNP rs1051730, as these SNPs are in almost perfect linkage disequilibrium with each other, meaning that they are almost perfectly correlated in the human genome.

assumption seems to hold for our instrument (Olea and Pflueger 2013; Andrews, Stock, and Sun 2019).

Second, our instrumental variable should be independent of confounding factors. An important advantage of using genetic variants as instruments is that they are randomly distributed at conception, conditional on population stratification variables, or, more stringently, parental genotype or family fixed effects. Therefore, the independence assumption is likely to hold when using SNPs as instruments (Smith et al. 2007), in particular in our ALSPAC sample, which is a very homogeneous sample from a relatively small geographic area. Moreover, we focus on mothers from European ancestry only, and thus a correlation between smoking-related genetic variants and the error term of the outcome Equation 2 is unlikely. Although not a proof, it is reassuring that our instrumental variable is not correlated to any of the background variables of the mother or child (see Section IV). Naturally, there is a mechanical correlation between the maternal SNP and the child's polygenic score for birth weight since the child's polygenic score for birth weight includes all SNPs, including rs1051730. The correlation between the SNP and the polygenic score for birth weight is, however, very modest and statistically insignificant since this SNP only represents one out of many SNPs in the polygenic score (see [Online Appendix A.7](#) for details). Still, in our main analyses we exclude the entire genetic region in which SNP rs1051730 resides from the polygenic score for birth weight such that the maternal SNP and the child's polygenic score are orthogonal. However, all of our results are insensitive to whether we include or exclude this specific linkage disequilibrium (LD) region from the polygenic score.⁸

Third, our instrumental variable is only allowed to impact the child's birth weight through maternal smoking. The so-called exclusion restriction is the most challenging one when employing genetic variants as instrumental variables as typically the biological function of a certain gene is not completely known and one cannot rule out so-called "biological pleiotropy"—that is, the same SNP affecting multiple outcomes (Lawlor et al. 2017). The main advantage of using SNP rs1051730 is that its biological function is well understood. It is known to cause an amino acid change in the alpha-5 subunit of the nicotinic receptors, and experiments have found that this change alters the responsiveness of the nicotinic receptors to nicotine (Bierut and Cesarini 2015). Hence, the SNP relates to nicotine dependence and the channel through which the SNP affects children's outcomes is plausibly maternal smoking. In accordance with this mechanism, when we stratify the sample according to whether the mother smoked during pregnancy (for example, Van Kippersluis and Rietveld 2018a,b), we do find a strong association between our IV and birth weight among smoking mothers, whereas there is no significant relationship among nonsmoking or former-smoking mothers. Even though the stratification into these subgroups may be endogenous, we believe this result (shown in Section IV.B) is reassuring and suggests that the exclusion restriction holds in our model.

Although instrumenting the average number of cigarettes smoked per day during pregnancy with our genetic instrument goes a long way in tackling the endogeneity of maternal smoking, there are still two issues with employing the IV in a 2SLS

8. Results are available upon request.

setup. First, while we are confident that our SNP solely affects maternal smoking, we cannot rule out an effect of pre-pregnancy smoking on offspring birth weight through, for example, mother's health or assortative mating. Second, since our cotinine measures are limited to 2,844 observations from the first trimester only, the possible misreporting of smoking affects our first stage and hence 2SLS results. Therefore, our main analyses are based upon the reduced form of the 2SLS approach (that is, the intention-to-treat effect of the SNP on offspring birth weight):

$$(4) \quad B_C = \tau + \kappa Z_M + X'_C \pi_C + X'_M \pi_M + \sigma$$

The reduced form does not rely on the possibly biased self-reported smoking measures, and a significant coefficient κ is a necessary condition for a causal effect of the instrumented variable (maternal smoking) on the outcome (birth weight). Still, we also present 2SLS results using various measures of maternal smoking in the first stage, to assess what a reasonable first stage (denominator) would be to scale our reduced form (numerator) effects into a plausible 2SLS estimate.

In order to assess the interaction between genes—as measured by the child's PGS for birth weight—and maternal smoking, we amend our Regressions 2, 3, and 4 by including a linear interaction term between the maternal SNP and the child's polygenic score.⁹ Additionally, we estimate Models 2, 3, and 4 separately for four quartiles of the PGS for birth weight to allow for possible nonlinearities in the interaction between the child's genes and maternal smoking.

IV. Results

In this section we present our main empirical results. We start by discussing the results of the conventional OLS regressions. Thereafter, we discuss the IV results using the maternal SNP as instrumental variable and assuming homogeneous effects. Finally, we turn our attention to the heterogeneity analyses using interaction terms between the PGS for birth weight and maternal smoking and using stratification by quartiles of the child's PGS for birth weight.

A. OLS Regression Results

Table 2 presents the results of OLS regressions in which the child's birth weight (in grams) is the outcome variable, and the number of cigarettes smoked per day is the explanatory variable. All specifications consistently show a statistically significant association between the number of daily cigarettes smoked by the mother and the child's birth weight, with every daily cigarette smoked associated with a reduction between 8 and 15 grams in birth weight. The coefficient of the PGS for birth weight is stable across specifications and statistically significant at the 1 percent level. Every

9. In the reduced form, therefore, we effectively interact the maternal SNP with the child's PGS, which constitutes a so-called gene–gene ($G \times G$) interaction. However, since we provide evidence below that plausibly the single channel through which the maternal SNP impacts the child's outcomes is maternal smoking during pregnancy, this $G \times G$ interaction effectively reflects a gene–environment ($G \times E$) interaction.

Table 2
Results of the OLS Regressions Explaining the Child's Birth Weight in ALSPAC

	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)
#Cigarettes smoked per day	-14.8** (1.3)	-12.7** (1.3)	-13.4** (1.7)	-13.7** (1.7)				
#Cigarettes smoked per day (adjusted)					-12.0** (1.3)	-8.3** (1.5)	-9.4** (1.8)	-9.5** (1.8)
Birth weight PGS (child)			108.2** (7.0)	104.6** (7.4)			118.5** (10.0)	112.8** (12.0)
#Cig. smoked per day × Birth weight PGS				2.2 (1.5)				
#Cig. smoked per day (adj.) × Birth weight PGS								1.3 (1.6)
Control variables	No	Yes	Yes	Yes	No	Yes	Yes	Yes
R-squared	0.019	0.059	0.101	0.101	0.021	0.069	0.128	0.128
N	7,598	7,598	5,006	5,006	3,784	3,784	2,408	2,408

Notes: Coefficients are displayed with robust standard errors in parentheses; Columns 1-4 use the self-reported measure for smoking, and Columns 5-8 use the self-reported measure for smoking corrected using cotinine levels. PGS, polygenic score. All regressions correct for genetic relatedness among the mothers using the first four principal components of the genetic relationship matrix. +*p* < 0.1, **p* < 0.05, ***p* < 0.01.

standard deviation increase in the PGS increases one's birth weight by around 105–119 grams, consistent with the findings of, for example, Trejo (2020). The interaction between the number of cigarettes smoked per day and the child's polygenic score for birth weight is very small and not statistically significant. Similar patterns are found when using the binary indicator for whether the mother smoked or not during pregnancy. [Online Appendix A.8](#) presents these results.

An interesting result stemming from Table 2 is that the correction of the self-reported smoking measure using cotinine levels lowers the coefficients from -13.4 to -9.4 (and from -144.7 to -57.8 on the extensive margin; see [Online Appendix A.8](#)).¹⁰ Analyses presented in [Online Appendix A.9](#) may explain why measurement error in the smoking variable biases the effect away from zero. These analyses show that mothers who smoke, as indicated by their cotinine level, but who do not report to be smokers, are more similar to the nonsmoking mothers than to self-reported smoking mothers. One possible explanation is that the mothers who smoke and choose not to report are more aware of the dangers of smoking and therefore more reluctant to report smoking. However, while being better informed about smoking, they might be more careful overall during their pregnancy compared with mothers who report to be smoking. An alternative explanation could be that since our cotinine variable comes from a single measurement somewhere during pregnancy, it is a poorer measure of the average number of cigarettes per day smoked throughout pregnancy than the self-reported measure. However, this does not explain the pattern for the extensive margin of smoking in [Online Appendix A.8](#) since in this case updating the smoking status with this measure implies an unambiguous improvement with respect to the original classification.

