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About The Triple Helix 
at The University of Chicago

The Triple Helix, Inc. (TTH) is the world’s largest completely student-run organization dedicated to taking an interdisciplinary approach toward evaluating the true impact of historical and modern advances in science. Of TTH’s more than 25 chapters worldwide, the University of Chicago chapter is one of the largest and most active. Over the past year, we, TTH at The University of Chicago have vastly expanded the size and scope of our chapter. We have held more public lectures than ever before, and increased attendance at these events by over 100%. Our E-Publishing division has grown immensely. In fact, it has become more active than any other chapter's E-Publishing division. Additionally, general chapter participation at this time involves more than 300 undergraduates.

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About Pharmakon 
at The University of Chicago

Pharmakon is an inter-institutional undergraduate organization for the exploration and advancement of pharmacological disciplines, biotechnology, and other cutting edge scientific fields. We offer our members a unique perspective into the foundational disciplines of the industries at the forefront of finding cures, building unforeseen machines, and helping adapt the world to human needs. Independently organized and administered, Pharmakon is one of the best funded and fastest growing Registered Student Organizations at the University of Chicago where it was founded in 2011. Our work spans multiple journals, community development initiatives, and projects of every size and scope, from speaker series to campus-wide surveys to industry site visits. We welcome you to join our growing family of thinkers, tinkerers, and all-around passionate people invested in the growth and development of science that changes lives.

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Introduction

For centuries, chronic conditions, “disease or conditions that are long lasting in nature,” have had a major influence on mortality (1). Today, over 100 million Americans have chronic conditions, and the number of Americans with chronic conditions is projected to increase to 160 million by 2040 (2). While approximately 75% of the people with chronic conditions do not have activity limitations, they remain a major cause of disability and consume 70% of health care spending (3) (4). Although chronic conditions are unfavorable problems in society, currently the main approach has been to increase health spending on chronic conditions. The total cost of chronic conditions in 1990 was $659 billion (5). In 2003, the total cost of chronic conditions had increased to $1.3 trillion (6). By 2020, one estimate of the total cost for chronic conditions projects $4.13 trillion in spending, demonstrating a significant and untenable trend of increase. Directly extrapolating from the data, an increase of one year of schooling across the general population would decrease the number of chronic conditions by, at a conservative estimate, approximately 1.4 percent, providing multiple possible benefits for the economy with public policy. From the results, financial stress, depression and relative body weight mediate approximately 51% of the effects of education level of an individual on his or her number of chronic conditions, revealing an important part of the mechanism.

Literature Review

From existing literature, the relationship between education level and the number of chronic conditions remains ambiguous. An early article shows most people who report about their chronic conditions have fewer than 12 years of education, while the general population has a mean of 12 years of education (7). Although significant correlation may exist between education level and the number of chronic conditions, the relationship from the observations in existing literature remains open for exploration. Some articles find that education programs about chronic conditions have no significant effects on the number of chronic conditions for people in the general population. One extensive meta-study of 320 articles on the effects of illness education programs finds almost no change in chronic conditions (8). Other studies confirm the small effect of education programs on patients’ chronic conditions (9) (10) (11).

Another study suggests chronic disease management principles and the characteristics of the Future of Family Medicine model can improve conditions of patients with diabetes, a type of chronic condition (13). A study from Crete indicates that health and nutrition education at local primary schools over a six-year intervention period for first grade students can reduce risk levels for chronic conditions (14).

The existing literature indicates that the investigation of the relationship between education level and chronic conditions has mostly involved the effect of targeted education programs about chronic conditions on those chronic conditions. However, the highest year of education completed for an individual as an indication of education level in the relationship between education level and chronic conditions is a new direction and remains unexplored. Education programs about chronic conditions may not provide the full benefits of general educational education. The study examines the relationship and mediating factors between the education level of an individual and his or her number of chronic conditions, with highest year of education completed as the indication for education level. The discussion section further examines the possible theories behind the interactions of the mechanisms.

Hypothesis

Existing literature shows an ambiguous relationship between education level and number of chronic conditions, but a significant relationship can exist. This study uses the highest year of education completed to determine education level. Therefore, the first hypothesis is that, for the years 1986 to 1994 in America, as the highest year of education completed increases for an individual, his or her number of chronic conditions decreases significantly. The second hypothesis is that, from 1986 to 1994 in America, financial stress, depression and relative body weight together significantly mediated the effect of the highest year of education completed for an individual on his or her number of chronic conditions.

Analytic Model

The analytic model involves the highest year of education completed for an individual, his or her number of chronic conditions, financial stress, depression (CES-D scale, center of epidemiology studies depression scale that measures depression (15)) and relative body weight (using body mass index, or BMI). Highest year of education completed for an individual affects his or her financial stress, depression and relative body weight. Changes in financial stress, depression and relative body weight affect the number of chronic conditions for an individual.

The analytic model is presented below in figure 1.

Data

The dataset for the study, Americans’ Changing Lives, involves four waves of data from 1986, 1989, 1994 and 2002 in a national longitudinal panel survey covering sociological, psychological, mental and physical health items (16). The first wave represents the data in 1986 and the second wave resembles data in 1989. The third wave involves the data in 1994 and the fourth wave includes data in 2002. Each wave of data was collected in the same
The data type is survey data and the mode of data collection was face to face interview (16). The data set includes the population of those 25 and older living in the continental United States (16). The sampling method for the dataset includes a multistage stratified area probability sample (16). Three thousand, six hundred and seventeen people responded in 1986, 2,867 in 1989, 2,562 in 1994, and 3,671 in 2002 (16). The data set includes more cases than the number of cases in 1989 and 1994, including non-follow up cases from those two years. This paper’s analyses only use waves 1, 2 and 3 of the Americans’ Changing Lives data set to examine the follow-up conditions of people from wave 1 to wave 3.

To investigate the effect of education level on the number of chronic conditions, the lagged regression models include the response variable, number of chronic conditions, and the explanatory variable of focus, highest year of education completed. Some lagged regression models include the control variables (17). From the summary of variables (Table 1 in Appendix), the range of the variable, the number of chronic conditions, is from 0 to 8 and the mean of the variable is approximately 3.4736. From the histogram of the variable, the distribution is bell shaped with correlation value from –0.3732 to 0.6405. The results of the pair-wise correlation further justify the need to control for these possible confounding variables.

Methods

The analyses of the study use six lagged regression models to explore the longitudinal data. The first model refers to the regression of the number of chronic conditions in wave 3 on the highest year of education completed in wave 1. The second model involves the regression of the number of chronic conditions in wave 3 on the highest year of education completed in wave 1 with all the control variables. Each of the mediating factors, financial stress, depression and relative body weights is included in models 3, 4 and 5 separately with the regression of the number of chronic conditions in wave 3 on the highest year of education completed in wave 1 and all control variables. The sixth model contains the regression of the number of chronic conditions in wave 3 on the highest year of education completed in wave 1 with all the control variables and all three mediating factors, financial stress, depression and relative body weight. The regression equations of each model are indicated below.

