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UNDERSTANDING THE ROLE OF GENETIC HETEROGENEITY IN SMOKING INTERVENTIONS: EXPERIMENTAL EVIDENCE FROM THE LUNG HEALTH STUDY

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ABSTRACT

We examine whether genome-wide summary measures of genetic risk known as polygenic indices (PGIs) provide new insights into the efficacy of the Lung Health Study (LHS)–a large, randomized controlled trial (RCT) that evaluated the effect of a smoking cessation intervention program on cessation maintenance and lung function. Results indicate that the intervention was less successful for participants with higher PGIs for smoking initiation and intensity. Given the increasing availability and affordability of genomic data, we argue that in the context of RCTs, PGIs can further our understanding of heterogeneous treatment effects and the mechanisms that may be driving them.

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Abstract

We examine whether genome-wide summary measures of genetic risk known as polygenic indices (PGIs) provide new insights into the efficacy of the Lung Health Study (LHS)–a large, randomized controlled trial (RCT) that evaluated the effect of a smoking cessation intervention program on cessation maintenance and lung function. Results indicate that the intervention was less successful for participants with higher PGIs for smoking initiation and intensity. Given the increasing availability and affordability of genomic data, we argue that in the context of RCTs, PGIs can further our understanding of heterogeneous treatment effects and the mechanisms that may be driving them.

JEL Classification: I10, J10, J13

Keywords: Randomized controlled trial, heterogeneous treatment effects, polygenic index, smoking behavior, smoking cessation

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I. Introduction

Although 20th-century declines in smoking prevalence have persisted, tobacco use is still the leading cause of preventable disease, disability, and death in the U.S., accounting for approximately one in five deaths (CDC 2024). The persistence of smoking-related morbidity and mortality is due in part to differences in the success of smoking cessation efforts within individuals and across population subgroups (Surgeon General 2020). A growing body of research suggests cessation outcomes may in part be driven by complex interactions between genetic and environmental (including therapeutic) influences (Surgeon General 2020; Fletcher 2012; Panagiotou et al. 2019).[1] However, the integration of genetic data into the evaluation of smoking cessation efforts has been limited, and additional research is needed to better understand whether precision medicine approaches that offer different treatments to smokers based on their genetics could be effective at helping people quit (Surgeon General 2020; Panagiotou et al. 2019).

To date, randomized controlled trials (RCTs) of smoking cessation with genetic information have been limited to the analysis of candidate genes—an approach that requires a prior hypothesis that a specific gene affects responsiveness to smoking cessation therapies or drugs. A meta-analysis of candidate gene RCTs identified some evidence that individuals carrying specific genotypes may be more likely to quit smoking with the use of nicotine replacement therapies but overall found no clear statistical evidence for differences by genotype (Panagiotou et al. 2019). However, candidate gene studies of complex phenotypes like smoking may also fail to replicate due to low power at the individual gene level and/or inflated false positives resulting from

[1] Twin and family studies have established that smoking behavior is moderately to highly heritable, with genetics explaining 46-84 percent of the variability in smoking initiation and smoking persistence, 75 percent of the variability in nicotine dependence, and 50-58 percent of the variability in smoking cessation (Broms et al. 2006; Vink et al. 2005; Xian et al. 2003).

publication bias (Duncan & Keller 2011).[2] Thus, research that uses other statistical methods for genetic risk stratification may be needed to improve understanding and guide pharmacotherapy choice for smoking cessation treatments.

In particular, the candidate gene approach differs from methods that aggregate variants across the genome to construct more powerful measures of genetic risk. As will be explained in more detail herein, results from a genome-wide association study (GWAS), which performs a hypothesis-free search for associations between a phenotype and millions of genetic variants, can be used to construct a polygenic index (PGI) or a weighted average of individual genetic predisposition for that phenotype.[3] Because PGIs are objective, time-invariant, continuous measures that are more predictive than individual genetic variants, they may be beneficial for assessing heterogeneous treatment effects of programs or policies (Benjamin et al. 2012; Biroli et al. 2022). Moreover, in contrast to the traditional approach of identifying genetic risk based on subsets of the population with specific candidate genes, PGIs can identify underlying strata of disease risk in larger subsets of the population because they consider the cumulative impact of many common DNA variants spread across the genome (Fahed et al. 2022; Torkamani et al. 2018).

Additionally, given the low and continually falling cost of genomic profiling, PGIs may provide a cost-effective means to analyze biological pathways or mechanisms that drive treatment effects. Currently, for about $40 per person, researchers can profile common genetic variation and

[2] Individual genetic loci influencing the etiology of complex phenotypes like smoking have low penetrance, meaning no single gene produces a symptom or trait at a detectable level (Gibson 2012).

[3] PGIs have also been referred to in the literature as genetic risk scores (GRS), polygenic risk scores (PRS), or polygenic scores (PGS). We follow research that advocates for PGI terminology because it 1) can apply to clinical and behavioral outcomes in cases where a higher index does not correspond to increasing risk (e.g., educational attainment or subjective wellbeing), and 2) ethically, "index" has been viewed as more neutral compared to "score", which may give the false impression that a value judgment is being placed on individuals with higher or lower PGIs (Becker et al. 2021).

construct multiple PGIs for different phenotypes without incurring additional costs. Economists are increasingly utilizing PGIs in quasi-experimental studies to assess heterogeneous treatment effects from policy interventions (Schmitz and Conley 2017; Barcellos, Carvalho, and Turley 2018; Biroli et al. 2020; Fletcher and Lu 2021; Slob and Rietveld 2021). However, in the context of RCTs, PGIs remain underutilized despite their potential to enhance our understanding of how genetic diversity influences the estimation and interpretation of program effects.

In this study, we examine whether PGIs can further our understanding of treatment effect heterogeneity in a smoking cessation RCT using data from the Lung Health Study (LHS). To our knowledge, this is among the first studies in economics to use experimental variation to investigate genetic heterogeneity in treatment effects. The LHS was a large, multi-center RCT that evaluated the effect of a smoking cessation intervention program on cessation maintenance and lung function in 5,887 middle-aged smokers with early signs of chronic obstructive pulmonary disease (COPD). It was a relatively successful intervention that has been well-studied by clinicians and economists. The RCT had two treatment arms and a control arm. Both treatment groups received a smoking cessation intervention that combined behavior modification, the use of nicotine gum, and a five-year maintenance program to minimize relapse. In addition, the second treatment arm (SIA group) received a bronchodilator inhaler with the active drug ipratropium bromide (i.e., Atrovent) to assess whether it could further slow the rate of deterioration in lung function. In the five years following the initial intervention, 22 percent of treated participants had sustained quit rates compared with only five percent of control participants and showed significantly smaller declines in lung function (Anthonisen et al. 1994) and respiratory illness (Kanner and Anthonisen 2001). Downstream, the intervention reduced mortality in the treatment group by 15 percent (Anthonisen et al. 2005). In economics, research has explored the spillover impacts of the program, including

the effects of treatment intervention on spousal quit rates (Fletcher & Marksteiner 2017), increases in body mass index (BMI) (Courtemanche, Tchernis, and Ukert 2018), and improvements in mental health (Meckel and Rittenhouse 2022).

Here, we utilize genotyped data from 4,145 participants to assess whether the success of the intervention depended on PGIs for smoking initiation (SI), smoking cessation (SC), and intensity, or cigarettes per day (CPD). We found the program was less successful for participants with a higher load of genetic variants that predisposed them to smoking addiction. Specifically, although both treatment arms were 23 percentage points (ppt) more likely to quit smoking on average, the success of the intervention declined by approximately 2.5 ppt for every one standard deviation (SD) increase in the SI PGI. However, although sustained quit rates were lower in higher SI PGI participants, the treatment did reduce genetic disadvantage in smoking intensity for individuals in the SIA group, regardless of quit status. A one SD increase in the CPD PGI, which in part captures genetic predisposition to faster nicotine metabolism, reduced CPD by one additional cigarette from the average treatment effect (ATE) of nine cigarettes. Our estimates are robust to additional controls and their interaction with the treatment and cannot be replicated using observed variation in baseline values for CPD.

Further, we show that PGIs can provide insights into mechanistic pathways at the biological or behavioral level that may be driving treatment effects. In particular, our results for smoking cessation and intensity appear to be driven by genetic pathways implicated in nicotine addiction and metabolism, as opposed to other potential smoking-adjacent PGIs for body mass index (BMI), lung function, and depression.[4] We argue that the interpretation of treatment

[4] For example, Cawley, Dragone, and Scholder (2016) explore smoking as a weight control mechanism and suggest that part of cigarette demand may be driven by efforts to manage weight. Thus, the genetics of BMI may also play a role in understanding pathways that influence treatment success.

differences by these PGIs is narrower compared to other demographic or socioeconomic characteristics and by comparing across PGIs, we can better understand the degree to which different dimensions of genetic risk contribute to the success of smoking interventions. Conversely, when we interact the treatment with characteristics like education, sex, or marital status, as is common in economics literature, we observe differences that could have multiple interpretations. For example, educational differences could capture not only genetic differences but also variations in social norms, responsiveness to health risk information, financial resources, and/or time preferences (Lillard 2017; Galama, Lleras-Muney, and Van Kippersluis 2018). Additionally, we find suggestive evidence that differential results by PGI were more pronounced in the subset of treated individuals who received the bronchodilator in addition to the smoking cessation intervention. While further research is needed, this suggests additional pharmacogenomic or therapeutic effects of ipratropium that were not identified in the original study, which did not find any benefits from inhaler use.

The rest of the paper is structured as follows. Section 2 describes the LHS intervention, data, and PGI construction in more detail. Section 3 describes our empirical strategy. Section 4 presents our results, and Section 5 concludes.

II. Data

A. The Lung Health Study Intervention

The LHS RCT was conducted from 1989 to 1994 in heavy smokers aged 35-60 who were diagnosed with early stages of chronic obstructive pulmonary disease (COPD) and who were motivated to quit.[5] The study aimed to determine if a smoking cessation intervention and the use

[5] Heavy smoking was defined as use of 10 cigarettes on at least one day during the prior 30 days. See O'Hara et al. (1993) for a detailed description of the LHS study design.

of a bronchodilator could slow the rate of decline in lung function. Participants had to be relatively healthy smokers at baseline, meaning they were excluded from the study if they had serious illnesses.[6] A total of 5,887 participants were selected and randomized across ten participating clinical centers.