B. IV Regression Results Assuming Homogeneity

1. First stage

We start by analyzing the results of the first stage of our instrumental variable strategy in Table 3. The most important result is that our instrument has a significant and strong impact on maternal smoking intensity during pregnancy. A reference allele is estimated to increase the number of cigarettes per day by around half a cigarette. Hence, women with two reference alleles (about 11 percent of the sample) smoke on average one extra cigarette per day, an increase of 18 percent relative to the mean of our adjusted measure of the number of cigarettes smoked per day. In each specification, the coefficient for SNP rs1051730 is significant at the 1 percent significance level, and the effective F -statistic is at least 15 in each specification. The effective F -statistic (Olea and Pflueger 2013) drops the assumption of homoskedasticity, and it is therefore considered more appropriate than the standard F -statistic. One can also note that the coefficient is larger (albeit with larger standard errors) in the specification in which we only include mothers with a measure of cotinine (Columns 3 and 4). These differences suggest that our adjustment of the number of cigarettes indeed reduces measurement error in our treatment variable.

10. A similar decrease is still apparent when we analyze the self-reported smoking measure in the reduced sample for which we observe cotinine measurements. Results are available upon request.

Table 3*Results of the OLS (First Stage) Regressions Explaining Smoking in ALSPAC*

	#Cigarettes Smoked per Day		#Cigarettes Smoked per Day (Adjusted)	
	(1)	(2)	(3)	(4)
rs1051730	0.5** (0.1)	0.4** (0.1)	0.6** (0.2)	0.6** (0.1)
Control variables	No	Yes	No	Yes
R-squared	0.004	0.132	0.005	0.202
Effective F-statistic	25.3	27.2	15.6	15.1
N	7,598	7,598	3,784	3,784

Notes: Coefficients are displayed with robust standard errors in parentheses. Column 1–2 use the self-reported smoking measure, and Column 3–4 the self-reported smoking measure corrected using cotinine levels. All regressions correct for genetic relatedness among the mothers using the first four principal components of the genetic relationship matrix. + $p < 0.1$, * $p < 0.05$, ** $p < 0.01$.

2. Reduced form

Columns 1–2 in Table 4 show the reduced forms in our Baseline Sample 1. The coefficients imply that having one A allele of the SNP rs1051730 decreases offspring birth weight by on average 17 grams. The effect is statistically significant at the 10 percent level. The reduced form in the sample of 8,399 mothers—where we do not impose the baseline restriction of observing maternal smoking—reveals a reduced form of –19 grams, significant at the 5 percent level (not shown). We therefore conclude that our reduced form result supports the interpretation that maternal smoking causally reduces offspring birth weight. Reassuringly, the result remains stable when we add the maternal control variables. These results further support our assumption that this particular SNP is likely to be as good as randomly assigned in the relatively homogeneous population residing in the Avon area from which the ALSPAC participants were drawn.

To investigate the independence assumption more formally, we assess the relationship between the maternal SNP and the control variables in Table 5. In [Online Appendix A.10](#), we also verify that these variables are not correlated to the interaction term. We conclude that the instrument is uncorrelated with the control variables (nor with some other relevant background characteristics; see [Online Appendix A.10](#)), although we acknowledge that the set of variables analyzed is not exhaustive.

To gauge the validity of the exclusion restriction of our instrumental variable, we evaluated if the SNP has any effect on the outcomes of mothers who should *not* be affected by the SNP. Nonsmokers constitute such a sample, as the SNP rs1051730 is associated with the intensity of smoking. If the SNP has an impact on birth weight among children of mothers who did not smoke during pregnancy, then it suggests that there must be at least one other pathway other than smoking through which the instrument affects offspring birth weight (Van Kippersluis and Rietveld 2018a,b).

Table 4

Results of the OLS (Reduced Form) Regressions Explaining Birth Weight in ALSPAC

	Baseline Sample 1		Smokers (Cotinine > 100 ng/mL)		Nonsmokers (Cotinine < 100 ng/mL)	
	(1)	(2)	(3)	(4)	(5)	(6)
rs1051730	-16.7+ (9.6)	-16.7+ (9.5)	-42.9 (29.3)	-66.9* (29.4)	8.5 (17.8)	9.3 (17.6)
Control variables	No	Yes	No	Yes	No	Yes
R-squared	0.001	0.040	0.005	0.124	0.002	0.074
N	7,598	7,598	828	828	2,014	2,014

Notes: Coefficients are displayed with robust standard errors in parentheses. All regressions correct for genetic relatedness among the mothers using the first four principal components of the genetic relationship matrix. + $p < 0.1$, * $p < 0.05$, ** $p < 0.01$.

The existence of such a pathway would violate the exclusion restriction. In Columns 3–6 of Table 4, we estimate the reduced form in stratified subsamples based on the cotinine threshold we previously defined for active smoking (stratifying on basis of the self-reported smoking status gives very similar results). Columns 3–4 indicate that the relationship between the SNP rs1051730 and birth weight is negative (and statistically significant in Column 4) among smoking mothers, whereas Columns 5–6 indicate that this relationship is positive, close to zero, and nonsignificant among nonsmoking mothers. This result supports the idea that the SNP impacts birth weight solely through smoking intensity and not through other pathways.

Table 5

Results of the OLS (Reduced Form) Regressions Explaining the Control Variables in ALSPAC

	Mother's Birth Weight	Mother's Age	Mother's Marital Status	Mother's Education	Mother's Social Class	Grandmother's Education
rs1051730	-19.5 (13.3)	-0.0 (0.0)	-0.0 (0.0)	-0.1 (0.0)	0.0* (0.0)	0.1 (0.1)
R-squared	0.001	0.001	0.001	0.001	0.001	0.000
N	4,541	7,540	4,267	5,484	6,141	7,598

Notes: Coefficients are displayed with robust standard errors in parentheses. All regressions correct for genetic relatedness among the mothers using the first four principal components of the genetic relationship matrix. + $p < 0.1$, * $p < 0.05$, ** $p < 0.01$.

We acknowledge that these placebo tests are not sufficient to validate our exclusion restriction for at least two reasons. First, rejecting a nonzero effect among a group that should not be affected by the IV is obviously not evidence for a precise zero direct effect among the subgroup that is affected. Hence, this test can never validate the exclusion restriction. Second, the stratification into smokers and nonsmokers itself could naturally be endogenous to the IV. This implies that our group of mothers who do not smoke might be a slightly selected group of women who, despite having this SNP, decided not to smoke during pregnancy. It could be that this endogenous stratification biases the effect of the SNP on child's outcomes downwards, since this is a group of resilient mothers who do not smoke despite having the SNP. However, in [Online Appendix A.11](#), we show that the distribution of the effect allele between smokers and nonsmokers is not significantly different. Therefore, we conclude that selection into the group of smokers or nonsmokers based on the SNP is not likely to be a major factor of concern. In sum, the absence of any effect among the group of nonsmoking mothers in Columns 3–6 of Table 4 is consistent with the validity of our exclusion restriction, and the striking difference in sign and magnitude of the effect of the SNP on the child's outcome between smokers and nonsmokers supports a causal interpretation of the intensity of maternal smoking on birth weight of the offspring.

3. 2SLS

Having provided evidence in support of the IV assumptions, and to interpret the magnitude of the reduced form effects in terms of number of cigarettes, we now move to the 2SLS results in Table 6. There are several patterns that emerge. First, all the IV estimates point estimates are remarkably stable, regardless of the measure of smoking one utilizes. The estimates imply that one extra cigarette per day reduces offspring birth weight by around 36–40 grams.

Second, consistent with the validity of the independence assumption, the point estimates are hardly affected by the inclusion of control variables. If anything, in contrast with the OLS estimates from Section IV.A, correction of the number of cigarettes smoked per day based on cotinine levels slightly increases rather than decreases the magnitude of the estimates in absolute value. However, the differences between the unadjusted and adjusted measures are not statistically significant.