Model 1: Chronic conditions\textsubscript{wave3} = β0 + Education\textsubscript{wave1} \times X1 + \varepsilon

Model 2: Chronic conditions\textsubscript{wave3} = β0 + Education\textsubscript{wave1} \times X1 + Age\textsubscript{wave1} \times X2 + Sex\textsubscript{wave1} \times X3 + Race\textsubscript{wave1} \times X4 + Chronic conditions\textsubscript{wave1} \times X5 + Nonresponse\textsubscript{wave1} \times X6 + Familincome\textsubscript{wave1} \times X7 + \varepsilon

Model 3: Chronic conditions\textsubscript{wave3} = β0 + Education\textsubscript{wave1} \times X1 + Age\textsubscript{wave1} \times X2 + Sex\textsubscript{wave1} \times X3 + Race\textsubscript{wave1} \times X4 + Chronic conditions\textsubscript{wave1} \times X5 + Nonresponse\textsubscript{wave1} \times X6 + Familincome\textsubscript{wave1} \times X7 + Financialstress\textsubscript{wave1} \times X8 + \varepsilon

Model 4: Chronic conditions\textsubscript{wave3} = β0 + Education\textsubscript{wave1} \times X1 + Age\textsubscript{wave1} \times X2 + Sex\textsubscript{wave1} \times X3 + Race\textsubscript{wave1} \times X4 + Chronic conditions\textsubscript{wave1} \times X5 + Nonresponse\textsubscript{wave1} \times X6 + Familincome\textsubscript{wave1} \times X7 + Depression\textsubscript{wave1} \times X8 + \varepsilon

Model 5: Chronic conditions\textsubscript{wave3} = β0 + Education\textsubscript{wave1} \times X1 + Age\textsubscript{wave1} \times X2 + Sex\textsubscript{wave1} \times X3 + Race\textsubscript{wave1} \times X4 + Chronic conditions\textsubscript{wave1} \times X5 + Nonresponse\textsubscript{wave1} \times X6 + Familincome\textsubscript{wave1} \times X7 + Relativebodyweight\textsubscript{wave1} \times X8 + \varepsilon

Model 6: Chronic conditions\textsubscript{wave3} = β0 + Education\textsubscript{wave1} \times X1 + Age\textsubscript{wave1} \times X2 + Sex\textsubscript{wave1} \times X3 + Race\textsubscript{wave1} \times X4 + Chronic conditions\textsubscript{wave1} \times X5 + Nonresponse\textsubscript{wave1} \times X6 + Familincome\textsubscript{wave1} \times X7 + Financialstress\textsubscript{wave1} \times X8 + Depression\textsubscript{wave1} \times X8 + Relativebodyweight\textsubscript{wave1} \times X10 + \varepsilon

The main explanatory variable of focus is the highest year of education completed in an interval scale. The variable indicates the highest year of education completed of the respondent, a cleaned, recoded and imputed version of V1646, variable in the dataset (17). From the summary of variables (Table 1 in Appendix), the range of the variable is from 0 to 17, and the mean of the variables is approximately 11.46689 years of education. The median of the variable is 12, and there are 3,617 observations. There are 0 missing data from the total amount of observations for the survey in wave 1 and the standard deviation is approximately 3.4736. From the histogram of the variable, the normal distribution with the mean at 11.4689 years of education, but the curve is skewed to the left. On the histogram, the highest number of observations is located at approximately 12 years of education. The control variables are included in the multiple regression models to avoid bias in the coefficients by the confounding effect of omitted variables. These control variables have an effect on the number of chronic conditions and the highest year of education completed, showing possible confounding effects and a need to control for these variables in the models. From pair-wise correlation of all the variables (Table 2 in appendix), the control variables correlate significantly with the response variable, number of chronic conditions and the explanatory variable of focus, highest year of education completed, ranging with correlation value from 0.3732 to 0.6405. The results of the pair-wise correlation further justify the need to control for these possible confounding variables.
Table 3. Results table of standard linear model for multiple regression of model 1, 2, 3, 4, 5, & 6

<table>
<thead>
<tr>
<th>Variables</th>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
<th>Model 4</th>
<th>Model 5</th>
<th>Model 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Educationwave1 (to 17)</td>
<td>-0.1358***</td>
<td>-0.0229***</td>
<td>-0.0186**</td>
<td>-0.0168**</td>
<td>-0.0147*</td>
<td>-0.0109</td>
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<tr>
<td>(0.000)</td>
<td>(0.005)</td>
<td>(0.023)</td>
<td>(0.041)</td>
<td>(0.069)</td>
<td>(0.179)</td>
<td></td>
</tr>
<tr>
<td>Chronicwave2 (0 to 7)</td>
<td>0.5633***</td>
<td>0.5679***</td>
<td>0.5642***</td>
<td>0.5401***</td>
<td>0.5205***</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(0.000)</td>
<td>(0.000)</td>
<td>(0.000)</td>
<td>(0.000)</td>
<td>(0.000)</td>
<td></td>
</tr>
<tr>
<td>Racewave1 (1 to 5)</td>
<td>0.0654*</td>
<td>0.0687*</td>
<td>0.0635*</td>
<td>0.0573</td>
<td>0.0399</td>
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</tr>
<tr>
<td></td>
<td>(0.065)</td>
<td>(0.069)</td>
<td>(0.093)</td>
<td>(0.124)</td>
<td>(0.285)</td>
<td></td>
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<tr>
<td>Agewave1 (24 to 96)</td>
<td>0.0170***</td>
<td>0.0183***</td>
<td>0.0174***</td>
<td>0.0178***</td>
<td>0.0200***</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(0.000)</td>
<td>(0.000)</td>
<td>(0.000)</td>
<td>(0.000)</td>
<td>(0.000)</td>
<td></td>
</tr>
<tr>
<td>Sex (1 to 2)</td>
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<td>0.0379</td>
<td>0.0333</td>
<td>0.0658</td>
<td>0.0587</td>
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<td></td>
<td>(0.264)</td>
<td>(0.426)</td>
<td>(0.484)</td>
<td>(0.163)</td>
<td>(0.212)</td>
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<td>Nonresponsewave2 (0 to 1)</td>
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<td></td>
<td>(0.966)</td>
<td>(0.521)</td>
<td>(0.529)</td>
<td>(0.739)</td>
<td>(0.512)</td>
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<td>Familyincomewave1 (5,049.6 to 137,721.1)</td>
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<td>0.0000</td>
<td>0.0000</td>
<td>0.0000</td>
<td>0.0000</td>
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<tr>
<td></td>
<td>(0.487)</td>
<td>(0.995)</td>
<td>(0.720)</td>
<td>(0.580)</td>
<td>(0.721)</td>
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<tr>
<td>Finestresswave2 (-1.7603 to 2.7185)</td>
<td>0.0652***</td>
<td>0.0521***</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(0.001)</td>
<td>(0.044)</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Depressionswave2 (-1.1362 to 4.2540)</td>
<td>0.0584***</td>
<td>0.0801***</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>(0.000)</td>
<td>(0.044)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Bodyweightwave2 (13.8075 to 50.7770)</td>
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<td>0.0373***</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(0.000)</td>
<td>(0.000)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constant</td>
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<td>-0.0821</td>
<td>-0.0300</td>
<td>0.0234</td>
<td>-1.028</td>
<td>-1.147</td>
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<tr>
<td>Observation</td>
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<td>2.562</td>
<td>2.348</td>
<td>2.348</td>
<td>2.348</td>
<td>2.348</td>
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<tr>
<td>F statistic</td>
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<td>0.0000</td>
<td>0.0000</td>
<td>0.0000</td>
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<tr>
<td>R²</td>
<td>0.0963</td>
<td>0.4459</td>
<td>0.4473</td>
<td>0.4475</td>
<td>0.4614</td>
<td>0.4657</td>
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<tr>
<td>Adjusted R²</td>
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<td>0.4444</td>
<td>0.4454</td>
<td>0.4457</td>
<td>0.46505</td>
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</tr>
</tbody>
</table>

Source: Data from Americans’ Changing Lives from years 1986, 1989, & 1994

Note: Non-standardized coefficients are reported and p values are in parentheses.