Eligible participants were randomly distributed into one of three groups: 1) smoking intervention plus inhaler with the active drug ipratropium bromide (Atrovent) (SIA); 2) smoking intervention plus placebo inhaler (SIP); or 3) no intervention (control group). Treated participants joined a 12-session group program over ten weeks that focused on cognitive and behavioral strategies for quitting and proper use of inhalers and nicotine gum (Connett et al. 1993; O'Hara et al. 1993). They had regular clinic visits and maintenance programs throughout the five-year follow-up. Additionally, treated participants received either an inhaler with ipratropium bromide (SIA group) or a placebo (SIP group) to assess if bronchodilator therapy slowed the rate of lung function decline. The inhaler, prescribed three times daily (two puffs/time), aimed to reduce airway hyperreactivity and improve airflow. Participants were encouraged to use the inhaler throughout the five-year trial, receiving a new supply at each four-month visit.

We utilize data from all five annual visits. Outcomes of interest include smoking cessation, which was validated by either salivary cotinine or carbon monoxide levels, and self-reported information on average CPD.

B. Polygenic Indices (PGIs)

We constructed PGIs using genotyped data that were collected from European ancestry participants with at least three time points of lung function data (N = 4,287) (Hansel et al. 2013).

[6] See Online Appendix B2 for more specifics on the LHS intervention, including additional exclusionary criteria and program details.

LHS protocols did not exclude subjects based on race or ethnicity; however, only four percent of volunteers had non-European genetic ancestry backgrounds. GWAS are typically performed within ancestry groups because differences in allele frequency[7] and linkage disequilibrium (LD) structure across populations distort estimated relationships in pooled samples, and estimates for one group are not necessarily accurate or valid for another.[8] Although genotyped sample sizes for populations of non-European descent are beginning to reach sufficient power to produce separate GWAS of smoking behavior (e.g., Shrine et al. 2023), we are limited to the European ancestry subsample since genotype data on non-European ancestry participants were not available. After quality control (QC) and imputation of the genotyped data,[9] 4,145 participants remained.[10] Importantly, at baseline, the genotyped sample had similar demographics, BMI, and lung function as those who were not genotyped, and there is no evidence of selection into the sample by treatment status (**Online Appendix Tables A1-A2**).

PGIs were constructed using coefficient estimates from GWAS. A GWAS meta-analyzes large samples of genetic data to test for associations between millions of single nucleotide polymorphisms (SNPs), or areas on the genome that vary between individuals, and a given phenotype of interest.[11] SNP effect sizes from GWAS were then used to construct a PGI for each

[7] Allele frequency represents the incidence of a genetic variant in a population.

[8] LD occurs when genetic variants are correlated with each other because of a lack of ancestral recombination events at locations in the DNA over time but could also arise from non-random mating in the population.

[9] See Online Appendix B3 for details on QC and imputation of the genotyped data.

[10] Genotyped data were merged with phenotype data based on several characteristics (a common identifier across the two samples was not available). After QC, 4,196 respondents out of 5,887 remained, and 51 could not be matched to the phenotypic data. Our final sample consists of 4,145 genotyped participants or 20,725 person-year observations across all five waves of the study.

[11] In the discovery phase, a GWAS will pool large consortia of genetic data using meta-analysis and run regressions testing each SNP at the genome-wide significance level of 5x10-8. In the replication phase, significant associations found in the discovery phase are tested in independent samples.

participant by multiplying the number of reference alleles a participant has at each SNP by the GWAS coefficient estimate for that SNP, and then aggregating these values across the genome to create a weighted scalar of genetic predisposition as follows:

$$PGI_i = \sum_{j=1}^{n} \beta_j \alpha_{ij} \quad (1)$$

Where *j* indexes the SNP, *i* indexes the individual, β is the coefficient estimate for SNP *j* from the GWAS, and α is the number of reference alleles (0, 1, or 2) for individual *i* at SNP *j*. PGIs were constructed using β estimates from GWAS available for SI, SC, and CPD (Liu et al. 2019). Additionally, PGIs for phenotypes with known biological ties to smoking behavior were constructed to examine other potential mechanistic pathways that may be driving treatment effects, including PGIs for BMI (Yengo et al. 2018), lung function (FEV_1/FVC ratio)[12] (Shrine et al. 2019), and depression (Nagel et al. 2018). Correlations between these PGIs are relatively weak, indicating limited genetic overlap (all $r<0.20$) (**Online Appendix Figure A1**). To avoid overfitting, we confirmed that the LHS sample was not included in the GWAS of interest.

To maximize prediction, PGIs were constructed using the software PRS-CS-auto, which uses a Bayesian framework to readjust SNP β weights from the GWAS to account for local LD patterns (Ge et al. 2019).[13] All PGIs were standardized to have a mean of zero and a standard deviation of one for analysis. Higher PGIs for SI, SC, and CPD are associated with worse outcomes (i.e., a higher probability of becoming a regular smoker, a higher probability of not

[12] FEV_1/FVC is a ratio used in the diagnosis of lung diseases, particularly obstructive and restrictive lung conditions. It stands for forced expiratory volume in one second (FEV_1) over forced vital capacity (FVC) and is measured using spirometry. FEV_1 is the volume of air exhaled during the first second of forced exhalation and FVC is the total volume of air exhaled during the entire exhalation.

[13] PRS-CS-auto models local LD patterns and uses a Bayesian regression framework with continuous shrinkage priors on SNP effect sizes to accommodate diverse underlying genetic architectures. It automatically learns the continuous shrinkage prior from the GWAS summary statistics, and no validation dataset is needed. We used the 1000 Genomes Project Phase 3 European samples as the LD reference (Auton et al. 2015).

quitting, and increases in CPD). Similarly, for BMI, depressive symptoms, and lung function, higher PGIs are associated with worse outcomes. In analyses with PGIs, we account for population stratification by controlling for the first 20 principal components (PCs) of the genetic data (Price et al. 2006).[14]

Online Appendix Table A3 reports the predictive power of the PGIs in the LHS sample, or the incremental R^2 from a regression of the phenotype on the PGI after conditioning on the first 20 PCs. The SC PGI explains 0.2 percent of the variance in quit status (across all five visits), and the CPD PGI explains 3.3 percent of the variance in CPD at baseline. The BMI PGI explains 8.8 percent of the variance in BMI at baseline, and the FEV_1/FVC PGI explains 0.01 percent of the variance in FEV_1/FVC at baseline. These estimates are on par with the predictive power of these PGIs in larger population-based studies (Yengo et al. 2018; Liu et al. 2019). Further, if we stratify participants by PGI quintile, we see a gradual increase in the outcome mean across quintiles of the CPD, BMI, FEV_1/FVC, and depression PGIs (**Online Appendix Figures A2-A5**).[15]

Not surprisingly, because the SI PGI was trained to predict the probability of becoming a regular smoker or smoking at least 100 cigarettes, it only explains 0.03 percent of the variation in smoking cessation. However, we include it in our analyses because it captures other biological pathways that are distinct from those implicated in the SC or CPD PGIs that could interact with the treatment, including pathways involved in dopaminergic and neurotransmission systems that

[14] Although our analyses are limited to individuals of European ancestry, estimates still need to account for population stratification within ancestry that could confound associations between the PGI and the phenotype of interest. Population stratification arises when ancestral subpopulations are isolated geographically, with low rates of migration and gene flow throughout several generations (Hellwege et al. 2017). Cultural and environmental differences can also induce stratification, even if population subgroups inhabit the same geographical region (ibid). Additionally, assortative mating can produce population structure-related confounding effects (Young et al., 2019). PCs were calculated using PLINK software (Purcell et al. 2007).

[15] Results are not presented for smoking cessation because we do not have baseline pre-treatment values for quit status.

affect long-term reward processing and addiction (Liu et al. 2019). As a point of comparison, in **Online Appendix Table A3,** we also report incremental R^2 estimates between our outcomes of interest and demographic characteristics that are often used to analyze heterogenous treatment effects of smoking interventions, including sex and marital status. The PGIs either explain a greater proportion of the variance in our outcomes of interest, or their explanatory power is not significantly different from these characteristics.

The predictive power of a PGI depends on the trait's heritability and the power of the GWAS from which it was derived (Wray et al. 2019). Although the predictive power of the PGIs in the LHS sample is not negligible, it is a fraction of SNP-based measures of heritability for these phenotypes, which range from approximately five percent for smoking cessation to eight percent for SI and CPD (Liu et al. 2019).[16] Thus, the predictive power of these PGIs will likely increase as GWAS sample sizes continue to grow. However, because GWAS estimates exploit pooled samples of unrelated individuals, the predictive power of the PGI may also exceed what can be explained by direct genetic effects because estimates in unrelated individuals also capture indirect genetic effects and confounding from population stratification (Young 2019).[17] Conditioning on the first 20 PCs of the genetic data accounts for any confounding from population stratification (Price et al. 2006). Thus, the remaining variation in the PGIs reflects both direct and indirect genetic effects. To isolate direct genetic effects, researchers are beginning to conduct within-

[16] Heritability is often estimated using phenotype correlations between identical and non-identical twins, however GWAS data on unrelated individuals can also be used to estimate the phenotypic variation explained by SNPs on a genotyping array (Yang et al. 2017). These so-called SNP-based heritability estimates are typically lower than twin-based heritability estimates (Manolio et al. 2009). Some of this gap may be explained by rare genetic variants that are not captured on genotype arrays, which were designed to capture common genetic variation within ancestral populations.

[17] Indirect effects may arise because a genetic variant's effect is working through other (indirect) biological or environmental pathways. For example, a variant may influence a trait via its effect on parental behavior.

family GWASs that exploit genetic data on parent-offspring trios and sibling pairs (Howe et al. 2022). However, because larger genotyped family samples are needed to reach sufficient power, these efforts are still in their infancy.

C. Summary Statistics

Table 1 compares baseline characteristics for the sample by treatment status. Mean values at baseline are comparable across groups. On average, participants were approximately 48.5 years old at the start of the trial (SD=6.7), 35-39 percent female (SD=0.48), and had 13.6 years of education (SD=2.8). Participants were long-term heavy smokers, having smoked an average of one pack per day for 40.7 years (SD=18.2) and were currently smoking an average of 31 CPD at baseline (SD=12.5). The average FEV_1/FVC ratio across all groups was 63 percent (SD=5.5), which is seven ppt below the normal value of 70 percent, indicating early signs of lung function decline. The average BMI was 25.5 (SD=3.9), which is comparable to the U.S. average in 1990 for that age group (Freedman et al. 2002). The PGIs, which were standardized to have a mean of zero and an SD of one in the full analysis sample, exhibit similar distributions across treatment and control subgroups.

Online Appendix Figure A6 shows the per-wave averages for smoking cessation and CPD from baseline through wave five by treatment status for the genotyped sample. Overall, the treatment was successful: quit rates were approximately 38 percent for both treatment arms across all waves, compared to an initial 9 percent for the control group, which increased to 23 percent by the fifth visit. Average CPD declines were sharper for the treatment group (20) compared to the control group (13).