Third, and strikingly, the coefficients are considerably larger than in the baseline OLS regressions, although the confidence intervals span values from close to zero to almost 75 grams and thus cover the OLS estimates. The fact that the IV point estimates are larger than the OLS estimates is somewhat surprising if one considers the reduction in the coefficient by adding control variables to the OLS regression. This would suggest that omitted variables would bias the OLS estimates upwards, not downwards. However, the larger IV point estimates could possibly be explained by the IV results being less prone to random measurement error. An additional explanation could be that the local average treatment effect (LATE) among compliers (that is, the mothers on the margin induced to smoke by their genotype) is larger in magnitude than the average treatment effect on the treated (ATT) that OLS seeks to estimate.

Table 6*Results of the 2SLS Regression Explaining Birth Weight in ALSPAC*

	(1)	(2)	(3)	(4)
#Cigarettes smoked per day	-36.7+ (21.1)	-37.9+ (21.7)		
#Cigarettes smoked per day (adjusted)			-36.5+ (21.4)	-38.5 (23.9)
Control variables	No	Yes	No	Yes
Effective <i>F</i> -statistic	25.3	27.2	15.6	15.1
<i>N</i>	7,598	7,598	3,784	3,784

Notes: Coefficients are displayed with robust standard errors in parentheses. All regressions correct for genetic relatedness among the mothers using the first four principal components of the genetic relationship matrix. + $p < 0.1$, * $p < 0.05$, ** $p < 0.01$.

Another explanation could be a subtle violation of the exclusion restriction in terms of the timing of exposure. We are confident that our IV (SNP rs1051730) exclusively influences maternal smoking. However, since genotypes are fixed at conception, it is plausible that the SNP affects maternal smoking not just during but also already before pregnancy. If there is any effect of maternal smoking pre-pregnancy (for example, through worse health or assortative mating) on offspring birth weight, the 2SLS coefficients will be overestimated. In [Online Appendix A.12](#), we explore the relative importance of pre-pregnancy versus during-pregnancy smoking. The findings suggest that smoking during pregnancy is the dominant channel, but we cannot rule out a modest impact of pre-pregnancy smoking on offspring birth weight, potentially inflating our 2SLS results.

Finally, it could be that there still exists measurement error in our adjusted measures for the number of cigarettes smoked per day. This would attenuate the OLS estimates, yet plausibly leads to an overestimation of the IV estimates. This is because in the IV estimation, only the first stage includes the number of cigarettes smoked, and the resulting attenuated coefficient appears in the denominator of the 2SLS estimates and thus inflates the IV estimate. In [Online Appendix Section A.13](#), we drop the assumption that people who reported a positive number of cigarettes reported correctly. Rather, we assume that they underreported this number. However, even when on average mothers underreport the number of cigarettes smoked per day by ten, the IV point estimate is still somewhat larger than the OLS estimate, and it is estimated to be around -20 grams for every daily cigarette smoked during pregnancy.

Multiplying these IV estimates by the average number of cigarettes smoked per day among smoking mothers (around ten), would imply that offspring birth weight among smoking mothers is around 200–400 grams lower than among nonsmoking mothers. While these estimates are surrounded by pretty large uncertainty, they are in the same ballpark as earlier estimates by Lien and Evans (2005, 182 grams), Evans and Ringel (1999, 356 grams), and Kataoka et al. (2018, 320–435 grams). Still, the estimates do seem large compared to other well-known risk factors for birth weight,

such as nutrition (for example, Almond, Hoynes, and Schanzenbach 2011; Barber and Gertler 2008) and stress (Aizer 2011; Currie and Rossin-Slater 2013; Black, Devereux, and Salvanes 2016; Persson and Rossin-Slater 2018; Doyle, Schurer, and Silburn 2022). Therefore, since the 2SLS estimates rely on an imperfect measure of smoking in the first stage, and on the exclusion restriction that the single channel through which the SNP affects birth weight is smoking *during pregnancy*, we report our heterogeneity results on basis of the reduced form only in the next subsection.

C. Reduced Form Regression Results Assuming Heterogeneity

Our final analysis in the ALSPAC sample seeks to assess whether the effect of maternal smoking during pregnancy affects children differently with respect to their genetic propensity to be born with low or high birth weight. To estimate a genuine $G \times E$ interaction, one requirement is that the polygenic score for birth weight solely captures downstream effects of the child's genetic variation and is not reflecting aspects of the in utero environment shaped by, for example, maternal genetic characteristics. To be sure, the effects of the polygenic score on outcomes do not need to be purely biological and are often mediated by environmental responses to genetic risk. For example, high or low values for the polygenic score for birth weight could be associated with conditions such as preeclampsia or pregnancy diabetes, and this induces a different type of prenatal care. The child's polygenic score may also capture SNPs associated with, for instance, morning sickness, which in turn influence the mother's behavior during pregnancy. In these examples, the polygenic score triggers environmental and behavioral reactions, but these effects are still downstream consequences of genetic factors and can give rise to genuine gene-by-environment interactions.

What would be a concern to our interpretation is if maternal genetic risk for low birth weight induces the mother to alter her behavior or seek different forms of prenatal care. Through the inheritance of genetic risk, these differences in in utero environments would be correlated to the offspring polygenic score but would not be downstream consequences. This would challenge our interpretation of a $G \times E$ estimate. In [Online Appendix A.5](#), we explore the relationship between the child's polygenic score for birth weight and prenatal care in detail. We conclude that the child's polygenic score for birth weight is uncorrelated to prenatal care and maternal behavior, at least after conditioning on the maternal polygenic score.¹¹ This provides reassurance that our design enables the estimation of putative $G \times E$ effects.

Table 7 presents the reduced form regression in which we interact the maternal SNP rs1051730 with the child's polygenic score for birth weight. Note that we multiply the child's PGS by -1 to make sure both variables have negative effects on the outcome variable, facilitating the interpretation of the interaction term.

11. Controlling for the mother's polygenic score for birth weight may potentially remove some of the direct genetic effect we attempt to estimate because of the mechanical correlation between the mother's and child's polygenic score and the fact that the same weights were used to construct the two polygenic scores. Therefore, we abstain from routinely controlling for the mother's polygenic score in the main analyses. However, the results remain very similar upon inclusion of this variable in the models (see [Online Appendix A.5 Table A7](#)).

Table 7*Results of the OLS (Reduced Form) Regression Explaining Birth Weight in ALSPAC*

	(1)	(2)
rs1051730	-1.4 (10.9)	-3.4 (10.8)
(-1) Birth weight PGS (child)	-113.5** (10.1)	-103.0** (10.0)
rs1051730 × (-1) Birth weight PGS (child)	-3.3 (10.5)	-5.8 (10.4)
Control variables	No	Yes
R-squared	0.045	0.086
N	5,006	5,006

Notes: Coefficients are displayed with robust standard errors in parentheses. PGS, polygenic score. All regressions correct for genetic relatedness among the mothers using the first four principal components of the genetic relationship matrix. + $p < 0.1$, * $p < 0.05$, ** $p < 0.01$.

In this model, both the direct effect of the SNP as well as the interaction term are nonsignificant, with both coefficients relatively close to zero. Apparently, the drop in sample size because of the restriction to include mother-child pairs for which the child's genotypes are observed causes the main effect of the SNP to be insignificant and smaller in magnitude compared to the estimate in Table 4. The effect of the PGS for birth weight is again significant at the 1 percent level with a similar coefficient compared with the OLS results. Even though the magnitude of the interaction term is very small (especially compared to the main effect of the PGS), concluding the absence of meaningful interactions between genes and maternal smoking in causing birth weight would be premature for two reasons.

First, Table 7 presents only the rather restrictive form of a multiplicative linear interaction, whereas nonlinear interaction could also be present. To investigate possible nonlinear interactions, we run the regression from Table 4 separately for subsamples based on quartiles of the distribution of the child's PGS of birth weight. The full set of regression results are available in [Online Appendix A.14](#), but Figure 2 (left) presents a graphical summary of the results. This figure again shows no evidence of meaningful heterogeneity in the effect of maternal smoking on the child's birth weight.