*p < 0.1; **p < 0.05; ***p < 0.01

Results and Findings

From table 3, the results for the standard linear model present statistically significant and substantially significant coefficients for the highest year of education in wave 1 for both model 1 and 2. To be clear about terms, statistically significant represents a significant result in terms of statistic methods and substantially significant represents a very large effect in the results. Model 1 demonstrates the total effect of the highest year of education completed in wave 1 on the number of chronic conditions in wave 3. Model 1 shows an increase in one additional year of education of an individual decreases his or her number of chronic conditions by 0.1358. By considering possible confounding variables, model 2 reveals the direct effect of the highest year of education completed in wave 1 on the number of chronic conditions in wave 3. Model 2 indicates an increase in one additional year of education of an individual decreases his or her number of chronic conditions by 0.0222. Considering the average number of chronic conditions to be approximately 1.5515 from (Table 1 in Appendix), a decrease 0.0222 in the number of chronic conditions for an additional year of education of an individual is substantially significant, representing approximately 1.4 percent decrease. The results of model 1 and model 2 confirm the first hypothesis. According to table 3, the results for the standard linear model also present less statistically significant and less substantially significant coefficients for the highest year of education completed in wave 1 for models 3, 4, 5 and 6. Model 3 demonstrates the mediating effect of financial stress in wave 2. Model 4 shows the mediating effect of depression in wave 2. Model 5 indicates the mediating effect of relative body weight in wave 2. From models 2 and 3, financial stress in model 3 mediates the coefficient of the highest year of education completed in wave 1 by 0.0036 and reduces the coefficient to the 5 percent statistically significant level. From models 2 and 4, depression in model 4 mediates the coefficient of the highest year of education completed in wave 1 by 0.0054 and reduces the coefficient to the 5 percent statistically significant level. From models 2 and 5, relative body weight in model 5 mediates the coefficient of the highest year of education completed in wave 1 by 0.0075 and reduces the coefficient to the 10 percent statistically significant level. By comparing models 2, 3, 4 and 5, relative body weight is the greatest mediator, financial stress is the weakest mediator, and depression is the medium mediator among the three mediating factors. Between models 2 and 6, the three mediating factors mediate the coefficient of the highest year of education completed in wave 1 by 0.0113 and make the coefficient not statistically significant. The comparison indicates that the three mediating factors reduce the coefficient by approximately 51 percent. The changes in the substantially significant and statistically significant coefficient of the highest year of education completed by the three mediating factors together show the substantial mediating power of combining all three mediating factors. The results from models 2, 3, 4, 5 and 6 confirm the second hypothesis. The findings about the analytic model of the mechanism are presented below in figure 4.

Figure 4. Analytic model about Mechanism and Causality
A significant decrease of approximately 1.4 percent in the number of chronic conditions for each additional year of education of an individual may improve public policy and economic implications. The total cost for the number of chronic conditions in 2003 was approximately $1.3 trillion (6). Based on the increasing trend for the total cost of chronic conditions, a decrease of 1.4 percent for the number of chronic conditions may save approximately $18.53 billion annually in the economy.

By increasing spending on education level, the government may make people healthier with fewer chronic conditions and improve people’s quality of life, achieving multiple economic benefits. Improvement in education level and reduction in chronic conditions may increase the quality of life (18). Quality of life is multidimensional, including physical wellbeing, material wellbeing, social wellbeing, emotional wellbeing, and development and activity (19). Better changes in the quality of life may create increased GDP per capita, productivity of the worker and welfare. The increase in the quality of life may provide people with a healthier body to produce more efficiently, effectively and efficiently (19). With a better human body to engage in production, people may produce more products and services for the market, increasing GDP and GDP per capita. The enhanced quality of life may also engender improved lifestyle and living conditions, creating greater well-being for an individual and a society. A greater quality of life may also lead to decreased government spending on health care, health care costs in firms and consumers in the economy. With a better quality of life, people may have fewer illnesses or none, diminishing health care spending.

More efficient advancement of technology may lead to reduced stress, as a more educated person may have less to worry about regarding his or her finances. The reduction in the financial stress may then help the medical conditions of the person, reducing their number of chronic conditions. In addition, an increase in the highest year of education completed may decrease depression, in turn alleviating the medical conditions of the person. Finally, an increase in the highest year of education completed may increase personal discipline, allowing more educated individuals to maintain a lower body weight and thus lead a healthier life.

The main threat to the inference of the method of the standard linear model of multiple regression is the possible violation of mean independence through omitted variable, reverse causation and measurement error. The exclusion of confounding variables as control variables in the model demonstrates the problem of omitted variables. The lagged regression models include some crucial control variables, but some possible control variables might be missing. One of the most important possible confounding variables is the region of neighborhood, but the region of neighborhood is not included in the dataset of Americans’ Changing Lives. The region of neighborhood has an effect on the education level and affects the number of chronic conditions for an individual with different environment conditions. However, the region of neighborhood may not limit the education opportunities of an individual too much to render it a fatal flaw. The weak effect of the region of neighborhood on the education level reveals the weak effect of region of neighborhood as a control variable, generating tiny bias in the models without a region of neighborhood variable. Until more hypothesized variables are found that should be included in the models, the findings appear to incorporate relatively small amounts of bias.

The effect of reverse causation is miniscule in the lagged regression. Reverse causation makes the direction of the causation, but lagged regression includes the temporal order of the causation, minimizing the problem of reverse causation. The reverse causation in the lagged regression models generates insignificant bias towards the findings.

Measurement error creates bias in the coefficients of the standard linear model for multiple regression. Measurement error such as errors in measuring the variable biases the coefficient towards zero, providing an underestimation. The effect of the highest year of education completed on the number of chronic conditions in reality is larger than the effect in the result from the lagged regression models, reinforcing the substantial significance of the causality. There are some limitations to the survey sample. The Americans’ Changing Lives may involve some misreporting in the self-reporting aspect of the survey. The number of chronic conditions variable provides adequate measures with many indicators. On the other hand, respondents might have some incentive to over report their highest year of education completed to appear more educated, overestimating their actual highest year of education completed. Although the highest year of education of an individual may not reflect his or her actual education level, the highest year of education completed is a close indication for education level (20). There are no missing follow up observations in model 1 and 2. The 214 missing observations in models 3, 4, 5 and 6 is less than 10 percent of the total follow up observations, showing a small bias in models 3, 4, 5 and 6.

In the lagged regression models, multicollinearity, a statistical problem resulting from high correlation among independent variables, is not a major issue (21). The largest value for pair-wise correlation between the independent variables is 0.6405. A correlation value of less than 0.6405 is not large enough to generate a large multicollinearity problem, indicating a small bias with multicollinearity in the results. Including the limitations of the models, the combination of minute bias from violation of mean independence, data sample and multicollinearity demonstrates a small bias effect in the findings. A small bias in the results makes the findings a good approximation for the actual effect, strengthening the substantial findings in from the models. The overestimation of highest year of school completed and the underestimation of the number of chronic conditions demonstrate an underestimation of the actual effect of highest year of school completed on the number of chronic conditions. An increase in one year of education of an individual decreases his or her

Figure 5. Scatter plot of highest year of school completed and number of chronic conditions

"Increasing educational level would improve the quality of life and health of people, creating positive economic implications for economic prosperity and growth."
number of chronic conditions by at least a 1.4 percent. From the scatter plot of highest year of education completed on the number of chronic conditions (Figure 2), a negative linear line is a good approximation for the data, reinforcing the results of the standard linear model of multiple regression.

Several additional methods and alternatives might strengthen the analyses of this model. Further study of standard linear regression model similar data in the same time period from other national surveys, such as the national longitudinal surveys to reinforce the findings (22). Another further study might incorporate possible missing variables to determine a better picture of the relationship and the mechanism. Other further study of the effect of the highest year of education completed on the three mediating factors and the effect of the three mediating factors on the number of chronic conditions could provide further insight into the magnitude of the relationships in each of the pathways in the mechanisms. Further surveys with better worded questions and more technologically advanced techniques of collecting data could eliminate some measurement error, reducing bias from the limitations and making the conclusions more substantial. Surveys might also include both subjective and objective measures of the same variable to provide a more comprehensive study of the relationship and mechanisms. These new methods could also provide a confirmation of the causality and mediating mechanisms of the findings.