III. Empirical Strategy

To examine whether treatment effects varied by PGI, we estimate the following equation:

$$Y_{ict} = \alpha + \beta Treated_i + \gamma PGI_i + \delta Treated_i \times PGI_i + \theta Female_i + PC_i'\pi + \rho_c + \sigma_t + \varepsilon_{it} \quad (2)$$

where Y_{ict} is the outcome of individual i observed at age c in visit t, $Treated_i$ is an indicator for whether individual i was assigned to one of the treatment arms, PGI_i is the polygenic index of interest for i, and PC_i is a matrix containing the first 20 PCs of the genetic data to account for population stratification. We also control for sex and include fixed effects for age (ρ_c) and visit (σ_t) to improve the precision of our estimates. Regressions are estimated separately for each treatment arm and both treatment groups combined. Standard errors are clustered at the individual level.

Our parameter of interest is δ, which captures the degree to which the average treatment effect (β) varies by participants' underlying PGI. If δ is significantly different from zero, it implies that the efficacy of the treatment was dependent on participants' underlying PGI. Models with continuous outcomes are estimated using ordinary least squares (OLS). For dichotomous degree outcomes, we report results estimated from linear probability models.

IV. Results

A. Heterogeneous treatment effects by PGI

Table 2 presents the main effects and heterogenous treatment effects for SC and CPD. Columns report results separately for both treatment arms combined (Composite) and for the SIA and SIP arms. Treated individuals were 23 ppt more likely to quit smoking, regardless of the treatment arm, which is comparable to results from the original trial. Since participants in the trial were already heavy smokers, we did not find a significant main effect of the SI PGI on quit status, which was trained to predict the probability of regular smoking relative to individuals who never

smoked. However, we do find that the treatment effect was smaller for participants with higher SI PGIs: a one SD increase in the SI PGI reduced the likelihood of quitting by an additional 2.5 ppt for both treatment arms combined. Conversely, while there is a statistically significant main effect of the SC PGI on quit rates, the effect of the treatment does not vary by the SC PGI (**Online Appendix Table A4**). This could reflect stronger interactive effects between the intervention and genetic variants identified in the SI GWAS, which play a larger role in sustaining neuronal pathways that regulate reward processing and addiction, as opposed to pathways implicated in the SC and CPD PGIs, which are more involved in regulating nicotine metabolism.[18]

The magnitude and significance of the SI PGI interaction appear to be driven by individuals in the SIA arm, where we observe a 3.5 ppt statistically significant reduction in quit rates for each SD increase in the PGI compared to a statistically insignificant reduction of 1.3 ppt for participants in the SIP arm. This may suggest additional pharmacogenomic effects of the ipratropium inhaler that were not identified in the original study, which did not detect differences in cessation or FEV_1/FVC between the SIA and SIP treatment arms. Ipratropium is an antimuscarinic that reduces airway reactivity in smokers by blocking the muscarinic cholinergic receptors, which in turn both decreases the production of certain proteins that increase mucous production and dilates bronchial smooth muscle in the lungs. Importantly, antimuscarinics can act on muscarinic receptors in the brain and have been shown to decrease the intensity of cravings in patients recovering from cocaine use (Grasing 2016). Because the SI PGI is enriched for central nervous system functions related to reward processing and addiction, this may explain why we see a potential pharmacogenomic

[18] For example, well-researched candidate genes that have been replicated in GWAS of CPD and SC include the nicotine metabolism gene *CYP2A6* and the *CHRNA5-A3-B4* gene cluster, which encodes subunits of nicotinic acetylcholine receptors (nAChR) (Liu et al. 2019). Conversely, genes implicated in SI are more related to the modulation of dopamine reward circuits that promote continued use of nicotine after initial exposure, including *BDNF* and *PPP1R1B*, which regulate neuronal plasticity that underlies reward-based learning (Furberg et al. 2010; Liu et al. 2019).

interaction with the SI PGI as opposed to the SC PGI. However, because estimates for the treatment arms are not significantly different from one another, this interpretation is suggestive and in need of further study.

Concerning smoking intensity, the treatment significantly reduced genetic disadvantage in CPD at the extensive margin, regardless of quit status: A one SD increase in the CPD PGI reduced CPD by one additional cigarette relative to the ATE of nine cigarettes. These results can also be seen in **Figure 1,** which plots the estimated treatment effects by PGI for quit status and CPD. The treatment increased genetic disparities in smoking cessation relative to the control group. In other words, the treatment was not as effective in curbing quit rates for participants with higher genetic risk; however, although higher PGI participants had more difficulties quitting, the intervention did appear to reduce genetic disparities in CPD such that by the end of the trial, treated participants with higher CPD PGIs were no longer smoking more CPD on average than participants with lower PGIs. Finally, the magnitude and significance of the CPD PGI interaction are stronger for participants in the SIA arm. However, like smoking cessation, these estimates are not statistically different between treatment arms.

B. Using PGIs to enhance understanding of treatment pathways

Examining the interplay between the treatment and other PGIs related to smoking behavior may provide additional clues on the mechanisms through which genetic factors are influencing treatment outcomes (Biroli et al. 2022; Barth, Papageorge, and Thom 2020). To assess whether our results are driven by smoking genetics as opposed to other genetic pathways that could influence smoking behavior, we added additional PGI interactions with the treatment to our empirical model (**Table 3**). These results also condition on interactions between the genetic PCs and the treatment. Importantly, we focused on PGIs that contain genetic variants with known

pleiotropic effects[19] on smoking or PGIs with biological ties to smoking behavior, including PGIs for BMI, FEV_1/FVC, and depression.[20] Of note, we do not include the educational attainment PGI in our analyses because past research has shown that its correlation with smoking PGIs for these birth cohorts is driven by the emergence of the educational gradient in smoking and is thus a byproduct of environmental forces as opposed to genetic differences in cognitive ability or risk preferences (Galama, Lleras-Muney, and Van Kippersluis 2018; Wedow et al. 2018;).[21]

Our results are robust to the inclusion of these additional PGIs, and their interactions with the treatment are smaller in magnitude and less precise than the SI and CPD PGI interaction effects. This suggests that differences in treatment success were operating primarily through the genetics of smoking as opposed to genetic pathways implicated in BMI, lung function, or depression PGIs.

C. Additional analyses and robustness checks

The magnitude of the PGI-by-treatment interaction effect is comparable to other heterogeneous treatment effects by gender, education, and marital status (**Table 4**). Being married increased the likelihood of smoking cessation for treated participants by 4.4 ppt, perhaps due to spousal spillover effects, which have been documented previously in the LHS (Fletcher and

[19] Pleiotropic effects could manifest as biological or mediated pleiotropy. Biological pleiotropy occurs when a genetic variant has a direct or independent influence on more than one trait, whereas mediated pleiotropy occurs when a variant affects smoking behavior through its effect on another trait (Solovieff et al. 2013).

[20] Multiple variants identified in GWAS of BMI appear to play a role in both increased obesity and smoking, including variants in the *CHRNA5-A3-B4* gene cluster (e.g., Thorgeirsson et al. 2013; Wang et al. 2017). For lung function, research has identified positive genetic correlations between CPD, SC, and the risk of lung cancer and COPD such that genetic variants that alter smoking are also thought to contribute to genetic risk for lung cancer and COPD, including variants in the *CHRNA5-A3-B4* gene cluster and chromosomal region 19q13.2, which includes *CYP2A6*, the gene encoding the enzyme that metabolizes nicotine (e.g., Parker et al. 2019; Bray et al. 2020). Finally, studies support the existence of genetic correlation between SI and depressive symptoms (Bulik-Sullivan et al. 2015; Zheng et al. 2017). Although more research is needed, results suggest that bidirectional associations between depressive symptoms and SI may be partially accounted for by shared genetic factors (Schmitz, Gard, and Ware 2019).

[21] This is consistent with prior research that suggests latent traits like intelligence play a limited role in explaining socioeconomic disparities in rates of smoking (Cutler and Lleras-Muney 2006; Pampel, Krueger, and Denney 2010).

Marksteiner 2017). Every one-year increase in education in the treated group increased the probability of cessation by 1.1 ppt. Treated female participants smoked 2.4 CPD more per day than treated males. There were no significant differences in CPD for treated participants by marital status or education.

As a counterpoint to the PGI estimates, we assessed whether we could draw similar conclusions for smoking cessation using pretreatment or baseline variation in smoking behavior (**Online Appendix Table A5** and **Figure A7)**. Since quit status cannot be observed pre-treatment, we used baseline variation in CPD. While baseline CPD is negatively associated with lower quit rates post-treatment, we do not find evidence of differences in smoking cessation by baseline CPD. Additionally, our SI PGI interaction findings are robust to controls for baseline CPD and its interaction with the treatment. These results suggest the SI PGI is capturing unique pre-treatment variation in quit status that is not captured in observed smoking behavior at baseline.

Finally, we evaluated whether the average effect estimated across all visits varied in the short or medium term. Effects remain consistent across visits except for the main effect of the treatment on smoking cessation and CPD (**Online Appendix Tables A6-A7**). Here, the treatment effect decreases by approximately one-third to one-half for smoking cessation and CPD, respectively, but the effects of the PGIs and their interaction with the treatment remain stable across visits. This implies that the relative advantages (or disadvantages) conferred to participants from their genetics remained relatively stable throughout the trial.

V. Conclusion

To improve public health, more effective smoking cessation efforts are needed to reduce disparities in smoking-related morbidity and mortality. Understanding factors that contribute to

disparities in treatment efficacy is crucial for evaluating existing policies and using data to forecast the success of new programs and interventions (Heckman 2001). This study leveraged advances in statistical genetics and data from a large smoking cessation RCT to assess whether the impact of the treatment varied by PGIs for smoking behavior. Results indicate that quit rates were lower for genetically at-risk participants. However, regardless of quit status, the treatment did reduce genetic disparities in smoking intensity such that treated participants with higher genetic risk were no longer smoking more CPD on average compared to their lower-risk counterparts.

This suggests the efficacy of cessation treatments may be improved by assigning participants to specific treatments based on the results of genetic testing. Likewise, focusing on participants who are more genetically responsive to interventions may increase the statistical power of RCTs by increasing the relative proportion of participants that are more responsive to the intervention, thereby decreasing sample size and cost while also increasing the benefits of the trial (Fahed, Philippakis, and Khera 2022). However, before pharmacogenetic stratification becomes routine, further clinical trials are needed, both to assess whether this approach improves overall cessation outcomes in a substantial way for participants in high-risk strata as well as to determine the cost-effectiveness of this approach (Surgeon General 2020).