A second reason why we cannot firmly state the absence of $G \times E$ interactions is that we may simply lack statistical power to detect it. The confidence intervals of the reduced form effect among the four quartiles of the PGS in Figure 2 (left) are rather wide, and the first-stage results in these samples are below conventional thresholds (see [Online Appendix A.14 Table A25](#)). Therefore, even though these results provide tentative evidence that strong interactions between a child's polygenic score for birth weight and maternal smoking do not exist, they are not conclusive. For this reason, we replicate these reduced form results in Section V using the much larger UK

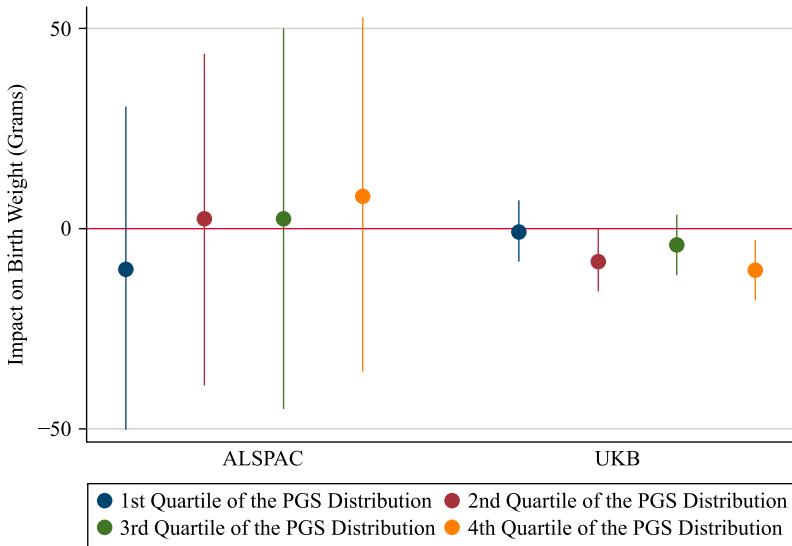


Figure 2

Results of the Reduced Form OLS Regressions Explaining Birth Weight Based on Quartiles of the Distribution of the Child's Polygenic Score (PGS) for Birth Weight

Notes: The figure display the coefficients with their robust 95 percent confidence intervals in ALSPAC and UK Biobank (UKB). More details about these regressions are available in [Online Appendix A.14](#).

Biobank to assess whether the absence of evidence can be attributed to low statistical power.

V. Replication

In this section, we provide the results of the replication analysis using data from the UK Biobank (UKB).

A. Data and Variables

The UKB is a UK data set collected with the aim of improving the prevention, diagnosis, and treatment of a wide range of serious and life-threatening illnesses. The UKB recruited approximately 500,000 people aged between 40–69 years in 2006–2010 from across the UK to take part in this project. They have undergone measurements and provided detailed information about themselves, as well as blood, urine, and saliva samples. Genotyping has been undertaken on all 500,000 participants. More information on the genetic section of the UKB can be found in Bycroft et al. (2017).

The UKB does not have the level of measurement detail as ALSPAC. For our replication purposes, the main data limitations are as follows. First, the UKB does not provide the average number of cigarettes smoked during pregnancy nor a cotinine

measure for cross validation. Second, it only has genetic information on the individual itself, and no family members were targetly genotyped.¹² Finally, no information about the socioeconomic background of the mothers is available, ruling out the possibility to add control variables to the model. Nevertheless, the sample size of the UKB is much larger than that of ALSPAC, enabling us to assess whether lack of statistical power is driving the absence of evidence of significant $G \times E$ interactions in birth weight in the main analyses with the following variables that are available.

1. Birth weight

Participants were asked to enter their own birth weight. Given that all individuals were alive past one year old, no outliers were removed. The mean birth weight is 3,325 grams, and the standard deviation is 665 grams.

2. Maternal smoking around birth

Participants were asked the following question: “Did your mother smoke regularly around the time when you were born?” They could reply with yes or no. This variable was collected from all participants except from those who indicated they were adopted as a child. Thirty percent of respondents answered “yes.”

3. *rs1051730*

This variable is equal to zero if the individual carries no A’s nucleotide for SNP *rs1051730*, one if they carry one A nucleotide, and two if they carry two A nucleotides. In the sample, around 45 percent do not carry any A nucleotides, 44 percent carry one A nucleotide, and the remaining 11 percent carry two A alleles. Note that this distribution is exactly the same as in ALSPAC. [Online Appendix A.2](#) provides more details on the quality control of the genetic data. Importantly, in the UKB analyses, we rely on the *individual’s* SNP rather than the preferred *maternal* SNP to instrument the *maternal* smoking decision during pregnancy. Essentially, this approach uses the child’s SNP as a proxy for the maternal SNP, which in turn is an instrumental variable for maternal smoking during pregnancy. While this may seem far-fetched, Yang, Millard, and Smith (2020) provide compelling evidence that with this strategy it is possible to detect causal effects of maternal smoking on offspring birth weight. It relies on (i) Mendel’s law that children randomly inherit 50 percent of the maternal genes and (ii) the same exclusion restriction as before that the single causal channel of the nicotine receptor gene is the intensity of smoking. Since unborn children clearly did not make any smoking decisions, it is plausible that the only reason why the child’s SNP affects their birth weight is through maternal smoking. While obviously using a child’s SNP as a proxy for their mother’s SNP is

12. The UKB has a small subsample of mother–child pairs who both volunteered to participate. This subsample consists of approximately 4,400 families (Young et al. 2022), which is a smaller sample than our main analysis sample from ALSPAC and therefore is not suitable to assess the robustness of our results.

introducing some measurement error, the additional power gained by the sample size enables us to replicate our main findings in ALSPAC using a larger sample.

4. Polygenic score for birth weight

We use the summary statistics of Warrington et al. (2019) depleted of the UKB to retrieve the relevant SNPs with their weights. We construct the PGS using the software LDpred (Vilhjálmsen et al. 2015). The predictive power of the PGS is 1.6 percent, and individuals in the lowest decile of the PGS distribution have on average a birth weight 300 grams lower than those in the highest decile. The R -squared of the PGS is lower in the UKB than it is in ALSPAC since the UKB was the largest sample in the GWAS. However, since the UKB is our holdout cohort for this analysis, we are forced to deplete the GWAS summary statistics from the UKB to avoid overfitting. [Online Appendix A.3](#) presents more details about the construction of the PGS.

5. Principal components

We add the first 20 principal components of the genetic relationship matrix, as provided by the UKB, to control for subtle population stratification (Price et al. 2006; Rietveld et al. 2014).

The inclusion of these control variables to our models does not qualitatively influence any of our results.

B. Results

In this subsection we present our IV results with and without assessing treatment effect heterogeneity. For reasons of brevity, the OLS results are presented in [Online Appendix A.8](#). Since the intensity of smoking during pregnancy was not reported in the UKB, it is not possible to replicate our first-stage results from ALSPAC directly. We can only check the relationship between the instrument and the smoking status of the mother on the extensive margin (smoking vs. not smoking). However, given the nature of the biological mechanism triggered by SNP rs1051730, this effect is expected to be much weaker. Nonetheless, if we run this first-stage regression (not shown), the coefficient is 0.004 and statistically significant at the 5 percent significance level. This result suggests that for each effect allele an individual is carrying the probability of the mother smoking around birth is 0.4 percent higher.