Conclusion

According to the standard linear model for multiple regression on the data from the America’s Changing Lives dataset, the findings confirm both hypotheses. The lagged regression models show that for the past eight years in America, from 1986 to 1994, as the highest year of education completed for an individual increases for one or her number of chronic conditions decreases significantly by 0.0222, approximately a 1.4 percent decrease. Financial stress, depression and relative body weight together mediate the effect of the highest year of education completed for an individual and her number of chronic conditions by approximately 51 percent, demonstrating a significant effect. Increasing educational level for all individuals as a public policy with economic benefits would achieve multiple purposes of improving the quality of life and health of people, creating positive economic implications for economic prosperity and growth. Further research on different data sources such as the national longitudinal survey with other methods or the standard linear model for multiple regression might confirm and reveal more about the causality and mechanisms of the relationship.
The establishment of proper communication between a patient and a care provider is vital, in the field of anesthesia, the care provider must be able to judge a patient’s awareness upon wakeup in order to determine the timing of extubation, which is often done by evaluating responses to simple commands such as “open your eyes.” However, in many cases, the anesthesiologist does not speak the patient’s native language, which can lead to complications and delays in extubation, simply due to the patient’s inability to understand specific commands. Consequently, this may cause discomfort in the patient’s post-operative awakening and recovery. This can be an issue not just for patients who do not speak English but for those who speak English as a second language, as well, since they may respond more quickly to the commands in their native language, suggesting a reversion to their native tongue. Overcoming this barrier is important to improving care for patients who speak English as a second language. We have been involved in an ongoing Institutional Review Board (IRB) approved study at the University of Chicago that examines the impact of general anesthesia on language preference at emergence in patients who learned English as a second language. The commands “open your eyes,” “squeeze my fingers,” and “wiggle your toes” are recorded in a familiar (usually a family member’s) voice onto a laptop computer in English and in the patient’s native language. The use of a familiar voice eliminates any discrepancies due to an unfamiliar dialect, accent, or pronunciation. Additionally, the patient chooses someone that they deem proficient enough to make the recordings in order to control the language competence of the familiar person. These commands are then played back to the patient upon their emergence from general anesthesia, using headphones in order to reduce the amount of ambient noise. The commands are played back every 30 seconds, alternating between English and the native language with five second gaps, until the patient follows the command. “Open your eyes” is played back first. Once a response is seen, “squeeze my fingers” is played, followed by “wiggle your toes.” This command order is used because motor control works in a head-to-toe manner. The patient’s background information as well as his or her response times are used to assess the degree of native language reversion. Two particularly interesting cases have arisen during our study that deserve discussion. The first was a case involving native language reversion in a 44-year-old woman who presented with a history of breast cancer and ovarian cancer was scheduled to undergo a laparoscopic salpingo-oophorectomy under general anesthesia, in order to remove a potentially cancerous mass. The patient had moved to the United States when she was five years old from the Philippines and subsequently began learning English in elementary school at the age of seven. Although her first language was Tagalog, the patient claimed to be significantly more fluent in English than Tagalog. On an ascending scale from one to ten, she rated her understanding of English to be a 10 and Tagalog to be a 3. Her mother recorded the commands — “open your eyes,” “squeeze my fingers” and “wiggle your toes” — in both languages, English and Tagalog. Prior to the surgery, the patient was asked if she knew the translation for all three phrases in both English and Tagalog. She answered that she knew “open your eyes” in both languages but only knew the other two commands in English. Interestingly, when the commands were played back in the operating room upon emergence from general anesthesia, she responded to “squeeze my fingers” only in Tagalog, while she responded to “open your eyes” and “wiggle your toes” in both English and Tagalog. This behavior is consistent with findings in the sleep literature where there is evidence of reversion to the native tongue during sleep in patients who speak English when in a conscious state. This may be because the native language is learned and retained in “implicit memory systems” located in the subcortical regions of the brain, while the later-acquired second language is stored “externally” in the cerebral cortex. As the patients wake up, the functionality of their “implicit” memory system is likely to recover prior to recovery of their “external” system.

Recovery Lapse: The Implications of Native Language Reversion Upon Emergence from General Anesthesia in English-Proficient Patients
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Proper communication between the care provider and a patient is vital for maximizing patient comfort. Upon emerging from anesthesia, a patient’s level of awareness is used to determine the timing of extubation, and is often assessed by responses to commands such as “open your eyes.” However, when a language barrier arises, it may be impossible for patients to respond to commands they do not understand. In a research study at the University of Chicago Department of Anesthesia and Critical Care, we measure responsiveness of non-native English speakers to basic commands in English and the patient’s native language upon emergence from general anesthesia. In one case, a 44-year-old Filipino woman reverted to her native tongue during emergence, despite claiming to be more fluent in English. In a second, an 18-year-old Mexican woman exhibited seizure-like activity upon hearing commands in English although she remained calm while hearing her native language. These two cases have important implications in the role of language in the field of anesthesia. The establishment of proper communication between a patient and a care provider is vital in the field of anesthesia, the care provider must be able to judge a patient’s awareness upon wakeup in order to determine the timing of extubation, which is often done by evaluating responses to simple physical commands such as “open your eyes” or “squeeze my fingers.” However, in many cases, the anesthesiologist does not speak the patient’s native language, which can lead to complications and delays in extubation, simply due to the patient’s inability to understand specific commands. Consequently, this may cause discomfort in the patient’s post-operative awakening and recovery. This can be an issue not just for patients who do not speak English but for those who speak English as a second language, as well, since they may respond more quickly to the commands in their native language, suggesting a reversion to their native tongue. Overcoming this barrier is important to improving care for patients who speak English as a second language. We have been involved in an ongoing Institutional Review Board (IRB) approved study at the University of Chicago that examines the impact of general anesthesia on language preference at emergence in patients who learned English as a second language. The commands “open your eyes,” “squeeze my fingers,” and “wiggle your toes” are recorded in a familiar (usually a family member’s) voice onto a laptop computer in English and in the patient’s native language. The use of a familiar voice eliminates any discrepancies due to an unfamiliar dialect, accent, or pronunciation. Additionally, the patient chooses someone that they deem proficient enough to make the recordings in order to control the language competence of the familiar person. These commands are then played back to the patient upon their emergence from general anesthesia, using headphones in order to reduce the amount of ambient noise. The commands are played back every 30 seconds, alternating between English and the native language with five second gaps, until the patient follows the command. “Open your eyes” is played back first. Once a response is seen, “squeeze my fingers” is played, followed by “wiggle your toes.” This command order is used because motor control works in a head-to-toe manner. The patient’s background information as well as his or her response times are used to assess the degree of native language reversion. Two particularly interesting cases have arisen during our study that deserve discussion. The first was a case involving native language reversion in a 44-year-old woman who presented with a history of breast cancer and ovarian cancer was scheduled to undergo a laparoscopic salpingo-oophorectomy under general anesthesia, in order to remove a potentially cancerous mass. The patient had moved to the United States when she was five years old from the Philippines and subsequently began learning English in elementary school at the age of seven. Although her first language was Tagalog, the patient claimed to be significantly more fluent in English than Tagalog. On an ascending scale from one to ten, she rated her understanding of English to be a 10 and Tagalog to be a 3. Her mother recorded the commands — “open your eyes,” “squeeze my fingers” and “wiggle your toes” — in both languages, English and Tagalog. Prior to the surgery, the patient was asked if she knew the translation for all three phrases in both languages. 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As the second patient, studies have shown that patients with “left hemisphere epilepsy have a higher likelihood of atypical language organization,” which is not surprising since the left hemisphere is dominant for language in most healthy individuals. Additionally, “clinical variables [such as levels of pharmacologic sedation]
have been shown to contribute to cerebral language reorganization in the setting of chronic seizure disorders," though these cannot all be reliable sources of the reorientation [4]. Thus, the changing levels of anesthesi- ma may have caused a temporary reorganization in her language comprehension during these seizing episodes. Alternatively, the patient’s seizure focus might be adja- cent to the “external” memory system where her second language (English) is stored but distant from the “implicit” memory system where her first language (Spanish) is stored.

Both of these cases have implications for anesthesia care where patients who speak English fluently may revert to their native tongue upon emergence [5] as this can lead to delays in extubation. Moreover, overcoming the language barrier can be extremely helpful in preventing extubation complications such as increased discomfort in the throat or nausea during recovery.

In this study that deals with patients’ responses to com- mands in their native language and English upon emer- gence from general anesthesia, two very intriguing cases were seen. In the first, the patient, a native Tagalog speaker who is more proficient in English after having lived in the United States for 39 years, was more respon- sive to Tagalog upon emergence from anesthesia. In the second case, a native Spanish speaker from Mexico who has lived in the United States for 13 years, but who is now equally fluent in English and Spanish, seized upon hear- ing commands in English but not in Spanish.