Despite these promises, several limitations warrant discussion. First, the predictive power of PGIs is dependent on trait heritability and the power of the GWAS from which they were derived, which in turn may limit their utility in certain settings (Daetwyler, Villanueva, and Woolliams 2008). For example, certain behavioral outcomes of interest to economists may be difficult to apply to a GWAS setting because they are not available in large studies with genetic data or because they are empirically difficult to measure or define. Moreover, if the heritability of a trait is low, the PGI may not have adequate predictive power to quantify strata of genetic risk.

Second, because PGIs capture phenotypic differences that arise from common DNA variants, they may misrepresent genetic risk in situations where rare variants play an outsize role in the onset or progression of a disease or trait (Lewis and Vassos 2020). Third, because GWAS meta-analyzes summary statistics across samples of unrelated individuals to achieve adequate sample size, they capture not only direct genetic effects but also indirect effects and confounding from population stratification (Young 2019). Although this presents a challenge for identifying causal variants, there is limited evidence in the literature regarding the extent to which these issues impact the use of PGIs for risk stratification and precision medicine. Fourth, because the majority of GWAS to date have been conducted in individuals of European ancestry, their predictive power may be limited in other ancestral groups (Martin et al. 2019).

However, we view these current challenges as temporary and empirically tractable as the size of genetic samples continues to increase dramatically due to persistent and rapid declines in the cost of whole genome sequencing. In particular, new statistical methods coupled with large-scale global efforts aimed at increasing the diversity of genetic samples are already reducing disparities in PGI prediction across ancestral populations (Ruan et al., 2022; Miao et al. 2023) and fueling the discovery of new disease-related variants (Gudmundsson et al. 2022). Increasing genetic samples in family and sib-based studies will improve the power of within-family GWAS and aid in decomposing direct and indirect genetic effects (Wu et al., 2021.; Howe et al. 2022). Finally, future improvements in algorithms and machine learning approaches that can incorporate other molecular and biomarker data alongside genetic data may outperform current PGI aggregation methods and improve our understanding of mechanistic pathways (Eldjarn et al. 2023).

Tables and Figures

Table 1. Mean baseline characteristics by treatment status for the LHS genetic sample

	Control		SIP		SIA	
	Mean	SD	Mean	SD	Mean	SD
Baseline characteristics						
Age	48.471	6.727	48.694	6.741	48.450	6.681
Female	0.351	0.478	0.362	0.481	0.394	0.489
Pack years	40.731	18.244	40.338	18.173	40.682	19.481
Years of education	13.647	2.769	13.563	2.849	13.630	2.833
Cigarettes per day (CPD)	30.950	12.501	31.468	12.524	31.333	13.173
Married	0.706	0.456	0.714	0.452	0.704	0.457
Body mass index (BMI)	25.508	3.804	25.769	3.862	25.318	3.854
FEV_1/FVC	63.028	5.450	63.055	5.432	62.750	5.659
Polygenic indices (PGIs)						
Smoking initiation (SI)	-0.067	0.979	0.047	1.000	0.021	1.018
Smoking cessation (SC)	-0.005	0.983	0.013	1.043	-0.008	0.974
Cigarettes per day (CPD)	-0.024	0.970	-0.041	0.998	0.063	1.029
Body mass index (BMI)	-0.020	0.970	0.012	0.985	0.008	1.043
FEV_1/FVC	0.038	0.996	-0.011	1.002	-0.027	1.002
Depression	0.023	1.001	-0.027	0.994	0.003	1.005
N	1383		1355		1407	

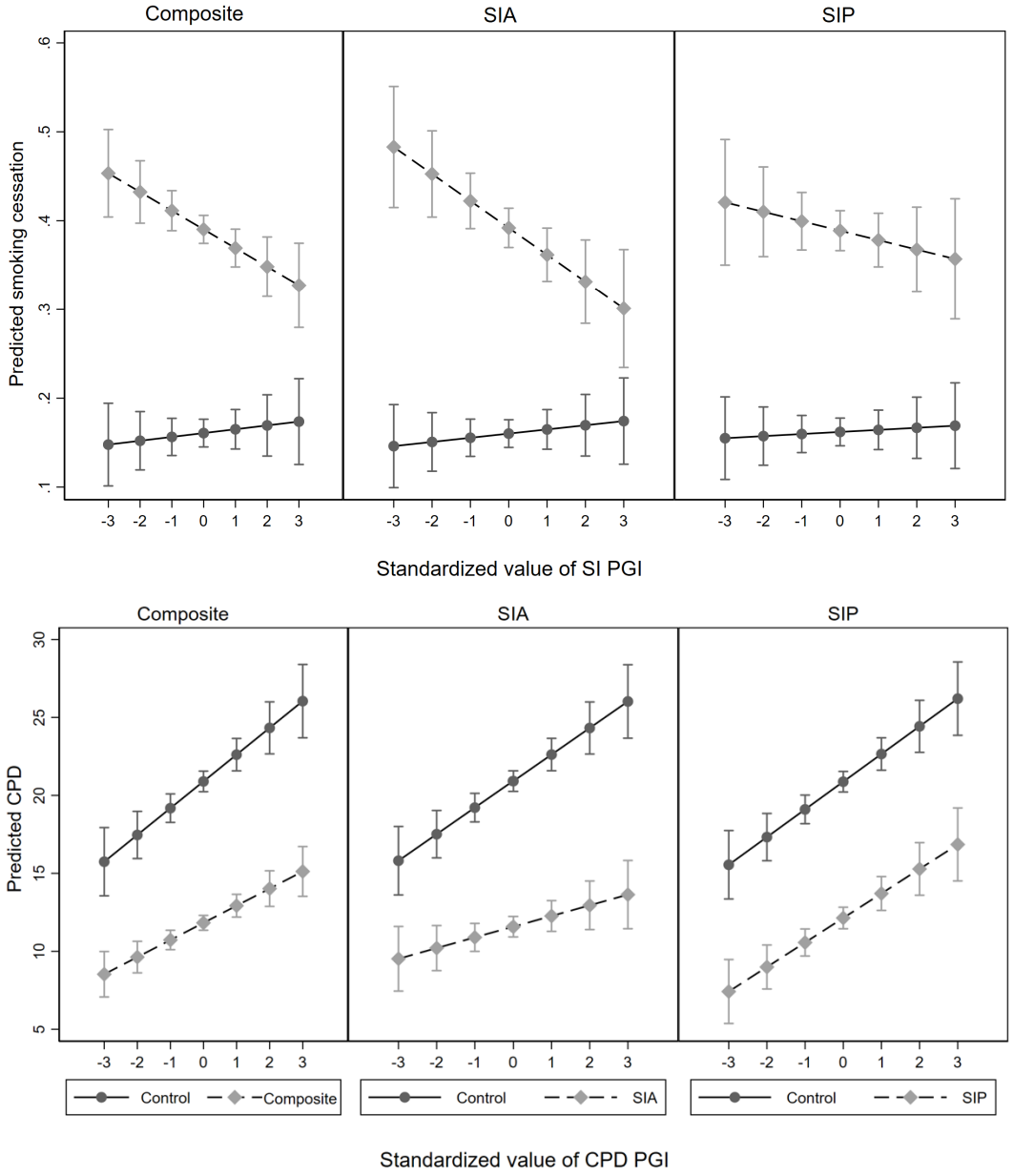
Note: The table presents the mean and standard deviation (SD) of baseline characteristics by treatment status for the LHS genetic sample. FEV_1/FVC: forced expiratory volume in one second (FEV_1) divided by forced vital capacity (FVC). SIA: smoking intervention plus Atrovent inhaler group. SIP: smoking intervention plus placebo inhaler group. Pack years are calculated by multiplying the number of cigarettes smoked per day by the number of years smoked. PGIs are standardized to have a mean of zero and an SD of one in the full sample.

Table 2. Heterogeneous treatment effects of the LHS intervention on smoking outcomes by PGIs for smoking initiation and cigarettes per day

	Composite	SIA	SIP
Panel I		Smoking Cessation	
Treated	0.230	0.232	0.227
	(0.011)	(0.014)	(0.014)
SI PGI (std)	0.004	0.005	0.002
	(0.008)	(0.008)	(0.008)
Treated × SI PGI (std)	-0.025	-0.035	-0.013
	(0.011)	(0.013)	(0.013)
N	20,725	13,950	13,690
Panel II		CPD	
Treated	-9.072	-9.340	-8.742
	(0.415)	(0.474)	(0.489)
CPD PGI (std)	1.717	1.703	1.776
	(0.370)	(0.371)	(0.370)
Treated × CPD PGI (std)	-0.618	-1.017	-0.204
	(0.441)	(0.502)	(0.508)
N	20,279	13,644	13,404

Note: SI: smoking initiation; CPD: cigarettes per day. Composite indicates both treatment arms combined. SIA: smoking intervention plus Atrovent inhaler group. SIP: smoking intervention plus placebo inhaler group. PGIs are standardized. All regressions control for age fixed effects, wave fixed effects, sex, and genetic PCs 1-20. Standard errors are clustered at the individual level.

Figure 1. Treatment effects of the LHS intervention on smoking cessation and cigarettes per day by PGI



Note: The figure shows predicted smoking cessation and cigarettes smoked per day (CPD) by standardized values of the smoking initiation (SI) and CPD PGIs, respectively. Composite indicates both treatment arms combined. SIA: smoking intervention plus Atrovent inhaler group. SIP: smoking intervention plus placebo inhaler group. Estimates are from regressions that control for age fixed effects, wave fixed effects, sex, and genetic PCs 1-20. Standard errors are clustered at the individual level. 95% confidence intervals are reported.