In Table 8, we present the reduced form effect of our IV on the birth weight of the respondent, for the full sample and stratified subsamples by smoking status of the mother. Some respondents did not report the smoking status of their mother, and therefore the subsamples do not sum up to the full sample. In the full sample, one effect allele of the SNP decreases birth weight by around 6 grams on average (Column 1). However, the effect is -17 grams in the subsample of individuals with a smoking mother (Column 2) and nonsignificant in the subsample of individuals with a nonsmoking mother (Column 3). Our results are consistent with those of Yang, Millard, and Smith (2020) and very close in magnitude to what they found: -18 grams for individuals with a smoking mother and -2 grams for individuals with a nonsmoking mother. The small differences might be explained

Table 8*Results of the OLS (Reduced Forms) Regressions Explaining Birth Weight in UK Biobank*

	Full Sample (1)	Smoking Mothers (2)	Nonsmoking Mothers (3)	Full Sample (4)
rs1051730	-5.7** (2.0)	-17.3** (4.0)	-1.3 (2.4)	-5.9** (2.0)
(-1) Birth weight PGS (child)				-83.0** (1.8)
rs1051730 × (-1) Birth weight PGS (child)				1.0 (2.0)
R-squared	0.001	0.001	0.001	0.016
N	256,702	67,915	160,530	256,702

Notes: Coefficients are displayed with robust standard errors in parentheses. PGS, polygenic score. All regressions correct for genetic relatedness using the first twenty principal components of the genetic relationship matrix. + $p < 0.1$, * $p < 0.05$, ** $p < 0.01$.

by the fact that the authors used SNP rs16969968 as a proxy instrument. This SNP is in almost perfect linkage disequilibrium with SNP rs1051730.

We cannot readily compare the reduced forms in the UKB and ALSPAC because we use the child's SNP (as a proxy-instrument) in UKB and the maternal SNP in ALSPAC. Still, given the random inheritance of SNPs, we can gauge the similarity of effect sizes. In ALSPAC, the correlation between rs1051730 among mothers and their children is 50.7 percent, and an additional A allele of the mother for this SNP is associated with a 16.7-gram decrease of the offspring birth weight (Table 4). In the UKB, an additional A allele of the child for this SNP is associated with a 5.7-gram decrease of birth weight. Hence, we may expect a partial correlation between the A allele of the child and birth weight in the UKB of $-16.7 \times 0.507 = -8.5$ grams. It is reassuring that this number is within the confidence interval of what we find in the UKB.

Given that we do not have a measure of the average number of cigarettes smoked during pregnancy in the UKB data set, we rely on the first stage estimated in ALSPAC (0.6; see Columns 3–4 of Table 3) to infer an IV estimate. A manually computed two-sample two-stage least squares (TS2SLS) estimate would be $-5.7 \times 2/0.6 = -19$ grams. Therefore, a rough estimate is that an average daily cigarette reduces birth weight by around 20 grams. This effect is somewhat smaller than what we find in our main analysis in ALSPAC, but pretty close to the estimates we find in ALSPAC after taking into account measurement error in self-reported smoking.

The results in the previous subsection indicate that the UKB is a suitable (second-best) sample to estimate the causal effect of maternal smoking on offspring birth weight. However, our main interest is in assessing the presence of heterogeneity of the treatment effect in the UKB. Column 4 of Table 8 presents the reduced form results including the interaction. The main effects of the SNP and the PGS are

significant, but, as in ALSPAC, the interaction term is close to zero. However, in contrast with the ALSPAC results, the standard error of the interaction term is now also very small, allowing us to rule out interaction terms outside the -1 to 3 gram bandwidth with 95 percent confidence. Further, the stratification of the reduced form effect by quartiles of the PGS shown in Figure 2 (right) further supports the claim of no meaningful interaction effect between the birth weight PGS and maternal smoking. Figure 2 shows remarkably narrower confidence intervals in the UKB than in ALSPAC but similarly shows no clearly discernible patterns. Moreover, the effect estimates across quartiles are not significantly different from each other. Overall, we take this as evidence that statistical power was not the main driver of the lack of evidence for an interaction effect in ALSPAC.

VI. Discussion and Conclusion

In this study, we show that maternal smoking as well as one's genetic predisposition contribute to offspring birth weight. In particular, we find that a one-cigarette increase in the average number of cigarettes smoked per day reduces birth weight, with point estimates varying from around 20 grams (UKB and ALSPAC with underreporting correction) to 40 grams (ALSPAC without underreporting correction). A one standard deviation increase in the polygenic score increases birth weight by around 80 (UKB) to 120 (ALSPAC) grams. Despite the strong and well-established main effects, our results suggest that there is no meaningful interaction effect among these two drivers of birth weight. Hence, maternal smoking does not exacerbate genetic inequalities, and even a high genetic predisposition to birth weight does not cushion or dampen the damaging environmental exposure of maternal smoking.

These findings contribute to the literature on the genetic and environmental determinants of offspring birth weight, an important barometer of pregnancy outcomes (Trejo 2020) and arguably the first observed realization of one's human capital. By using innovative identification strategies that simultaneously address measurement error and endogeneity concerns, our results reemphasize the damaging effects of smoking during pregnancy. Moreover, we highlight the role of genetic endowments implied in birth weight. Our main contribution is to show the absence of heterogeneity in the effect of maternal smoking according to the child's genotype. Hence, our results suggest that both nature (here measured by the polygenic score for birth weight) as well as nurture (here measured by maternal smoking during pregnancy) impact birth weight, but we do not find evidence of meaningful interactions or complementarities between the two.

Three main limitations should be acknowledged. First, birth weight is not the only relevant early-childhood outcome, and many genetic and environmental drivers could influence later life outcomes without affecting birth weight (Conti et al. 2018). Therefore, we cannot rule out meaningful interactions between genes and maternal smoking decisions for other life outcomes. In auxiliary analyses, we investigated the effect on weeks of gestation and whether the child is alive one year after birth in ALSPAC, but we did not detect meaningful main effects or interactions.¹³ Future

13. Results are available upon request.

studies may want to analyze whether such effects exist, as well as their size, in sufficiently powered analyses.

Second, it has been argued that maternal smoking before pregnancy may affect oocyte quality and thereby birth outcomes (for example, Oyesanya et al. 1995). Moreover, maternal smoking before pregnancy may influence partner choice or general health status of the mother (Sutton 1980; Agrawal et al. 2006), both of which could independently affect offspring birth weight. If true, this would represent an effect of maternal smoking *before* pregnancy, and our estimates should be interpreted as the effect of all prenatal smoking exposure rather than just exposure to smoking during pregnancy.

Finally, the polygenic score for birth weight is not a perfect measure of the child's genetic endowments for birth weight. It only captures common SNPs and not rare variants or other genetic variation across humans. Moreover, the polygenic score is constructed on the basis of a GSAS that is pooling various cohorts exposed to different environmental conditions. Mills, Barban, and Tropf (2020) therefore argue that a polygenic score may actually outweigh SNPs that are particularly resilient to environmental conditions, which would go against finding a significant $G \times E$ effect when using a polygenic score. The limited sample size and sparsity on control variables of the GWAS discovery analysis may also introduce measurement error in polygenic scores, and possibly a bias as a result of the omission of parental genotype from the GWAS. If parental genes influence the child's birth weight through other mechanisms than purely inheritance of genes, these other mechanisms would be captured in the polygenic score too. Nevertheless, within-family predictions with the polygenic score show that such bias is not a major concern for the polygenic score for birth weight, and interactions with other (endogenous) maternal characteristics such as BMI have been found (Trejo 2020).

However, what could be an issue is that the predictive power of the polygenic score for birth weight does not fully explain the heritability of birth weight (Warrington et al. 2019). With a more predictive polygenic score, small (interaction) effects may become statistically detectable, and hence it would be interesting to repeat our estimations as soon as results of a new GWAS on birth weight become available. We caution that these results are not to be expected in the next few years, as we draw on a very recent GWAS on birth weight to construct our polygenic scores, and it usually takes several years for the GWAS sample size to be sufficiently expanded to conduct a new GWAS.

Therefore, we believe that the present study contains the most comprehensive analysis of the impact of the heterogeneous impact of maternal smoking on birth weight by genetic endowments that is achievable today. As such, it can also serve as a template for future $G \times E$ studies on related exposures and outcomes.

References

- 1000 Genomes Project Consortium. 2015. "A Global Reference for Human Genetic Variation." *Nature* 526(7571):68–74.
- Agrawal, Arpana, Andrew C. Heath, Julia D. Grant, Michele L. Pergadia, Dixie J. Statham, Kathleen K. Bucholz, Nicholas G. Martin, and Pamela A.F. Madden. 2006. "Assortative Mating for Cigarette Smoking and for Alcohol Consumption in Female Australian Twins and Their Spouses." *Behavior Genetics* 36(4):553–66.