In both cases, there is a clear discrepancy between the responsiveness to English versus the native language.

In a patient’s primary language to some patients at emergence. Our study has evolved over time to meet this need. Originally, the care provider spoke commands written in transliterated form in the patient’s native tongue back to the patient, but this proved to be inad- equate. The utilization of wireless headphones and play- ing back a command recorded by a native, familiar voice has, thus far, been an improvement in the study, though it may not be the most effective solution to the language barrier, as family members are not always available for this service. Ideally, translation services at the hospital would provide a translator to wake the patient in his or her native language after the procedure, but the costs of maintaining an extensively staffed translation service for all possible foreign languages can become prohibitive. It would seem that a realistic option might be to have a database of these simple commands made in as many languages as possible, using the voices of native speak- ers that can be played back via headphones controlled by the anesthesia care provider. This database might also contain various other phrases in order to be prepared for a wakeup with complications. The issue of dialectic vari- ations might still be a challenge in some languages, but the availability of properly pronounced phrases could be checked by the patient or their family prior to surgery. Effective communication between patient and caregiver is vital in increasing patient responsiveness during emer- gence from anesthesia, we hope that projects like this one will help overcome some of the major challenges caused by language barriers in doctor-patient communi- cation in the operating room.

Disease is often discussed in the context of the medical institution, with effective prevention and treatment often attributed to strong doctor-patient relationships, adequate facilities, and cutting-edge research. However, health care is not an infinite resource, and the allocation of inputs that control the quantity and quality of care exist within a larger social context and are subject to external influence like any political or social issue.

Much of the research involving social influence in medicine focuses on racial disparities in health outcomes. African-Americans have higher rates of morbidity and mortality than whites for conditions like heart disease, cancer, diabetes, and cirrhosis of the liver [1], even if insurance status, income, age, and severity of conditions are controlled for [2]. Sickle-cell anemia (SCA), a disease that predominantly affects individuals of African descent, is often discussed within a racial framework, with authors pointing to disparities in treatment and funding when compared to similar genetic diseases that predominantly affect Caucasians. However, can these disparities be attributed solely to race, or might there be a larger mechanism at work? Using SCA as an example, we will examine the interplay between politics and health outcomes, arguing that while race can play a role in delivery of care, it is important to also recognize the importance of political activism and public awareness in addressing disparities.

Sickle-cell anemia is an autosomal recessive genetic blood disorder that is characterized by having two copies of a point mutation in the gene that codes for hemoglobin, causing red blood cells to be less effective in carrying oxygen and to form rigid, inflexible sickle-shaped cells in the blood. The disease originated in tropical regions as an evolutionary protection against malaria, because one copy of the point mutation causes RBCs to die more rapidly, preventing malaria from spreading. Today, having one copy is diagnosed as sickle-cell trait (SCT). Having two copies of the mutation, diagnosed as SCA, also confers resistance. However, because patients afflicted with this condition cannot produce any normal hemoglobin, their cells polymerize and form sickled cells. As the cells travel through the bloodstream, they have more difficulty squeezing through the smallest blood vessels. Eventually, they occlude capillaries and block...
blood flow, especially in the extremities, resulting in intense pain at these sites. These “pain crises” can last for hours, days, or even weeks, and are the main symptom associated with SCA. In 1910, SCA was discovered in the United States by Chicago physician James Herrick [3], ushering in a new wave of genetic science. SCA rapidly became the most studied genetic disease [4], but early findings worked to set up barriers along racial lines.

In 1910, SCA was discovered in the United States by Chicago physician James Herrick [3], ushering in a new wave of genetic science. SCA rapidly became the most studied genetic disease [4], but early findings worked to set up barriers along racial lines.

Because pain is the most noticeable symptom of SCA, racism and black suffering," and “disease lobbies," began to portray SCA sufferers as “afflicted by unjust suffering” [4].

Even today, ethnographic research demonstrates that there are still lingering racial tensions underlying perceptions about heavy pain medication usage [4].

Because pain is the most noticeable symptom of SCA, many authors propose that SCA still suffers from a disparate lack of political activism and advocacy. Public preferences and the common good” [14]. Effective advocacy and public awareness can go a long way to receiving more funding.

This trend does not just apply for government funding, but also for private donations. The best example of a policy champion for medical conditions is Jerry Lewis, who hosted the Muscular Dystrophy Association (MDA) Labor Day Telethon for over 40 years before his departure in 2010 [15]. The MDA has made a concerted effort to get celebrities involved in fighting MD, and the Telethon has featured hundreds of celebrities and made connections with dozens of national sponsors [15]. During Lewis’s tenure as MDA National Chairman, the Telethon raised almost $2.5 billion dollars for MD research [16], and it is likely that even individuals who are not familiar with MD are able to identify the disease with Lewis and “Jerry’s Kids.”

Cystic Fibrosis also has its share of celebrity support, most notably from singer Celine Dion [17] and former NFL quarterback Boomer Esiason [18]. The Cystic Fibrosis Foundation is also known for fighting heavily for improvements in quality of care, seeking to establish clinical best practice guidelines and implementing a formal accreditation process for CF centers [9]. These are important steps that improve patient care. Conversely, SCA does not have a large celebrity backing, and the Sickle Cell Disease Association of America does not currently have the financial resources to launch large-scale development programs [9]. SCA activists in the past were essential in pushing Congress to implement universal newborn screens for SCA in almost every state [9], but public awareness appears to have decreased in recent years.

| Table 1. Funding Disparities between Cystic Fibrosis and Sickle Cell Anemia [9] |
|--------------------------------|--------------------------------|
| **Cystic Fibrosis**               | **Sickle-Cell Anemia**            |
| U.S. Prevalence                  | 80,000                            |
| NIH Funding per person (2004 FY) | $4,267, 30,000                     |
| No. of grants funded (2004)      | 459                               |
| Total public and private support per person | $9,340, 331                        |
| Cystic Fibrosis Foundation 2003 Revenue | $162,231,000                     |
| Sickle Cell Disease Association of America 2003 Revenue | $498,577, N/A                      |

**SCA rapidly became the most studied genetic disease [4], but early findings worked to set up barriers along racial lines**

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[4] Adriaan van der兼, et al. (2007). “SCA rapidly became the most studied genetic disease [4], but early findings worked to set up barriers along racial lines.”

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The table above shows the funding disparities between Cystic Fibrosis and Sickle Cell Anemia. Cystic Fibrosis receives significantly more funding compared to Sickle Cell Anemia. The table includes the number of grants funded, the total public and private support per person, and the foundation’s revenue. The data highlights the need for increased funding and awareness for Sickle Cell Anemia.
It has been shown that disparities in funding and care still exist, but responsibility for alleviating SCA disparities cannot be placed solely on medical personnel. There is still a great deal of work to be done when it comes to improving outcomes for patients with SCA, and supporters of SCA research need to reach back to find their roots during the 1960s and 1970s, when they used grassroots advocacy to make substantial progress from the “racial impurity” discussions of the past. One of the best ways to foster activism is to in- spirce advocates for improved care. Many hospitals for children are well versed in SCA treatment, especially those that deal with chronic illness. However, there are few dedicated SCA clinics for adults [9], so as these teens transition to adulthood, it will be up to them to make themselves heard to ensure that they have resources for the future. With enough support, it may become easier for institutions to recruit celebrities and high-profile individuals to the cause. To get into the minds of the American public, SCA needs to have a face, a large organization, a set of corporate sponsors, or some other notable characteristic that will cause people to listen. The Wellstone Triangle is a concept in political advocacy that seeks to explain how to promote and champion progressive public policy. Named for former Senator Paul Wellstone, and now championed by the Wellstone Action group, the Triangle emphasizes that grassroots advocacy, sound policy knowledge, and strong political campaigning are essential for leadership. Similarly, good SCA activism should strive to incorporate all of these items, focusing on engaging with the media, helping federal agencies accountable, and advocating for increased funding.