Table 3. Heterogeneous treatment effects of the LHS intervention on smoking outcomes by PGIs for smoking, body mass index, lung function, and depression

	Composite	SIA	SIP
		Smoking cessation	
Treated	0.229	0.230	0.227
	(0.011)	(0.014)	(0.014)
SI PGI (std)	0.002	0.002	0.001
	(0.008)	(0.008)	(0.008)
Treated × SI PGI (std)	-0.020	-0.029	-0.010
	(0.011)	(0.014)	(0.014)
CPD PGI (std)	-0.014	-0.014	-0.015
	(0.008)	(0.008)	(0.008)
Treated × CPD PGI (std)	0.012	0.032	-0.007
	(0.012)	(0.014)	(0.014)
BMI PGI (std)	0.004	0.004	0.004
	(0.009)	(0.009)	(0.009)
Treated × BMI PGI (std)	-0.012	-0.018	-0.009
	(0.012)	(0.014)	(0.015)
FEV_1/FVC PGI (std)	0.003	0.003	0.004
	(0.009)	(0.009)	(0.009)
Treated × FEV_1/FVC PGI (std)	0.000	0.001	-0.001
	(0.012)	(0.014)	(0.014)
Depression PGI (std)	0.003	0.003	0.003
	(0.008)	(0.008)	(0.008)
Treated × Depression PGI (std)	-0.012	-0.017	-0.007
	(0.012)	(0.014)	(0.014)
N	20,725	13,950	13,690
		CPD	
Treated	-9.066	-9.260	-8.805
	(0.424)	(0.485)	(0.497)
SI PGI (std)	0.019	0.015	0.045
	(0.340)	(0.340)	(0.339)
Treated × SI PGI (std)	0.404	0.699	0.086
	(0.419)	(0.480)	(0.487)
CPD PGI (std)	1.820	1.815	1.845
	(0.372)	(0.373)	(0.371)
Treated × CPD PGI (std)	-0.796	-1.329	-0.307
	(0.449)	(0.515)	(0.519)
BMI PGI (std)	-0.245	-0.245	-0.243
	(0.363)	(0.364)	(0.363)
Treated × BMI PGI (std)	0.142	0.318	0.034
	(0.437)	(0.494)	(0.506)
FEV_1/FVC PGI (std)	0.254	0.253	0.216
	(0.349)	(0.351)	(0.350)

Treated × FEV_1/FVC PGI (std)	0.192	0.075	0.362
	(0.430)	(0.497)	(0.497)
Depression PGI (std)	-0.268	-0.267	-0.258
	(0.348)	(0.349)	(0.348)
Treated × Depression PGI	0.726	0.919	0.534
	(0.430)	(0.490)	(0.507)
N	20,279	13,644	13,404

Note: Composite indicates both treatment arms combined. SIA: smoking intervention plus Atrovent inhaler (ipratropium bromide) group; SIP: smoking intervention plus placebo inhaler group. FEV_1/FVC: forced expiratory volume in one second (FEV_1) over forced vital capacity (FVC). PGIs are standardized. All regressions control for age fixed effects, wave fixed effects, sex, genetic PCs 1-20, and genetic PCs 1-20 interacted with the treatment. Standard errors are clustered at the individual level.

Table 4. Heterogeneous treatment effects of the LHS intervention on smoking outcomes by smoking PGIs and demographic characteristics

	Composite	SIA	SIP
	Smoking Cessation		
Treated	0.054	-0.015	0.139
	(0.064)	(0.076)	(0.080)
SI PGI (std)	0.005	0.005	0.003
	(0.008)	(0.008)	(0.008)
Treated × SI PGI (std)	-0.023	-0.031	-0.012
	(0.011)	(0.013)	(0.013)
Married	0.013	0.016	0.012
	(0.018)	(0.018)	(0.018)
Treated × Married	0.044	0.074	0.009
	(0.025)	(0.030)	(0.031)
Years of Education	0.005	0.005	0.004
	(0.003)	(0.003)	(0.003)
Treated × Years of Education	0.011	0.015	0.006
	(0.004)	(0.005)	(0.005)
Female	-0.010	-0.010	-0.009
	(0.017)	(0.017)	(0.017)
Treated × Female	-0.016	-0.017	-0.015
	(0.024)	(0.029)	(0.030)
N	20,720	13,945	13,685
	CPD		
Treated	-7.856	-6.844	-8.996
	(2.360)	(2.648)	(2.766)
CPD PGI (std)	1.699	1.689	1.735
	(0.364)	(0.365)	(0.365)
Treated × CPD PGI (std)	-0.695	-1.072	-0.266
	(0.437)	(0.496)	(0.509)
Married	-2.838	-2.922	-2.848
	(0.782)	(0.780)	(0.784)
Treated × Married	-0.188	-0.515	0.283
	(0.962)	(1.102)	(1.121)
Years of Education	-0.266	-0.265	-0.243
	(0.125)	(0.125)	(0.125)
Treated × Years of Education	-0.140	-0.244	-0.032
	(0.149)	(0.166)	(0.176)
Female	-3.627	-3.616	-3.657
	(0.698)	(0.697)	(0.698)
Treated × Female	2.357	3.336	1.373
	(0.851)	(0.973)	(0.988)
N	20,274	13,639	13,399

Note: Composite indicates both treatment arms combined. SIA: smoking intervention plus Atrovent inhaler group. SIP: smoking intervention plus placebo inhaler group. PGIs are standardized. All regressions control for age fixed effects, wave fixed effects, sex, and genetic PCs 1-20. Standard errors are clustered at the individual level.

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SUPPLEMENTAL APPENDICES

Understanding the Role of Genetic Heterogeneity in Smoking Interventions: Experimental Evidence from the Lung Health Study

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APPENDIX A

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Appendix A

Table A1. Mean Baseline Characteristics of the Lung Health Study (LHS) Sample by Genotyped Status

Variables	Not Genotyped	Genotyped	p-value of difference in means
Body mass index (BMI)	25.650	25.529	0.280
Cigarettes per day (CPD)	31.328	31.249	0.830
FEV_1/FVC	62.923	62.943	0.899
Age	48.306	48.537	0.236
Pack years	40.127	40.586	0.401
Years of education	13.598	13.614	0.844
Female	0.375	0.370	0.703
N	1,742	4,145	

Note: The table reports average respondent background characteristics for LHS participants stratified by genotyped status. All variables were measured at baseline before the treatment was administered. We additionally report the p-values of the differences in means for each variable.

Table A2. Impact of Treatment Status on the Probability of Being Genotyped in the Lung Health Study (LHS)

	Genotyped
Treated	0.001
	(0.013)
N	5,887

Note: The table reports the effect of treatment on the probability of being genotyped in the LHS. The total number of participants is 5,887. The regression controls for age fixed effects and sex. Robust standard errors are reported in parentheses.

Table A3. Incremental R^2 Values of Polygenic Indices and Demographic Characteristics

PGIs	Smoking cessation (all waves)	CPD (baseline)	BMI (baseline)	FEV_1/FVC (baseline)
SC PGI	0.19%			
Bootstrapped SE	(0.056)			
p-value	0.002			
SI PGI	0.03%			
Bootstrapped SE	(0.02)			
p-value	0.242			
CPD PGI		3.33%		
Bootstrapped SE		(0.55)		
p-value		0.000		
BMI PGI			8.82%	
Bootstrapped SE			(0.84)	
p-value			0.000	
FEV_1/FVC PGI				0.01%
Bootstrapped SE				(0.35)
p-value				0.000
Demographic characteristics				
Sex	0.07%	2.15%	8.39%	0.26%
Bootstrapped SE	(0.037)	(0.433)	(0.83)	(0.16)
p-value	0.053	0.000	0.000	0.097
Married	0.17%	0.03%	0.87%	0.01%
Bootstrapped SE	(0.056)	(0.062)	(0.31)	(0.05)
p-value	0.003	0.639	0.006	0.788

Note: The table reports the incremental R^2 values of PGIs and demographic characteristics for smoking cessation (SC), smoking initiation (SI), cigarettes per day (CPD), body mass index (BMI), and lung function, or forced expiratory volume in one second over forced vital capacity (FEV_1/FVC). For all the variables except smoking cessation, we use baseline measures (data on smoking cessation is not available before the treatment). Each estimate comes from a regression of the outcome variable on the PGI or demographic characteristic after residualizing out the first 20 genetic principal components (PCs) to account for population stratification. Bootstrapped standard errors with 1000 replications and corresponding p-values are reported in parentheses.

Table A4. Heterogeneous Treatment Effects of the LHS Intervention on Smoking Cessation by SC PGI

	Composite	SIA	SIP
	(1)	(2)	(3)
	Smoking Cessation		
Treated	0.229	0.232	0.227
	(0.011)	(0.014)	(0.014)
SC	-0.015	-0.013	-0.017
	(0.008)	(0.009)	(0.008)
Treat × SC PGI (std)	-0.009	-0.002	-0.014
	(0.011)	(0.014)	(0.013)
N	20,725	13,950	13,690

Note: The table reports the heterogeneous effects of the treatment on the probability of quitting smoking. Composite indicates both treatment arms combined. SIA: smoking intervention plus Atrovent inhaler group. SIP: smoking intervention plus placebo inhaler group. The PGI is standardized. All the regressions control for age fixed effects, wave fixed effects, sex, and the first 20 principal components (PCs) of the genetic data to account for population stratification. Standard errors clustered at the individual level are reported in the parentheses.

Table A5. Heterogeneous Treatment Effects of the LHS Intervention on Smoking Cessation by Baseline CPD and SI PGI

	Composite	SIA	SIP
	Smoking Cessation		
Panel I			
Treated	0.229	0.230	0.227
	(0.011)	(0.014)	(0.014)
Baseline CPD (std)	-0.029	-0.030	-0.028
	(0.009)	(0.009)	(0.009)
Treat × Baseline CPD (std)	0.012	0.009	0.017
	(0.012)	(0.014)	(0.015)
Panel II			
Treated	0.231	0.233	0.228
	(0.011)	(0.014)	(0.014)
Baseline CPD (std)	-0.028	-0.029	-0.028
	(0.009)	(0.009)	(0.009)
Treat × Baseline CPD (std)	0.013	0.010	0.017
	(0.012)	(0.014)	(0.015)
SI PGI (std)	0.004	0.005	0.002
	(0.008)	(0.008)	(0.008)
Treat × SI PGI (std)	-0.025	-0.034	-0.013
	(0.011)	(0.013)	(0.013)
N	20,725	13,950	13,690

Note: Panel I of this table reports heterogeneous treatment effects of cigarettes smoked per day (CPD) at baseline on smoking cessation. These regressions control for age fixed effects, wave fixed effects, and sex. Panel II adds the smoking initiation (SI) PGI and its interaction. Regressions in Panel II also control for the first 20 principal components (PCs) of the genetic data to account for population stratification. Standard errors clustered at the individual level are reported in parentheses.