- Aizer, Anna. 2011. "Poverty, Violence, and Health the Impact of Domestic Violence during Pregnancy on Newborn Health." *Journal of Human Resources* 46(3):518–38.
- Almond, Douglas, Kenneth Y. Chay, and David S. Lee. 2005. "The Costs of Low Birth Weight." *Quarterly Journal of Economics* 120(3):1031–83.
- Almond, Douglas, and Janet Currie. 2011. "Killing Me Softly: The Fetal Origins Hypothesis." *Journal of Economic Perspectives* 25(3):153–72.
- Almond, Douglas, Janet Currie, and Valentina Duque. 2018. "Childhood Circumstances and Adult Outcomes: Act II." *Journal of Economic Literature* 56(4):1360–446.
- Almond, Douglas, Hilary W. Hoynes, and Diane W. Schanzenbach. 2011. "Inside the War on Poverty: The Impact of Food Stamps on Birth Outcomes." *Review of Economics and Statistics* 93(2):387–403.
- Andrews, Isaiah, James H. Stock, and Liyang Sun. 2019. "Weak Instruments in Instrumental Variables Regression: Theory and Practice." *Annual Review of Economics* 11(1):727–53.
- Banderali, Giuseppe, Alma Martelli, Massimo Landi, Francesca Moretti, Francesca Betti, Guido Radaelli, Carlota Lassandro, and Elvira Verduci. 2015. "Short and Long Term Health Effects of Parental Tobacco Smoking during Pregnancy and Lactation: A Descriptive Review." *Journal of Translational Medicine* 13(1):1–7.
- Barber, Sarah L., and Paul J. Gertler. 2008. "The Impact of Mexico's Conditional Cash Transfer Programme, Oportunidades, on Birthweight." *Tropical Medicine & International Health* 13(11):1405–14.
- Barcellos, Silvia H., Leandro S. Carvalho, and Patrick Turley. 2018. "Education Can Reduce Health Differences Related to Genetic Risk of Obesity." *Proceedings of the National Academy of Sciences* 115(42):E9765–E9772.
- Beauchamp, Jonathan P., David Cesarini, Magnus Johannesson, Matthijs J.H.M. van der Loos, Philipp D. Koellinger, Patrick J.F. Groenen, James H. Fowler, J. Niels Rosenquist, A. Roy Thurik, and Nicholas A. Christakis. 2011. "Molecular Genetics and Economics." *Journal of Economic Perspectives* 25(4):57–82.
- Berrettini, Wade. 2013. "Genetics of Nicotine Addiction." In *Biological Research on Addiction*, Comprehensive Addictive Behaviors and Disorders, Volume 2, ed. Peter M. Miller, 453–60. New York: Elsevier.
- Bharadwaj, Prashant, Julian V. Johnsen, and Katrine V. Løken. 2014. "Smoking Bans, Maternal Smoking and Birth Outcomes." *Journal of Public Economics* 115(1):72–93.
- Bharadwaj, Prashant, Petter Lundborg, and Dan-Olof Rooth. 2018. "Birth Weight in the Long Run." *Journal of Human Resources* 53(1):189–231.
- Bierut, Laura Jean. 2010. "Convergence of Genetic Findings for Nicotine Dependence and Smoking Related Diseases with Chromosome 15q24-25." *Trends in Pharmacological Sciences* 31(1):46–51.
- Bierut, Laura, and David Cesarini. 2015. "How Genetic and Other Biological Factors Interact with Smoking Decisions." *Big Data* 3(3):198–202.
- Biroli, Pietro, Titus J. Galama, Stephanie Von Hinke, Hans Van Kippersluis, Corenlius A. Rietveld, and Kevin Thom. 2022. "The Economics and Econometrics of Gene-Environment Interplay." Tinbergen Institute Discussion Paper 2022-019/V. <https://papers.tinbergen.nl/22019.pdf> (accessed September 12, 2024).
- Black, Sandra E., Paul J. Devereux, and Kjell G. Salvanes. 2007. "From the Cradle to the Labor Market? The Effect of Birth Weight on Adult Outcomes." *Quarterly Journal of Economics* 122(1):409–39.
- . 2016. "Does Grief Transfer across Generations? Bereavements during Pregnancy and Child Outcomes." *American Economic Journal: Applied Economics* 8(1):193–223.
- Boyd, Andy, Jean Golding, John Macleod, Debbie A. Lawlor, Abigail Fraser, John Henderson, Lynn Molloy, Andrew R. Ness, Susan M. Ring, and George Davey Smith. 2013. "Cohort Profile: The 'Children of the 90s'—The Index Offspring of the Avon Longitudinal Study of Parents and Children." *International Journal of Epidemiology* 42(1):111–27.

- Bradford, David W. 2003. "Pregnancy and the Demand for Cigarettes." *American Economic Review* 93(5):1752–63.
- Bycroft, Clare, Colin Freeman, Desislava Petkova, Gavin Band, Lloyd T. Elliott, Kevin Sharp, Allan Motyer, Vukcevic Damjan, Olivier Delaneau, Jared O'Connell, et al. 2017. "Genome-Wide Genetic Data on ~500,000 UK Biobank Participants." BioRxiv.
- Chabris, Christopher F., James J. Lee, David Cesarini, Daniel J. Benjamin, and David I. Laibson. 2015. "The Fourth Law of Behavior Genetics." *Current Directions in Psychological Science* 24(4):304–12.
- Conti, Gabriella, Mark Hanson, Hazel Inskip, Sarah Crozier, Cyrus Cooper, and Keith M. Godfrey. 2018. "Beyond Birthweight: The Origins of Human Capital." IZA Discussion Paper 13296. Bonn, Germany: IZA.
- Cunha, Flavio, and James Heckman. 2007. "The Technology of Skill Formation." *American Economic Review* 97(2):31–47.
- Currie, Janet. 2009. "Healthy, Wealthy, and Wise: Socioeconomic Status, Poor Health in Childhood, and Human Capital Development." *Journal of Economic Literature* 47(1):87–122.
- Currie, Janet, and Enrico Moretti. 2007. "Biology as Destiny? Short- and Long-Run Determinants of Intergenerational Transmission of Birth Weight." *Journal of Labor Economics* 25(2):231–64.
- Currie, Janet, and Maya Rossin-Slater. 2013. "Weathering the Storm: Hurricanes and Birth Outcomes." *Journal of Health Economics* 32(3):487–503.
- Doyle, Mary-Alice, Stefanie Schurer, and Sven Silburn. 2022. "Unintended Consequences of Welfare Reform: Evidence from Birthweight of Aboriginal Children in Australia." *Journal of Health Economics* 84:102618.
- Dudbridge, Frank. 2013. "Power and Predictive Accuracy of Polygenic Risk Scores." *PLoS Genetics* 9(3):e1003348.
- England, Lucinda J., Juliette S. Kendrick, Paul M. Gargiullo, S. Christine Zahniser, and W. Harry Hannon. 2001. "Measures of Maternal Tobacco Exposure and Infant Birth Weight at Term." *American Journal of Epidemiology* 153(10):954–60.
- Evans, William N., and Jeanne S Ringel. 1999. "Can Higher Cigarette Taxes Improve Birth Outcomes?" *Journal of Public Economics* 72(1):135–54.
- Figlio, David, Jonathan Guryan, Krzysztof Karbownik, and Jeffrey Roth. 2014. "The Effects of Poor Neonatal Health on Children's Cognitive Development." *American Economic Review* 104(12):3921–55.
- Fletcher, Jason M. 2012. "Why Have Tobacco Control Policies Stalled? Using Genetic Moderation to Examine Policy Impacts." *PLoS One* 7(12):e50576.
- Fraser, Abigail, Corrie Macdonald-Wallis, Kate Tilling, Andy Boyd, Jean Golding, George Davey Smith, John Henderson, John Macleod, Lynn Molloy, Andy Ness, Susan Ring, Scott M. Nelson, and Debbie A. Lawlor. 2013. "Cohort Profile: The Avon Longitudinal Study of Parents and Children: ALSPAC Mothers Cohort." *International Journal of Epidemiology* 42(1):97–110.
- Furberg, Helena, YunJung Kim, Jennifer Dackor, Eric Boerwinkle, Nora Franceschini, Diego Ardisino, Luisa Bernardinelli, Pier M. Mannucci, Francesco Mauri, Piera A. Merlini, et al. 2010. "Genome-Wide Meta-Analyses Identify Multiple Loci Associated with Smoking Behavior." *Nature Genetics* 42(5):441–47.
- Hamilton, Barton H. 2001. "Estimating Treatment Effects in Randomized Clinical Trials with Non-compliance: The Impact of Maternal Smoking on Birthweight." *Health Economics* 10(5):399–410.
- Heckman, James J. 2007. "The Economics, Technology, and Neuroscience of Human Capability Formation." *Proceedings of the National Academy of Sciences* 104(33):13250–55.
- Horikoshi, Momoko, Robin N. Beaumont, Felix R. Day, Nicole M. Warrington, Marjolein N. Kooijman, Juan Fernandez-Tajes, Bjarke Feenstra, Natalie R. van Zuydam, Kyle J. Gaulton, Niels Grarup, Jonathan P. Bradfield, et al. 2016. "Genome-Wide Associations for Birth Weight and Correlations with Adult Disease." *Nature* 538(7624):248–52.