Few would argue that race has not played a pivotal role in affecting the outcomes for those affected by Sickle Cell Anemia in America, but advocates for improvement should not let racial tensions discourage them from engaging in activism. SCA activists need to realize that funding and care disparities transcend race and highlight a larger disparity in public awareness. Race feeds into SCA disparities through this mechanism, but it is not the only cause of funding and care disparities. Advocacy should focus on SCA as a life-altering disease, not merely a “black” disease. Political diseases are going to require political ends to remedy disparities, and with the right voices in place, steps can be taken to improve care for all.

References
17. Chang Hee Choi, Simo Huang, Eileen Shiuan, Michael Helzer, and Navtej Singh* Advisor: Dr. R. Stephanie Huang, Asst. Professor of Medicine, University of Chicago
18. References
20. Scientific Background
ADHD (Attention Deficit Hyperactivity Disorder) ADHD, according to the American Psychiatric Association in the 4th edition of its Diagnostic and Statistical Manual (DSM-IV), is a neurobiological syndrome used to describe children, adolescents, or adults who are inattentive, impulsive, and hyperactive [1]. As of 2007, the Centers for Disease Control and Prevention (CDC) have reported that about 5.4 million children 4 to 17 years old have been diagnosed with ADHD, or about 9.5% of children in the United States [2]. Currently, psychostimulants such as Mixed Amphetamine Salts like Adderall are the most effective first-line treatment used by primary care physicians and pediatricians to treat ADHD.

Mixed Amphetamine Salts Adderall® and Adderall Extended-Release (Adderall XR®) are formulations of chemical compounds called mixed amphetamine salts (MAS), a psychostimulant introduced in 1944 to treat Attention Deficit Hyperactivity Disorder (ADHD) in children and adults [3]. Mixed Amphetamine Salts (MAS) currently used in Adderall® are a 3:1 mixture of D-Amphetamine and L-Amphetamine. The D-enantiomer is known to be the more potent and longer acting of the two, while the L-enantiomer is thought to contribute to the overall effects of the drug in a synergistic manner. Adderall® and Adderall Extended-Release (Adderall XR®) are available in an oral form and are commonly prescribed to manage symptoms of ADHD in children and adults. The medication works by increasing the levels of dopamine and norepinephrine in the brain, which helps improve focus, attention, and impulse control in individuals with ADHD. The long-acting formulation, Adderall XR®, is designed to provide sustained release of Adderall® over an extended period, typically 12 hours, for better management of ADHD symptoms throughout the day.

Figure 1. D-L-Amphetamine. Note that D- and L-amphetamines are mirror images of each other, they are not superimposable. Such compounds are called enantiomers.
of D- and L-amphetamine salts (Fig. 1). Both compounds have the same chemical composition but differ in their three-dimensional structure. In Figure 1, solid wedges represent bonds that point out of the paper towards the viewer whereas dashed wedges point into the paper. One can see that although D and L compounds are mirror images of each other, they are not identical; rotating the L-compound 180° makes its methyl (-CH₃) group point inwards whereas D-amphetamine’s methyl group points outwards. In organic chemistry, such compounds with non-superimposable mirror images are called enantiomers.

The initial discovery of psychostimulants’ distinct calming effect in children’s behavior was made purely by accident more than 70 years ago, by a Rhode Island psychiatrist named Charles Bradley [4]. Bradley originally intended to treat headaches in children who had various behavioral disorders but found that treating them with a 1:1 mixture of D/L-amphetamines known as Benzedrine* demonstrated “a spectacular improvement in school performance” with increased drive to accomplish their goals and accelerated comprehension and academic achievement [5]. Since then, many other stimulants such as methylphenidate (Ritalin®) and lisdexamfetamine (Vyvanse®) have demonstrated therapeutic effects on ADHD patients, and it is known that mixed Amphetamine Salts also produce qualitatively similar behavioral effects in children and adults not suffering from ADHD [6].

**MAS Mechanism of Action**

**Neurophysiology**

The brain is a complex network of billions of specialized cells called neurons. Although scientists understand with some confidence how each neuron transmits signals, understanding how the signals collectively lead to the macroscopic state of the mind remains a mystery [7]. Likewise, the specific neurophysiological mechanism by which psychostimulants affect neuronal cellular processes is well-known compared to the relative lack of knowledge about the overall clinical mechanisms of stimulant action. Still, there have been significant advances in understanding the neurophysiological and biochemical actions of D- and L-amphetamine salts. In order to understand the mechanism by which MAS exert their psychological effects, it is necessary to first understand some general neurophysiology of the brain. Neurons, the basic building blocks of the nervous system, are specialized cells that are interconnected for input and output of signals. Within a neuron, a signal is transmitted electrically via the movement of sodium ions (Na+) across the cell membrane. At the synapse, the junction where one neuron meets another, the signal passes from one cell to another. There are two types of synapses, electrical and chemical. In the electrical synapse, the two neurons have cell membranes that are interconnected by special channels so that the electric signals can simply flow through. In a chemical synapse, however, the two neurons are brought very close to another but are still physically apart. Hence, once the electric signal reaches a neuronal terminus, it elicits the release of chemical messengers called neurotransmitters which diffuse across the cleft and physically bind to the receptors of the other neuron receiving the signal. Binding of the neurotransmitter at the receiving neuron triggers the influx of ions into that neuron, thereby eliciting another electrical signal that can be further transmitted to its neighbors.

**Dopamine, Norepinephrine, and Amphetamine’s Action Mechanism**

Many chemical substances, either endogenous or synthetic, are known to function as neurotransmitters. Of those, amphetamine is structurally and chemically similar to dopamine (DA) and norepinephrine (NE), neurotransmitters derived from the amino acid tyrosine and collectively known as the catecholamines (Fig. 2). The DA system is known to regulate motor output, specializing in maintaining a physical “tonic readiness to respond” whereas the NE system mediates attention processes such as selective attention, arousal, and perception [6]. D- and L-amphetamines do not directly act as neurotransmitters but exert a function by promoting the action of the DA and NE system. Amphetamine is known to facilitate the release of DA and NE into the synaptic cleft, and D-amphetamine is known to be much more potent than the L-compound [6]. In addition, because amphetamine is structurally related to DA and NE, it competes with the endogenous neurotransmitters for both reuptake and breakdown [4]. Amphetamine causes an increase in concentration of dopamine and norepinephrine in the synaptic cleft, and therefore, the receiving neurons are more frequently activated for a longer duration. As NE and DA regulate attention and preparation for response, it can be suggested that amphetamine’s stimulating effect on these systems eventually leads to enhanced attention-related processes among those treated with MAS.