Table A6. Heterogeneous Treatment Effects of the LHS Intervention on Smoking Cessation by Smoking Initiation PGI and Annual Visit

	Annual Visit				
	1	2	3	4	5
Panel 1			Composite		
Treated	0.288	0.240	0.235	0.205	0.183
	(0.012)	(0.013)	(0.014)	(0.014)	(0.015)
SI PGI (std)	0.002	0.007	0.011	-0.003	0.002
	(0.007)	(0.009)	(0.010)	(0.011)	(0.012)
Treat × SI PGI (std)	-0.021	-0.020	-0.033	-0.014	-0.033
	(0.012)	(0.013)	(0.013)	(0.014)	(0.015)
N	4,145	4,145	4,145	4,145	4,145
Panel II			SIA		
Treated	0.296	0.243	0.232	0.204	0.187
	(0.015)	(0.016)	(0.016)	(0.017)	(0.017)
SI PGI (std)	0.003	0.007	0.011	-0.001	0.002
	(0.008)	(0.009)	(0.010)	(0.011)	(0.012)
Treat × SI PGI (std)	-0.031	-0.032	-0.038	-0.027	-0.043
	(0.015)	(0.016)	(0.016)	(0.017)	(0.017)
N	2,790	2,790	2,790	2,790	2,790
Panel III			SIP		
Treated	0.278	0.235	0.236	0.205	0.178
	(0.015)	(0.016)	(0.017)	(0.017)	(0.018)
SI PGI (std)	-0.001	0.004	0.008	-0.007	-0.000
	(0.008)	(0.009)	(0.010)	(0.011)	(0.012)
Treat × SI PGI (std)	-0.010	-0.004	-0.026	0.003	-0.020
	(0.015)	(0.016)	(0.016)	(0.017)	(0.018)
N	2,738	2,738	2,738	2,738	2,738

Note: This table reports the heterogeneous treatment effects of the SI PGI on smoking cessation stratified by annual visits post treatment. There were five follow-up visits recorded in the LHS. Panel I reports the effects for both treatment groups combined (SIA and SIP) relative to the control group. Panel II reports the effects for those participants who were assigned to the SIA group compared to the control group. Panel III reports the effects of the SIP participants in comparison with the control group. Each regression controls for age fixed effects, wave fixed effects, sex, and the first 20 principal components to account for population stratification.

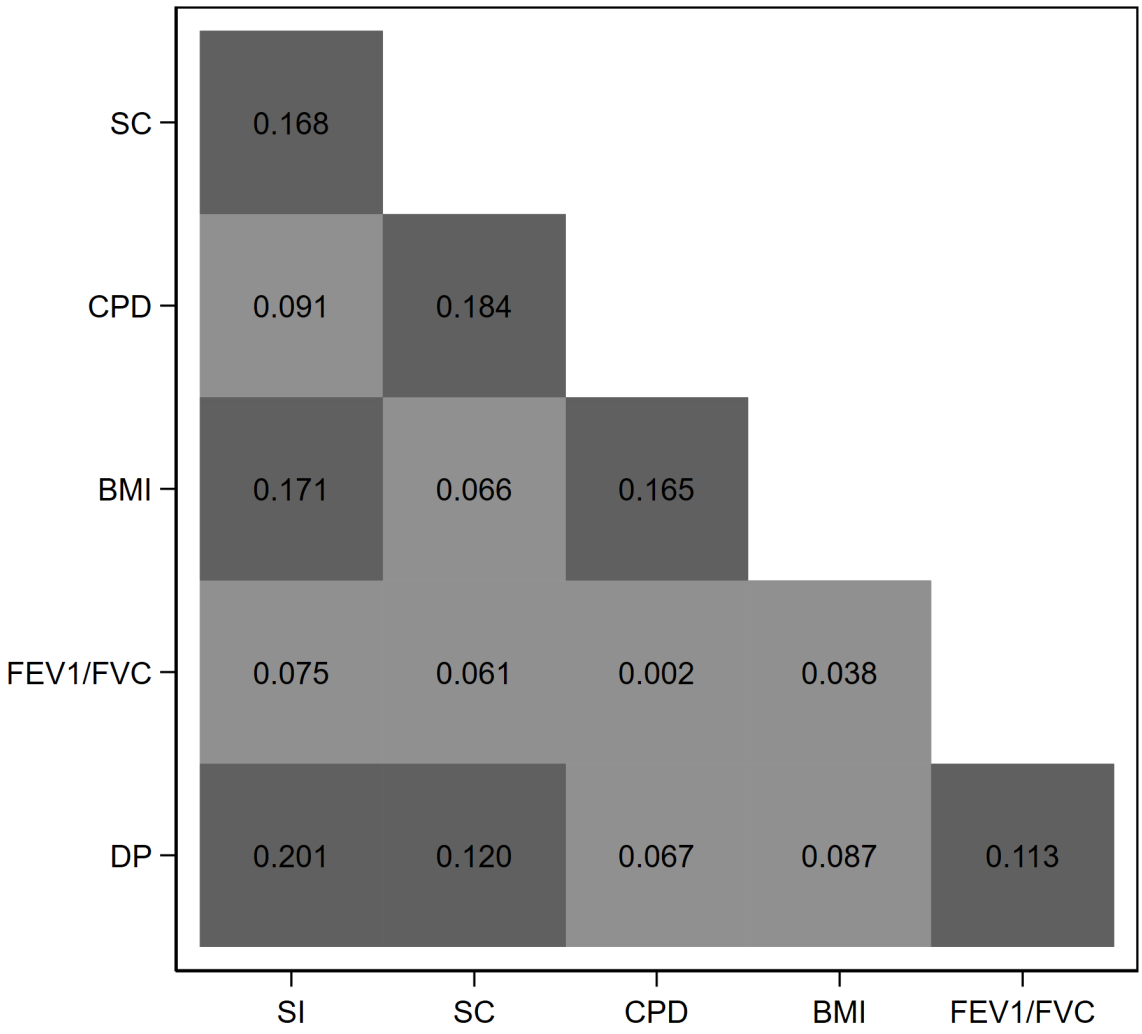
Table A7. Heterogeneous Treatment Effects of the LHS Intervention on Cigarettes per Day by CPD PGI and Annual Visit

	Annual Visit				
	1	2	3	4	5
Panel 1	Composite				
Treated	-11.995	-9.850	-9.330	-7.727	-6.626
	(0.491)	(0.486)	(0.484)	(0.488)	(0.484)
CPD PGI (std)	1.814	1.544	1.872	1.673	1.665
	(0.437)	(0.429)	(0.427)	(0.436)	(0.441)
Treat × CPD PGI (std)	-0.961	-0.313	-0.799	-0.485	-0.560
	(0.514)	(0.512)	(0.506)	(0.513)	(0.515)
N	4,050	4,038	4,027	4,019	4,145
Panel II	SIA				
Treated	-12.319	-9.995	-9.657	-7.906	-6.935
	(0.565)	(0.559)	(0.550)	(0.557)	(0.550)
CPD PGI (std)	1.842	1.503	1.861	1.601	1.623
	(0.437)	(0.432)	(0.430)	(0.440)	(0.446)
Treat × CPD PGI (std)	-1.724	-0.824	-1.153	-0.805	-0.681
	(0.580)	(0.587)	(0.577)	(0.582)	(0.578)
N	2,727	2,719	2,708	2,700	2,790
Panel III	SIP				
Treated	-11.531	-9.589	-8.895	-7.522	-6.248
	(0.575)	(0.570)	(0.572)	(0.571)	(0.563)
CPD PGI (std)	1.886	1.637	1.937	1.761	1.741
	(0.438)	(0.434)	(0.431)	(0.440)	(0.444)
Treat × CPD PGI (std)	-0.174	0.184	-0.487	-0.182	-0.460
	(0.591)	(0.592)	(0.587)	(0.590)	(0.591)
N	2,675	2,671	2,657	2,663	2,738

Note: This table reports the heterogeneous treatment effect of the CPD PGI on CPD stratified by annual visits post treatment. There were five follow-up visits recorded in the LHS. Panel I reports effects for both treatment groups combined (SIA and SIP) relative to the control group. Panel II reports effects for participants who were assigned to the SIA group compared to the control group. Panel III reports effects for SIP participants compared to the control group. Each regression controls for age fixed effects, wave fixed effects, sex, and the first 20 principal components (PCs) of the genetic data to account for population stratification.