- Horikoshi, Momoko, Hanieh Yaghootkar, Dennis O. Mook-Kanamori, Ulla Sovio, H. Rob Taal, Branwen J. Hennig, Jonathan P. Bradfield, Beate St. Pourcain, David M. Evans, Pimphen Charoen, et al. 2013. "New Loci Associated with Birth Weight Identify Genetic Links between Intrauterine Growth and Adult Height and Metabolism." *Nature Genetics* 45(1):76–82.
- Joubert, Bonnie R., Janine F. Felix, Paul Yousefi, Kelly M. Bakulski, Allan C. Just, Carrie Breton, Sarah E. Reese, Christina A. Markunas, Rebecca C. Richmond, Cheng-Jian Xu, et al. 2016. "DNA Methylation in Newborns and Maternal Smoking in Pregnancy: Genome-Wide Consortium Meta-analysis." *American Journal of Human Genetics* 98(4): 680–96.
- Kataoka, Mariana C., Ana Carneiro, Anna Ferrari, Maíra Malta, Maria Carvalhaes, and Cristina Parada. 2018. "Smoking during Pregnancy and Harm Reduction in Birth Weight: A Cross-Sectional Study." *BMC Pregnancy and Childbirth* 18(1):1–10.
- Kidd, Jeffrey M., Gregory M. Cooper, William F. Donahue, Hillary S. Hayden, Nick Sampas, Tina Graves, Nancy Hansen, Brian Teague, Can Alkan, Francesca Antonacci, et al. 2008. "Mapping and Sequencing of Structural Variation from Eight Human Genomes." *Nature* 453(7191):56–64.
- Kim, Sungroul. 2016. "Overview of Cotinine Cutoff Values for Smoking Status Classification." *International Journal of Environmental Research and Public Health* 13(12):1236.
- Kong, Augustine, Gudmar Thorleifsson, Michael L. Frigge, Bjarni J. Vilhjalmsón, Alexander I. Young, Thorgeir E. Thorgeirsson, Stefania Benonisdóttir, Asmundur Oddsson, Bjarni V. Halldorsson, Gisli Masson, et al. 2018. "The Nature of Nurture: Effects of Parental Genotypes." *Science* 359(6374):424–28.
- Kramer, Michael S. 1987a. "Intrauterine Growth and Gestational Duration Determinants." *Pediatrics* 80(4):502–511.
- . 1987b. "Determinants of Low Birth Weight: Methodological Assessment and Meta-analysis." *Bulletin of the World Health Organization* 65(5):663–737.
- Langone, John J., Hilda B. Gjika, and Helen Van Vunakis. 1973. "Nicotine and Its Metabolites. Radio Immunoassays for Nicotine and Cotinine." *Biochemistry* 12(24): 5025–30.
- Lawlor, Deborah, Rebecca Richmond, Nicole Warrington, George McMahon, George Davey Smith, Jack Bowden, and David M. Evans. 2017. "Using Mendelian Randomization to Determine Causal Effects of Maternal Pregnancy (Intrauterine) Exposures on Offspring Outcomes: Sources of Bias and Methods for Assessing Them." *Wellcome Open Research* 2(11):1–23.
- Lehrer, Steven F., and Weili Ding. 2017. "Are Genetic Markers of Interest for Economic Research?" *IZA Journal of Labor Policy* 6(1):2.
- Li, Chang Qing, Richard A. Windsor, Laura Perkins, Robert L. Goldenberg, and John B. Lowe. 1993. "The Impact on Infant Birth Weight and Gestational Age of Cotinine-Validated Smoking Reduction during Pregnancy." *JAMA* 269(12):1519–24.
- Lien, Diana S., and William N. Evans. 2005. "Estimating the Impact of Large Cigarette Tax Hikes the Case of Maternal Smoking and Infant Birth Weight." *Journal of Human Resources* 40(2):373–92.
- Lindqvist, Rune, Lena Lendahls, Örjan Tollbom, Hans Åberg, and Anders Håkansson. 2002. "Smoking during Pregnancy: Comparison of Self-Reports and Cotinine Levels in 496 Women." *Acta Obstetrica et Gynecologica Scandinavica* 81(3):240–44.
- Liu, Jason Z., Federica Tozzi, Dawn M. Waterworth, Sreekumar G. Pillai, Pierandrea Muglia, Lefkos Middleton, Wade Berrettini, Christopher W. Knouff, Xin Yuan, Gérard Waeber, et al. 2010. "Meta-Analysis and Imputation Refines the Association of 15q25 with Smoking Quantity" *Nature Genetics* 42(5):436–40.