**Abuse and Its Effects**

**Abuse of Prescription Stimulants on College Campuses**

Amphetamines such as Adderall are an important topic in contemporary culture because the illicit use of prescription medication contributes a significant portion to the substance abuse problem widely prevalent in American colleges. Adderall, in line with similar drugs like Ritalin and other methylphenidates, are part of the social stigma associated with pressure-driven college students who need an ‘edge’ in fulfilling their academic goals. Its effects of increased wakefulness and enhanced focus can be seen as easy temptation within the college environment, whether it be for recreational stimulation (achieving a ‘high’) or for periods of academic stress. A study at the University of Michigan conducted in 2007 found that 69% of students reported prescription stimulant use like Adderall and Ritalin improved concentration and 67% said that use of the drugs helped them study [1]. One web-based survey of 4580 college students conducted in 2006 elucidates the actual reach of such abuse. The data showed 8.3% of students (362) had used prescription drugs illicitly in their life and 5.9% (269) had used prescription drugs illicitly in the past year. 75.8% of these 269 students who reported recent illicit use of prescription drugs had taken an amphetamine-destroxamphetamine agent (i.e. Adderall) while 24.5% had taken a methylphenidate (i.e. Ritalin, Concerta) [2]. Interestingly, another survey taken at the University of Michigan asked undergraduates how many of their peers they perceived to be using prescription drugs for non-medical purposes. Students reported perceived usage rates of 70.2% for prescription stimulants and 69.9% for prescription opioids. This shows a gross exaggeration to actual usage rates (5.9% for recent use and 8.3% for lifetime use) suggesting a pervasive belief that prescription medicine abuse is common and normal behavior [3]. However, data on actual usage rates show that a significant proportion of the misuse is driven by the stigma associated with Adderall abuse of prescription medication. Though these estimates are well below perceived usage rates, this openness to misuse of prescription medication in ‘Generation Rx’ may pose a problem for future years as perceptions of heightened drug abuse can signal a relaxed context in determination of a norm which could potentially bring actual usage rates closer to the ones perceived. Furthermore, studies have shown a growing trend in prescription drug abuse. The Substance Abuse and Mental Health Services Administration (SAMHSA) and the National Survey on Drug Use and Health (NSDUH) have reported an increase in non-medical use of pain relievers among 18-25-year-olds from 41.7% in 2002 to 46.6% in 2007 [4]. Data from the National Center for Addiction and Substance Abuse (CASA) suggests that non-medical use of stimulants and painkillers has tripled from 1992 to 2009 [5]. While these studies reveal the trends in abuse of performance enhancers such as Adderall across American colleges, they do not highlight the secondary effects resulting from misuse of prescription medication and there is little data to show a clear formulation of the consequences for ‘Generation Rx’.

**Side Effects of Adderall**

The increasing rates of nonmedical use of prescription stimulants such as Adderall represent an important public health concern. Due to their mechanism of action, amphetamine stimulants like Adderall can cause rapid development of tolerance. Increased tolerance leads to a compensating increase in dosage rates leading to greater difficulty in user withdrawal [6]. Other known side effects have also been published. Most of these represent short-term effects though, if persistent, they can require a visit to the physician’s office. Regarding Adderall and similar stimulants, there is a wide spectrum of typical effects. Affecting the GI tract are dry mouth, loss of appetite, nausea, diarrhea, and weight loss. Affecting the nervous system is insomnia, agitation, anxiety, dizziness, depression, seizures, stroke, euphoria, tics, and headaches. Finally, tachycardia (fast heart rate), palpitations, elevated blood pressure, myocardial infarction (heart attack),
and sudden death may also result in the cardiovascular system. Other significant side effects include impotence, changes in libido, and psychotic episodes [7]. The risk and significance of these side effects increase when looking at the subset of the population taking Adderall. Among full-time college students, nonmedical Adderall users were more than 1.5 times as likely as their peers to have used alcohol in the past month (95.4% vs. 63.0%). They were also twice as likely to have been binge drinkers (89.5% vs. 41.4%) and more than 3 times as likely to have been heavy alcohol users (55.2% vs. 15.6%). Adderall abusers were also more likely to have used illicit drugs in contrast to nonusers. Abusers were at least twice as likely to have used marijuana, cocaine, hallucinogens, LSD, ecstasy, inhalants, tranquilizers, or methamphetamine than nonusers [8]. Thus, there is a significant trend of polydrug usage among Adderall abusers; the complex interactions of varying drugs can increase the chance of deleterious side effects.

A Corporate Background
In 1996, Shire Pharmaceuticals, then based in the U.K., introduced Adderall IR which became a very successful drug for ADHD patients, especially children. The drug quickly became Shire’s best-selling product and source of revenue. However, towards the end of the 1990s, Shire became increasingly worried about its dependence on Adderall IR and the imminent rise of generic versions and in late 2001 released a new once-daily extended-release formulation called Adderall XR in hopes of switching Adderall IR patients to XR in light of impending generic competition [1]. Competition with generic Adderall began unexpectedly early in February 2002 when an American company Barr Pharmaceuticals began selling the first generic Adderall IR in the US [2]. Shire sued Barr over the similarities of the appearance of its generic but lost the suit. Furthermore, despite Shire’s efforts to remain competitive with its new XR brand, the company still suffered significant losses due to its dependency on Adderall IR (which accounted for almost half of the company’s sales) and lack of a broader product base. This significant setback, Shire reestablished proprietary market dominance by July 2002 when Adderall XR became more popular than Adderall IR and its many generic formulations, and Shire’s profits were once again on the rise. In November 2001, a 17 year patent for Adderall XR use in children was approved in the US by the FDA [3]. Although the formulation was protected until 2018, Shire’s market exclusivity expired in 2004 permitting the entrance of generic extended release formulations much earlier than the patent expiration. In February 2003, Barr filed for permission to sell a generic version of Adderall XR by submitting an Abbreviated New Drug Application (ANDA). Shire again filed suit against Barr claiming infringement of Adderall XR’s patent, though Barr refuted the allegations. Ultimately, Shire hoped to delay Barr’s entry into the extended-release market since, regardless of outcome, US law dictates that the court must be given sufficient time to decide the issue before the company launches a generic drug in question can be launched. Consequently, Barr was not permitted to sell its product until 30 months after the filing date [4]. Later that year in August, Shire won another patent for Adderall XR, strengthening its suit against Barr. However, Barr again challenged the ruling, delaying its settlement until January 2006. Due to postponement of the trial with Barr Pharmaceuticals, Shire and Barr did not settle on an agreement until August 2006; the delays were an economic benefit for Shire and the final settlement also landed in Shire’s favor. Under this deal, Barr was prohibited from producing a generic Adderall XR for three more years but as part of the agreement was to purchase Adderall IR from Shire for $563 million [7]. Similarly, in November of 2003, Impax Laboratories, another US company, announced plans to launch a generic Adderall XR, further increasing the pressure of competition on Shire. A month later, Shire filed a lawsuit against Impax on the same premises as the Barr suit, preventing Impax from marketing its drug for 30 months [3]. Shire’s decision to challenge both Barr and Impax constituted an advantageous economic strategy that ultimately delayed the onset of generic competition until 2006 and gave Shire needed time to develop new pipeline drugs. In January 2004, Shire defeated Pharmacia over Impax and the two companies agreed upon a settlement that prohibited Impax from selling generic versions of Adderall XR until 2010 and required Impax to pay royalties. Although Shire defended its prize drug from Barr and Impax, it allowed smaller companies such as Teva Pharmaceuticals and Colony Pharmaceuticals to produce generic Adderall and did not take legal action against them [6]. The settlements with both Impax and Barr, however, ended with major victories for Shire. In addition, Shire won FDA approval for Adderall XR for treatment of adult ADHD in August 2004. With this step, Adderall XR became the first stimulant drug approved for adult ADHD in the US and a new adult market at least twice the size of the pediatric market opened up greater opportunities for Shire. This expansion was compounded with the discovery that around 65% of children with ADHD continued to rely on stimulants well past childhood. Shire was able to use the additional revenue from the Adderall XR sales to broaden its drug portfolio and reduce its dependency on Adderall [8]. However, despite its efforts, Adderall XR remained Shire’s top-selling medication throughout the decade and Shire allotted much of its energy and resources towards protecting Adderall XR’s monopoly. Knowing full well that generic versions of XR would come to the market by 2009, Shire developed a new and improved version of XR and intended it to potentially replace Adderall XR as the top-selling ADHD medication. This new drug, called NRP104, was approved in October 2006 by the FDA [9]. To further secure its presence in the ADHD market and limit growing competition, Shire purchased New River Pharmaceuticals for $2.6 billion to gain control of Vyvanse, a potential successor of Adderall XR which boasted a longer effect and was approved by the FDA in February 2007 [10]. However, Vyvanse’s performance on the market proved to be disappointing and Adderall XR remained Shire’s best-selling drug even as generic versions began to crop up in April 2009. In February 2005, Shire’s Adderall XR was banned by the Canadian health regulatory organization Health Canada for six months after international reports questioned the safety of the drug. These reports highlighted the deaths of 14 children and 5 adults after taking Adderall XR, though none of the deaths occurred in Canada. At that time, the Canadian market contributed to around $10 million, or less than 2% of Shire’s annual sales [10]. Adderall XR was still permitted in the US since the FDA believed there was little evidence link the drug to the reported deaths and that the potential risks of XR needed to be further investigated. The contrasting actions between the FDA and Health Canada highlight the differences between healthcare regulation laws between the two countries. In Canada, regulators have the power to ban a drug from the market while the safety of the drug is being investigated whereas, in the US, such an action is usually not permitted [10]. The ban was highly criticized by healthcare professionals and patients who depend on Adderall. Subsequently in August 2005, Health Canada lifted the ban on Adderall after they declared that it did not pose a greater health risk than the other comparable ADHD medications on the market such as Ritalin; a new black box warning was added, however, reflecting the potential dangers of the drug [11].