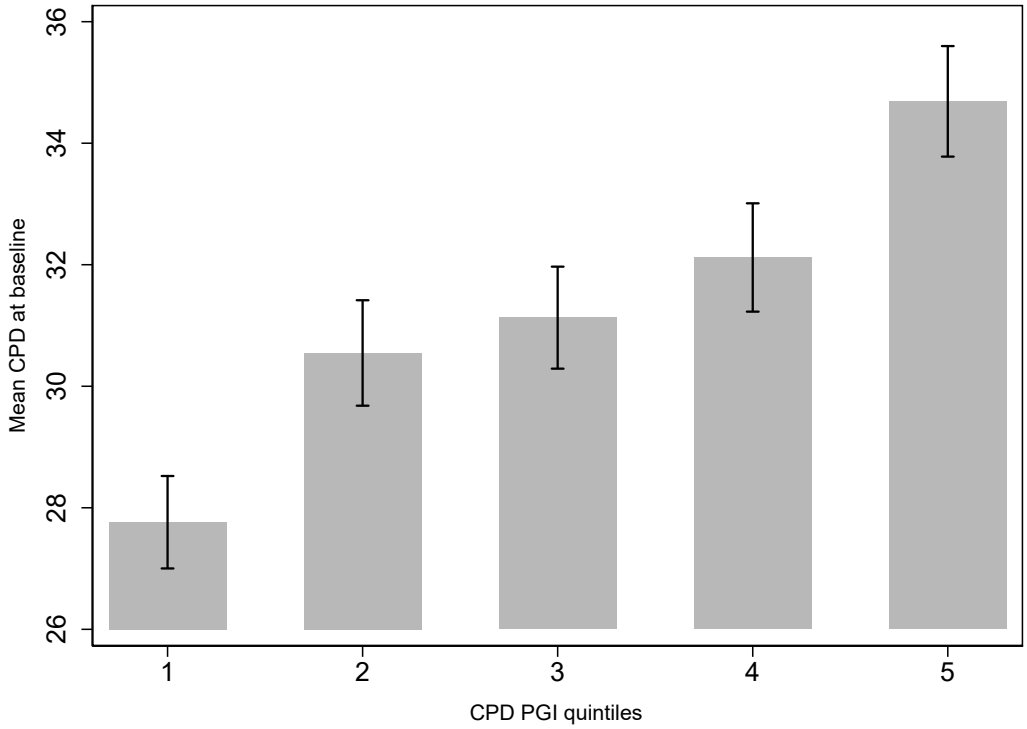
Figures

Figure A1. PGI Correlation Matrix in the LHS Sample



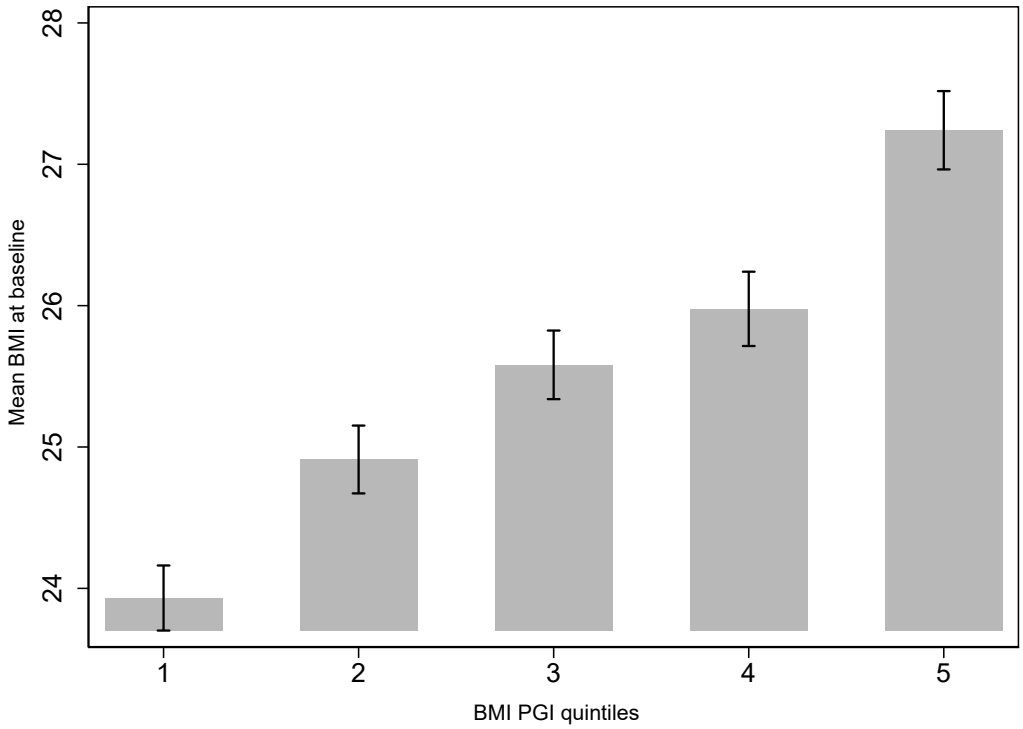
Note: The heatmap presents the correlation coefficients between the following PGIs: smoking initiation (SI), smoking cessation (SC), cigarettes per day (CPD), body mass index (BMI), lung function, or forced expiratory volume in one second over forced vital capacity (FEV_1/FVC), and depression (DP). Lighter cells indicate weaker correlations, while darker cells indicate stronger correlations.

Figure A2. Mean Cigarettes Per Day at Baseline by CPD PGI Quintile



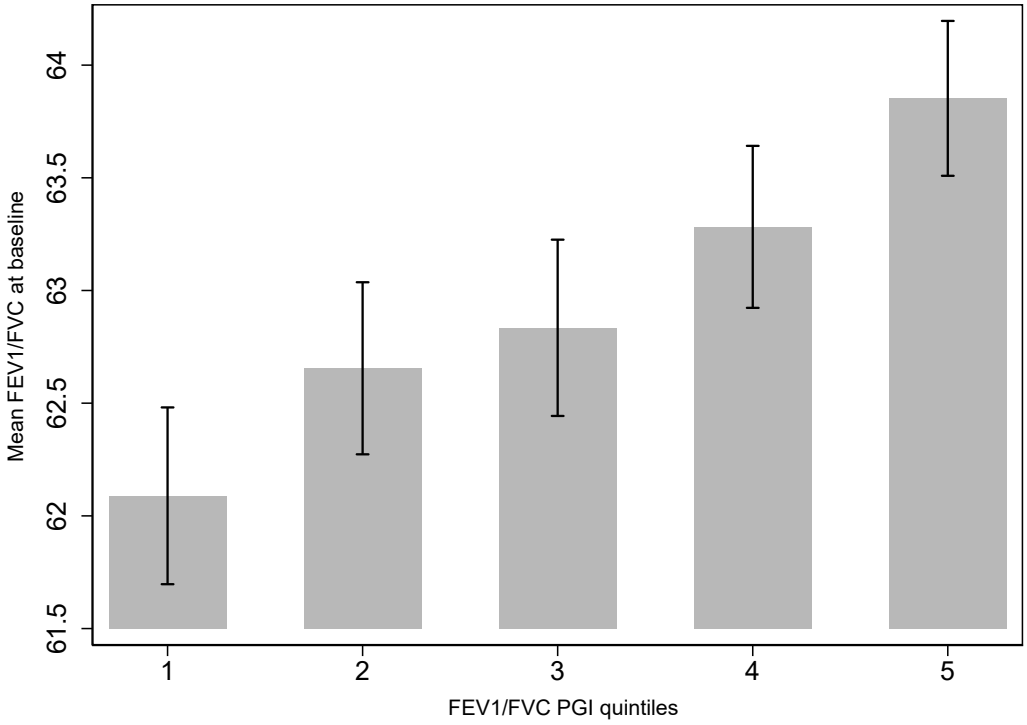
Note: The figure plots the mean number of cigarettes per day (CPD) at baseline by CPD PGI quintiles. 95% confidence intervals are reported.

Figure A3. Mean Body Mass Index at Baseline by BMI PGI Quintile



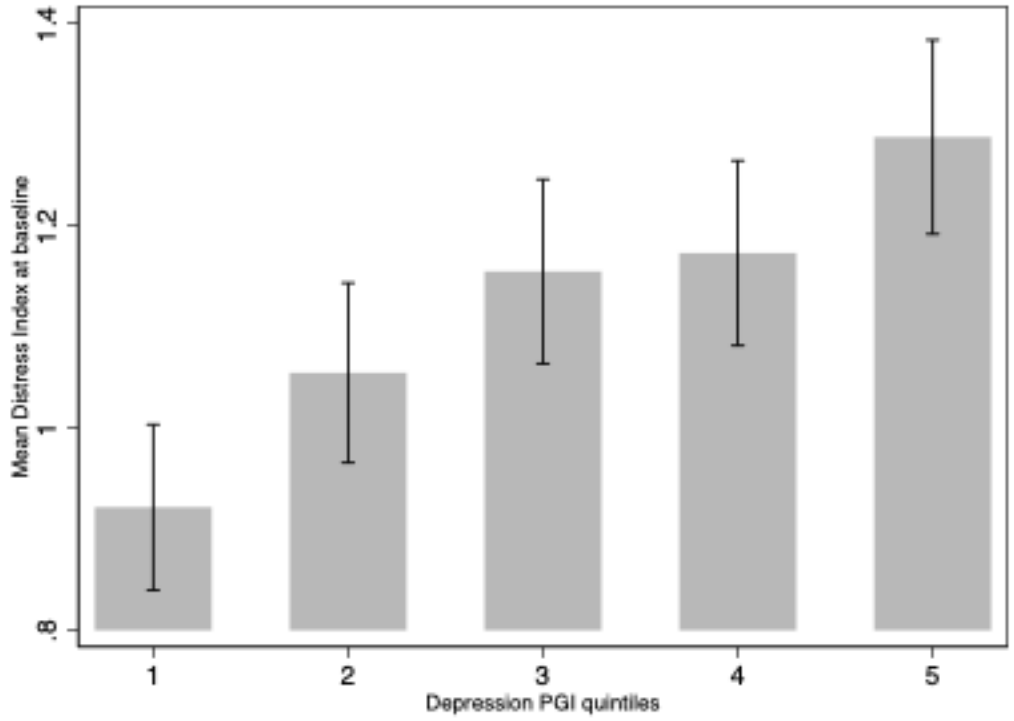
Note: This figure plots the mean body mass index (BMI) at baseline by BMI PGI quintiles. 95% confidence intervals are reported.

Figure A4. Mean FEV_1/FVC at Baseline by FEV_1/FVC PGI Quintile



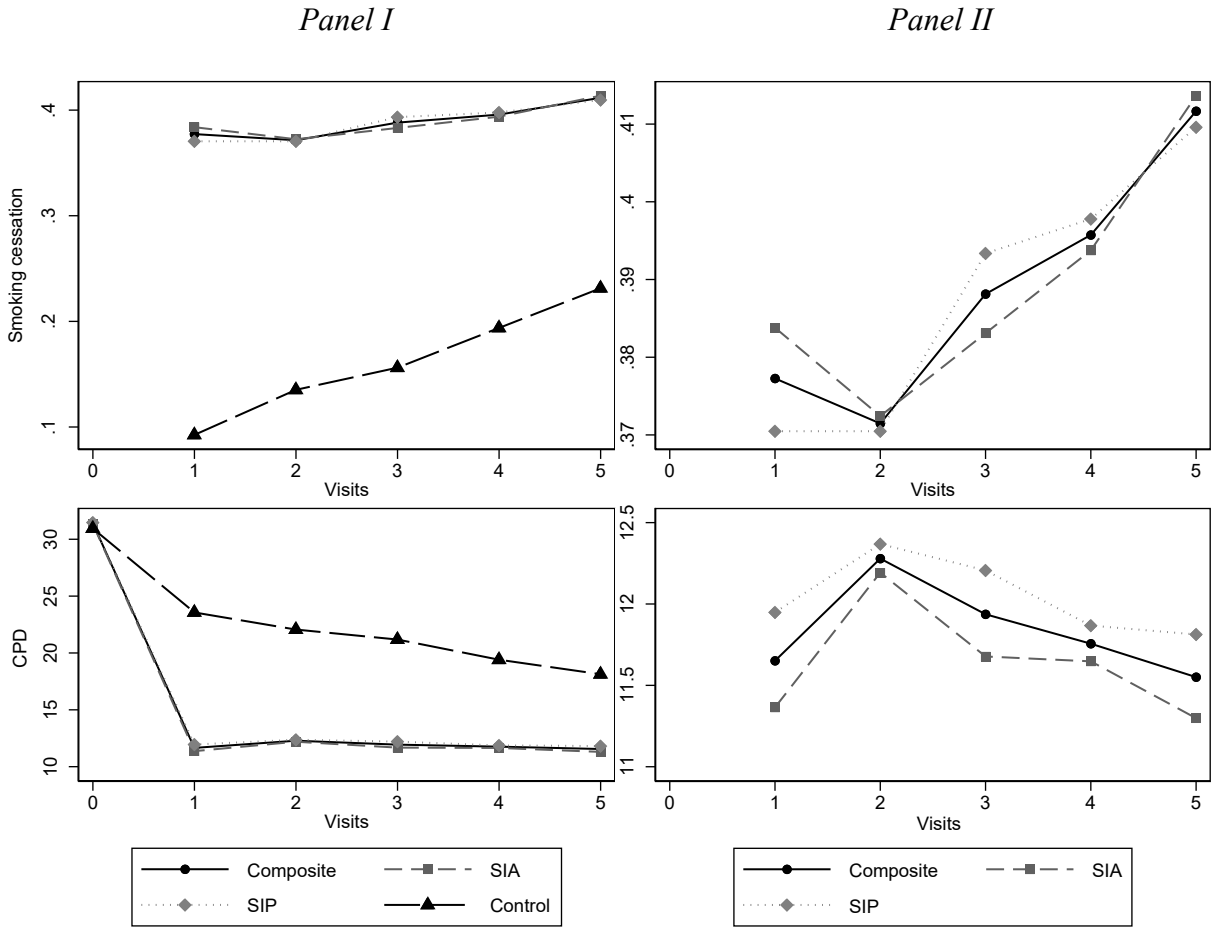
Note: The figure plots mean lung function, or forced expiratory volume in one second over forced vital capacity (FEV_1/FVC) at baseline by FEV_1/FVC PGI quintiles. 95% confidence intervals are reported.