- Liu, Mengzhen, Yu Jiang, Robbee Wedow, Yue Li, David M Brazel, Fang Chen, Gargi Datta, Jose DavilaVelderrain, Daniel McGuire, Chao Tian, et al. 2019. "Association Studies of up to 1.2 Million Individuals Yield New Insights into the Genetic Etiology of Tobacco and Alcohol Use." *Nature Genetics* 51(2):237–44.
- Mejdoubi, Jamila, Silvia C.C.M. van den Heijkant, Frank J.M. van Leerdam, Matty Crone, Alfons Crijnen, and Remy A. HiraSing. 2014. "Effects of Nurse Home Visitation on Cigarette Smoking, Pregnancy Outcomes and Breastfeeding: A Randomized Controlled Trial." *Midwifery* 30(6):688–95.
- Mills, Melinda C., Nicola Barban, and Felix C. Tropf. 2020. *An Introduction to Statistical Genetic Data Analysis*. Cambridge, MA: MIT Press.
- Olea, José, and Carolin Pflueger. 2013. "A Robust Test for Weak Instruments." *Journal of Business & Economic Statistics* 31(3):358–69.
- Oyesanya, Olufunso A., Maria Teresa Zenzes, Peng Wang, and Robert F. Casper. 1995. "Cigarette Smoking May Affect Meiotic Maturation of Human Oocytes." *Human Reproduction* 10(12):3213–17.
- Pazokitoroudi, Ali, Alec M. Chiu, Kathryn S. Burch, Bogdan Pasaniuc, and Sriram Sankararaman. 2021. "Quantifying the Contribution of Dominance Deviation Effects to Complex Trait Variation in Biobank-Scale Data." *American Journal of Human Genetics* 108(5):799–808.
- Persson, Petra, and Maya Rossin-Slater. 2018. "Family Ruptures, Stress, and the Mental Health of the Next Generation." *American Economic Review* 108(4–5):1214–52.
- Polderman, Tinca J.C., Beben Benyamin, Christiaan A. De Leeuw, Patrick F. Sullivan, Arjen Van Bochoven, Peter M. Visscher, and Danielle Posthuma. 2015. "Meta-Analysis of the Heritability of Human Traits Based on Fifty Years of Twin Studies." *Nature Genetics* 47(7):702–9.
- Price, Alkes L., Nick J. Patterson, Robert M. Plenge, Michael E. Weinblatt, Nancy A. Shadick, and David Reich. 2006. "Principal Components Analysis Corrects for Stratification in Genome-Wide Association Studies." *Nature Genetics* 38(8):904–9.
- Raffington, Laurel, Travis Mallard, and K. Paige Harden. 2020. "Polygenic Scores in Developmental Psychology: Invite Genetics in, Leave Biodeterminism Behind." *Annual Review of Developmental Psychology* 2:389–411.
- Rietveld, Cornelius A., Dalton Conley, Nicholas Eriksson, Tõnu Esko, Sarah E. Medland, Anna A.E. Vinkhuyzen, Jian Yang, Jason D. Boardman, Christopher F. Chabris, Christopher T. Dawes, et al. 2014. "Replicability and Robustness of Genome-Wide Association Studies for Behavioral Traits." *Psychological Science* 25(11):1975–86.
- Ringel, Jeanne S., and William N. Evans. 2001. "Cigarette Taxes and Smoking during Pregnancy." *American Journal of Public Health* 91(11):1851–56.
- Royer, Heather. 2009. "Separated at Girth: US Twin Estimates of the Effects of Birth Weight." *American Economic Journal: Applied Economics* 1(1):49–85.
- Rutter, Michael. 2006. *Genes and Behavior: Nature–Nurture Interplay Explained*. Blackwell Publishers, Oxford, UK.
- Schmitz, Lauren L., and Dalton Conley. 2017. "The Effect of Vietnam-Era Conscript and Genetic Potential for Educational Attainment on Schooling Outcomes." *Economics of Education Review* 61(1):85–97.
- Sexton, Mary, and J. Richard Hebel. 1984. "A Clinical Trial of Change in Maternal Smoking and Its Effect on Birth Weight." *JAMA* 251(7):911–15.
- Simon, David. 2016. "Does Early Life Exposure to Cigarette Smoke Permanently Harm Childhood Welfare? Evidence from Cigarette Tax Hikes." *American Economic Journal: Applied Economics* 8(4):128–59.
- Slob, Eric, and Cornelius A. Rietveld. 2021. "Genetic Predispositions Moderate the Effectiveness of Tobacco Excise Taxes." *PLoS ONE* 16(11):e0259210.

- Smith, George Davey. 2003. "Mendelian Randomization: Can Genetic Epidemiology Contribute to Understanding Environmental Determinants of Disease?" *International Journal of Epidemiology* 32(1):1–22.
- Smith, George Davey, Debbie A. Lawlor, Roger M. Harbord, Nicholas J. Timpson, Ian N. M. Day, and Shah Ebrahim. 2007. "Clustered Environments and Randomized Genes: A Fundamental Distinction between Conventional and Genetic Epidemiology." *PLoS Medicine* 4(12):e352.
- Sutton, Graham C. 1980. "Assortative Marriage for Smoking Habits." *Annals of Human Biology* 7(5):449–56.
- Tappin, David, Linda Bauld, David Purves, Kathleen Boyd, Lesley Sinclair, Susan MacAskill, Jennifer McKell, Brenda Friel, Alex McConnachie, Linda De Caestecker, et al. 2015. "Financial Incentives for Smoking Cessation in Pregnancy: Randomised Controlled Trial." *British Medical Journal* 350:h134.
- Tappin, David M., Rodney P. Ford, and Philip J. Schluter. 1997. "Smoking during Pregnancy Measured by Population Cotinine Testing." *New Zealand Medical Journal* 110(1050):311–14.
- Trejo, Sam. 2020. "Exploring Genetic Influences on Birth Weight." SocArXiv. <https://doi.org/10.31235/osf.io/7j59q>
- Turkheimer, Eric. 2000. "Three Laws of Behavior Genetics and What They Mean." *Current Directions in Psychological Science* 9(5):160–64.
- Tyrrell, Jessica, Ville Huikari, Jennifer T. Christie, Alana Cavadino, Rachel Bakker, Marie-Jo A. Brion, Frank Geller, Lavinia Paternoster, Ronny Myhre, Catherine Potter, et al. 2012. "Genetic Variation in the 15q25 Nicotinic Acetylcholine Receptor Gene Cluster (CHRNA5–CHRNA3–CHRN4) Interacts with Maternal Self-Reported Smoking Status during Pregnancy to Influence Birth Weight." *Human Molecular Genetics* 21(24):5344–58.
- Van Kippersluis, Hans, and Cornelius A. Rietveld. 2018a. "Beyond Plausibly Exogenous." *Econometrics Journal* 21(3):316–31.
- . 2018b. "Pleiotropy-Robust Mendelian Randomization." *International Journal of Epidemiology* 47(4):1279–88.
- Vilhjálmsón, Bjarni J., Jian Yang, Hilary K. Finucane, Alexander Gusev, Sara Lindström, Stephan Ripke, Giulio Genovese, Po-Ru Loh, Gaurav Bhatia, Ron Do, Tristan Hayeck, and Hong-Hee Won, et al. 2015. "Modeling Linkage Disequilibrium Increases Accuracy of Polygenic Risk Scores." *American Journal of Human Genetics* 97(4):576–92.
- Visscher, Peter M., Naomi R Wray, Qian Zhang, Pamela Sklar, Mark I. McCarthy, Matthew A. Brown, and Jian Yang. 2017. "10 Years of GWAS Discovery: Biology, Function, and Translation." *American Journal of Human Genetics* 101(1):5–22.
- Von Hinke, Stephanie, George Davey Smith, Debbie A Lawlor, Carol Propper, and Frank Windmeijer. 2016. "Genetic Markers as Instrumental Variables." *Journal of Health Economics* 45(1):131–48.
- Wang, Xiaobin, Ira B. Tager, Helen Van Vunakis, Frank E. Speizer, and John P. Hanrahan. 1997. "Maternal Smoking during Pregnancy, Urine Cotinine Concentrations, and Birth Outcomes. A Prospective Cohort Study." *International Journal of Epidemiology* 26(5):978–988.
- Wang, Xiaobin, Barry Zuckerman, Colleen Pearson, Gary Kaufman, Changzhong Chen, Guoying Wang, Tianhua Niu, Paul H. Wise, Howard Bauchner, and Xiping Xu. 2002. "Maternal Cigarette Smoking, Metabolic Gene Polymorphism, and Infant Birth Weight." *JAMA* 287(2):195–202.
- Warrington, Nicole M., Robin N. Beaumont, Momoko Horikoshi, Felix R. Day, Øyvind Helge-land, Charles Laurin, Jonas Bacelis, Shouneng Peng, Ke Hao, Bjarke Feenstra, et al. 2019. "Maternal and Fetal Genetic Effects on Birth Weight and Their Relevance to Cardio-Metabolic Risk Factors." *Nature Genetics* 51(5):804–14.
- Wehby, George L., Jason M. Fletcher, Steven F. Lehrer, Lina Moreno, Jeffrey C. Murray, Allen Wilcox, and Rolv Lie. 2012. "A Genetic Instrumental Variables Analysis of the Effects of Prenatal Smoking on Birth Weight: Evidence from Two Samples." *Biodemography and Social Biology* (57):3–32.

- Yang, Qian, Louise A.C. Millard, and George Davey Smith. 2020. "Proxy Gene-by-Environment Mendelian Randomization Study Confirms a Causal Effect of Maternal Smoking on Offspring Birthweight, but Little Evidence of Long-Term Influences on Offspring Health." *International Journal of Epidemiology* 49(4):1207–8.
- Young, Alexander I., Seyed Moeen Nehzati, Stefania Benonisdotir, Aysu Okbay, Hariharan Jayashankar, Chanwook Lee, David Cesarini, Daniel J. Benjamin, Patrick Turley, and Augustine Kong. 2022. "Mendelian Imputation of Parental Genotypes Improves Estimates of Direct Genetic Effects." *Nature Genetics* 54(6):897–905.