Legality and Legal Status
Attention Deficit Disorder (ADD) and Attention Deficit Hyperactivity Disorder (ADHD) were first clinically described in 1902 at which time the leading prescription drug for these conditions was Benzine. Stimulants such as Benzine were shown to be effective in treating indicative symptoms of the disorder (at the time both ADD and ADHD were lumped together as a single disorder), but Benzine was eventually abandoned because of its adverse effects compared to other treatments. It was believed, for instance, that the use of Benzine resulted in a higher instance of cancer, though testing on this topic has proven inconclusive [12]. The story of Adderall, or dextroamphetamine saccharate, begins in 1960 when this new stimulant was approved by the US Food and Drug Administration (FDA) to treat ADD and ADHD. The patent initially belonged to Shire Pharmaceuticals, the developers of this new drug, but the production rights were subsequently acquired by Barr Pharmaceuticals, and Barr was in turn bought by Teva Pharmaceuticals (2-3). Since then, the patent rights have changed rather significantly within the United States and other countries. In the early 1990s when the instance of ADD and ADHD in children was discovered to be on the rise, the production of amphetamines and methylphenidates ballooned in the U.S. from 2000kg to over 14000kg by the end of the decade (4-8). This sharp increase in overall use was acutely felt in the U.S. as opposed to other countries where the recreational use of amphetamines was not as popular due to the wider availability of stimulants such as cocaine and MDMA, as in eastern European countries [4]. It was this dramatic spike in usage of amphetamines that brought the legality of these drugs in the United States to the forefront of debate on prescription drugs, especially given the widespread concern that children are overdiagnosed with ADHD (9-14). The Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV)
lists the symptoms of ADHD as “lack of attention to details/careless mistakes; lack of sustained attention; poor listener; failure to follow through on tasks; poor organization; avoids tasks requiring sustained mental effort; loses things, easily distracted, forgetful[1]. At least six of these symptoms must have persisted for more than six months in individuals older than seven years old, and these symptoms must result in clinically significant im-
paired functioning in personal, academic, or occupational roles and situations. The DSM-IV criteria for ADHD (9-16). The subjectiveity of these symptoms combined with the requirement of symptoms to persist in two set-
tings is often seen as problematic because this means that, in the case of children and adolescents, teachers and other educators are responsible for a large part of the diagnosis process (9-16). Besides the fact that these individuals are untrained in medical diagnoses, several studies have indicated a large bias as to which children or adolescents educators identify as symptomatic or hav-
ing impairment (9-16). Noting that Adderall is scheduled in line with other amphetamines in many countries and citing statistics that the majority of Adderall usage is pre-
scribed for children, the Food and Drug Administration required Shire to seek reapproval for their Adderall production in 2003 when the company attempted to expand its production to new doses. The FDA approved the addition of Adderall XR 5, Adderall XR 10, Adderall XR 15, Adderall XR 20, Adderall XR 25, and Adderall XR 30 (increasing variations in mg per capsule) to Shire’s rep-
ertoire of ADHD and ADD treatments (17-22). A dramatic increase in dosage which further called into question the ethics of prescribing strong stimulants to children. It is also worth noting that the FDA approved the Adderall XR series for use in 2003, report-
ing only a brief series of Phase 4 trials before the various dosages were approved for adult consumption (17-22). This quick approval of an adult Adderall by the FDA af-
fects those already on the drug, the government continues its control over the production of the substance though it may not be banned outright due to the high level of medical use and necessity. This control may cause friction between the pharmaceutical companies which produce the drugs and enforcement agencies who monitor it, as recent Adderall shortages have indicated, though the situation is not likely to change soon.

Financial and Strategic Considerations: Ownership
Adderall, in both its formulations and many generic it-
erations, is one of the world’s best selling ADHD drugs. Because of its popularity and a rush to expand markets across the world has bestowed the drug with a somewhat fragmented history. The original producer, Shire Pharmaceuticals, would eventually sell production rights to DuraMed Pharmaceuticals which was subse-
quently purchased by Teva Pharmaceuticals through its Barr Pharmaceuticals acquisition. This history has situ-
tated the generic and commercial versions of the drug in various divisions of these and other companies through other contractual agreements. As of the most recent generic version of Adderall Instant Release (IR) is sold by Teva Pharmaceuticals under its Barr Division and a brand-name version is sold under its DuraMed Division, while Adderall Extended Release (XR) has continued to be sold by Shire. CorePharma, Sandoz, and Ranbaxy, now owned by the Japanese pharmaceutical company Daiichi Sankyo, all have a stake in the production and distribution of generic iterations of Adderall.

Generic and Brand Name Market Interaction
The series of acquisitions undertaken by Teva and its subsidiaries helping it become the world’s largest pro-
ducer of generic medicines allows the organization to leverage its experience in components selling the generic (Barr) and brand name (Duramad) versions of a drug. The re-
sulting product positioning carries implications for sup-
ply and demand as well as strategy. Primarily, this case of “co-opetition” requires pharmaceutical producers to balance the increased profits available to the company if they restrict production to the market with the continued support of the FDA and enforcement agencies who monitor it, as recent Adderall shortages have indicated, though the situation is not likely to change soon.

Supply Disruptions and Customer Adaptation
From the late 2000s to early 2010s, there has been a widely-reported shortage of all Adderall formulations on the prescription market. Shire has cited “API (active pharmaceutical ingredient) issues and uneven product distribution patterns” while Teva, the largest producer, also cites “API issues” as the key cause of the shortage on the FDA’s Current Drug Shortages list [2]. Since the DEA fulfills quotas for the usage of amphetamine and methylphenidate use are produced. Adderall and other mixed amphetamine salts (MAS), the industry continues to point out the possibility of bureaucratic misjudgment or interference though the DEA maintains that quotas are currently satisfying supply needs. “We’ve given them quota sufficient to meet the needs and then it’s up to them how they manufacture their product,” said Gary Boggs, a supervisi-
tory special agent for the Office of Diversion for the Drug non-governmental sponsors. Due to this urgent need of prescription drug abuse prevention resources, the ques-
tion of corporate responsibility again comes into play when a company transfers rights of a drug at some point of its production. Here, the creation of a public good (the educational and supportive materials made open to all) is directly commissioned by Teva, the company responsible for formulating the drug. Although the DEA is responsible for collecting and distributing the drug, the government continues its control over the production of the substance though it may not be banned outright due to the high level of medical use and necessity.

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Enforcement Administration. “Company business decisions surrounding competition, marketing — and profit margins — are behind many of the troubles that patients have encountered. Manufacturers might make more of an expensive brand-name drug and not enough of a generic version. Or they may distribute too much product in one place, causing a shortage somewhere else” [3]. As children and increasingly adults find themselves having to purchase proprietary formulations due to waning generic supply, questions of corporate motivation and regulatory efficacy come to mind. Though the companies maintain that a lack of pharmaceutical ingredients is to blame, a temporary drought in the market has turned greater attention to the DEA’s quo. 

“Officials at the Food and Drug Administration say the shortages are a result of overly strict quotas set by the Drug Enforcement Administration, which, for its part, questions whether there really are shortages or whether manufacturers are simply choosing to make more of the expensive pills than the generics” writes Gardner Harris in the New York Times [4]. The DEA, however, is pursuing a precarious balance to curb abuse, especially among college-aged adolescents who may fall victim to longer term effects; “We see people abuse it in college and then continue to abuse it nonmedically once they leave” [5].

References

Scientific Background

Abuse and the Effects
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