Figure A5. Mean Depression Symptoms at Baseline by Depression PGI Quintile



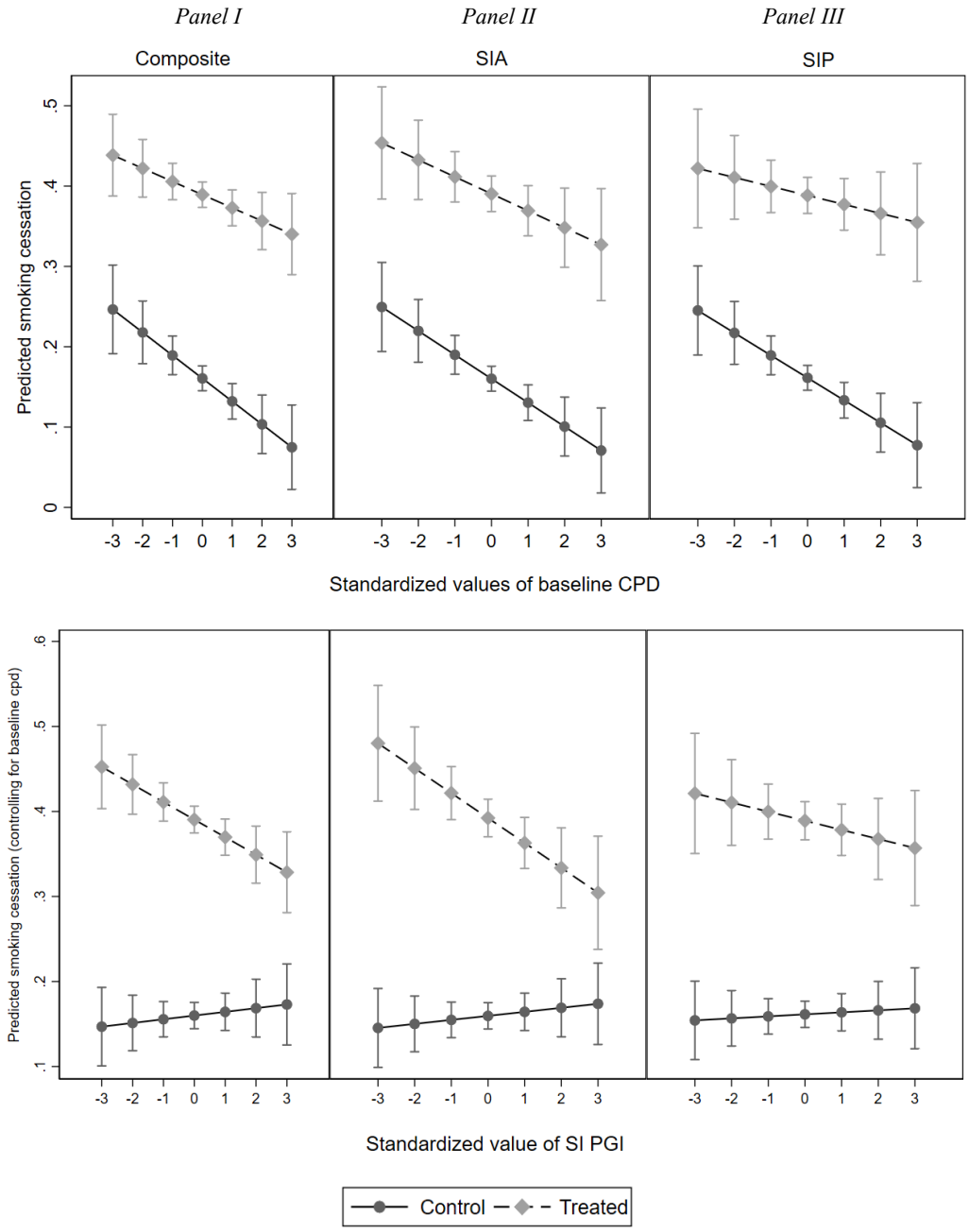
Note: This figure plots the average distress index at baseline by depression PGI quintile. The distress index is the sum of five symptoms related to depression: irritability, insomnia, mood changes, nervousness, and psychological illness. The LHS asks participants about these mental conditions via the following question: "Indicate the extent to which you have been troubled in the last four months by any of the following. Please indicate 'Severe,' 'Moderate,' 'Mild,' or 'Not at all.'" For each condition, we construct a dichotomous variable that takes the value of one if the respondent reports mild to severe symptoms and zero otherwise. We then form the distress index by summing across these mental health conditions at baseline. An increase in the distress index indicates worsening mental health. 95% confidence intervals are reported.

Figure A6. Per-wave Means of Smoking Cessation and CPD by Treatment Status



Note: Panel I shows the averages of smoking cessation and CPD by treatment status at baseline before treatment was administered and across all five annual follow-up visits. SIA: smoking intervention plus Atrovent inhaler (ipratropium bromide) group; SIP: smoking intervention plus placebo inhaler group. Averages are shown for the two treatment arms separately, for the composite treatment group (SIA and SIP), and the control group. Since we do not have information on smoking cessation at baseline, the first diagram under Panel I starts at the first visit. Panel II presents a zoomed-in version of the Panel I figures for the three treatment groups. Since baseline CPD was the same across groups, Panel II only plots means for the five follow-up visits.

Figure A7. Heterogeneous Treatment Effects of the LHS Intervention on Smoking Cessation by Baseline CPD and SI PGI



Note: Panel I corresponds to the composite treatment group ('1' if either SIA or SIP and '0' if control), Panel II corresponds to the SIA treatment group ('1' if SIA and '0' if control), and Panel III corresponds to the SIP treatment group ('1' if SIP and '0' if control). The top row presents the heterogeneous treatment effects on smoking cessation using variations in baseline CPD. These regressions control for age fixed effects, wave fixed effects, and sex. The lower row plots predicted treatment effects for smoking cessation by SI PGI that also control for baseline CPD and its interaction with the treatment. These regressions also control for the first 20 PCs of the genetic data. The grey diamonds represent the treated groups (composite/SIA/SIP) and the black circles represent the control group. Standard errors are clustered at the individual level and 95% confidence intervals are plotted with the estimates.

Appendix B

B1. List of Abbreviations

1. LHS: Lung Health Study
2. RCT: Randomized controlled trial
3. ATE: Average treatment effect
4. SIA: Smoking intervention plus inhaler with the active drug ipratropium bromide group
5. SIP: Smoking intervention plus placebo inhaler group
6. PGI: Polygenic index
7. PC: Principal component
8. SI: Smoking initiation
9. SC: Smoking cessation
10. CPD: Cigarettes smoked per day
11. FEV_1/FVC: Forced expiratory volume in one second over forced vital capacity
12. DP: Depression
13. GWAS: Genome-wide association study
14. SNP: Single nucleotide polymorphism
15. LD: Linkage disequilibrium

B2. Additional Information on the Lung Health Study Intervention

1. Exclusionary criteria

Individuals were excluded from the study if they had serious illnesses such as cancer, heart disease, stroke, or other significant medical conditions like high blood pressure, were using bronchodilators, beta-blockers, nitrates, or insulin, or if they consumed more than 25 alcoholic drinks per week or were binge drinkers. To reduce attrition, individuals were also excluded if they anticipated moving more than 75 miles from the clinical center or were unwilling to participate in the behavior intervention if randomized into the treatment group.

2. Intervention details

Each center recruited approximately 600 participants and assigned 400 individuals to the treatment group and 200 to the control group. Women comprised approximately 37 percent of enrolled subjects and 96 percent of the sample was white. The smoking cessation intervention program was designed to help individuals cope with their addiction and included several key features throughout the five-year trial (Connett et al. 1993; O'Hara et al. 1993):

- An initial message from a physician was delivered soon after randomization to give the participant information regarding their lung impairment, the adverse health effects of smoking, the importance of smoking cessation to reduce health risks, and a prescription for the inhaler and nicotine gum. Participants were encouraged to limit their nicotine gum use to the first 6 months of the trial and were provided with a reduction strategy if they had difficulty tapering their use.
- A meeting with an intervention specialist (held immediately after the physician meeting) explained the program and helped participants choose a quit date.

- An intensive 12-session group intervention program spread over 10 weeks provided cognitive and behavioral strategies for quitting and instructions for proper inhaler and nicotine gum use.
- Clinic visits every four months across all five years of follow-up.
- A maintenance program to minimize relapse and provide long-term support with problems such as weight gain and stress management.
- An extended intervention program for smokers who relapsed included options for individual counseling, physician visits, or additional group meetings.

References

Connett, J., J. Kusek, W. Bailey, P. O'Hara, and M. Wu. 1993. "Design of the Lung Health Study: A Randomized Clinical Trial of Early Intervention for Chronic Obstructive Pulmonary Disease." *Controlled Clinical Trials* 14: 3S-19S.

O'Hara, P., J. Grill, M. A. Rigdon, J. E. Connett, G. A. Lauger, and J. J. Johnston. 1993. "Design and Results of the Initial Intervention Program for the Lung Health Study." *Preventive Medicine* 22 (3): 304–315.

B3. Quality Control and Imputation of the Genotyped Data

We performed pre-imputation quality control (QC) on the genotype data using PLINK software (Purcell et al. 2007). We only kept autosomal non-biallelic SNPs with a minor allele frequency (MAF) > 0.01 and Hardy Weinberg equilibrium test p-value ≥ 1.0e-6. We used the UCSC liftOver tool to lift over the genome coordinates from hg18 to hg19. We phased and imputed the genotype data using the HRC reference panel version r1.1 2016 from the Michigan Imputation server (Das et al. 2016). After imputation, we removed the duplicated and strand ambiguous SNPs, SNPs with imputation quality<0.9, and SNPs with MAF<0.01. After QC, 12,030,369 SNPs remained. PGIs were then constructed using SNPs that overlapped between the LHS and GWAS samples. Number of SNPs used to construct each PGI: SI=1,044,939; SC=1,057,529; CPD=1,057,519; BMI=920,776; FEV_1/FVC=1,052,022; Depression=1,017,199.

References

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Purcell, Shaun, Benjamin Neale, Kathe Todd-Brown, Lori Thomas, Manuel A R Ferreira, David Bender, Julian Maller, Pamela Sklar, Paul I W De Bakker, et al. 2007. "PLINK: A Tool Set for Whole-Genome Association and Population-Based Linkage Analyses." *American Journal of Human Genetics* 81 (3): 559–75.