博士論文

Does income inequality affect adolescent drug use behavior in low- and middle-income countries? ―A multi-national, multilevel study

（所得格差は低・中所得国の青少年の薬物使用に影響を与えているか―マルチレベル分析による複数国データを用いた検討）

宮本かりん

CONTENTS

List of Tables

List of Figures

Appendixes

Abstract

Background: Several studies highlight the influence of macro-level factors such as income inequality (the Gini index) on adolescent drug use. A stepping-stone theory framework was used to examine the relationship between income inequality and adolescent drug use, and the starting age of drug use in developing countries. The hypothesis was that country-level income inequality increases adolescent drug use.

Method: Survey data were used to assess the relationship between drug use probability and the Gini index by adjusting for individual, community, and country-level factors. Then, the mediation effect of the Gini index on smoking was assessed. The Cox model was used to assess the hazard ratio for onset of drug use.

Result: A significant country-level fixed effect of the Gini index on drug use was observed, but not in a random effect model. However, the survival analysis did not support the hypothesis that higher income inequality is associated with earlier drug use initiation.

Discussion: Unadjusted factors correlated with the Gini index might have made the association between the Gini index and drug use difficult to observe. In addition, the mediation effect of the Gini index was difficult to determine, as the main effect was not significant. The result of the survival study might have been caused by the composition effect of data.

Conclusion: Country-level income inequality was not associated with adolescent drug use in a multilevel model, but greater income inequality was observed as a protective factor in adolescent early drug use in a survival model.

Introduction

Drug use continues to become an increasingly serious problem. The World Health Organization (WHO) defined substance misuse as “use of a substance for a purpose not consistent with legal or medical guidelines, as in the nonmedical use of prescription medications” (1). Moreover, the Substance Abuse and Mental Health Services Administrations (SAMHSA) defined drug abuse as “non-medical use of a substance for psychic effect, dependence, or suicide attempt or gesture” (2). In this study, the word *drug* is used as “psychoactive substances other than alcohol or tobacco.” Furthermore, drug abuse is a prominent health indicator (3).

The various factors contributing to increasing drug use at the population level include macro-level factors. In this study, the researcher focused on income inequality, as this is not a factor individuals can change by their behavior, and it contributes to social volatility and instability (4). To date, numerous studies have been done on the relationship between income inequality and the health of populations. Wilkinson found that when social inequality decreases, life expectancy increases (6). Moreover, Kawachi and colleagues identified a negative correlation between life expectancy and income inequality (7). To explain these phenomena, Wilkinson published the income inequality hypothesis (8). Since then, a substantial amount of data and research have been published on the topic.

Contemporary researchers have attempted to explain the effects of income inequality on population health through the compositional and the contextual effects. In terms of the compositional effect, researchers seek the causes of poor average health status by examining the composition of people in a society (9), (10). From the contextual perspective, researchers attempt to explain the causal relationship using factors that characterize the region or community. The contextual effect focuses mainly on increased stress levels at the society level caused by observing the differences in social status, having less social capital in a community, or feeling relative deprivation, all of which lead to increased psychological stress (11). The contextual point of view further stresses monetary policy and government expenditure on the public sector, with supporters of the theory arguing that ineffective policy and poor income redistribution occur due to lobbying by the rich, whose interests are more prone to be reflected in policy (12).

Another approach is explaining the relationship between income inequality and health from the perspective of social capital. In a society where information sharing is limited, people tend to be less compassionate and less supportive of government expenditure. In addition, relative deprivation—a concept put forward by Runciman to describe the feelings that arise when a person sees another person possesses something he or she lacks—plays a key role in this approach (13, 14). Furthermore, stress induced by fear of losing in the social context has been proposed as a contributing factor (15). In a society where income inequality is large, the obsession to win is also large, while relatively poor social network functions increase the fear of losing, which eventually elevates stress levels.

Most studies on income inequality and health outcomes were based on data from developed countries. However, income inequality in these societies may be mitigated by the support available to disadvantaged people through existing social safety networks, such as unemployment benefits, homeless shelters, and universal health care, as well as support from citizens through volunteering and charity. Thus, in this study, data from developing countries was used to assess the effects of income inequality on the probability of drug use.

This thesis consists of two sections. The first section addresses the assessment of income inequality and the probability of lifetime drug use, reporting the results of the multilevel analysis and mediation analysis of parental smoking and the early onset of smoking. The second section deals with the effect of income inequality on the age at first drug use, examined using a survival model. In both sections, previous studies are first reviewed.

Study 1: Does higher income inequality increase the probability of adolescents' lifetime drug use in low- and middle-income countries?

1. Review

1.1. Adolescent drug use

Drug use is an immense problem throughout the world. In the United States, drug use cost the country an estimated $193 billion in 2007 (16). Adolescent drug use is especially worrying, as adolescence is a critical period for brain development.

The US Monitoring the Future Survey showed that the prevalence of drug use has gradually increased from 2008 to 2013 among all age groups, including 8^{th}, 10^{th}, and 12^{th} grade pupils (17). In 2012, about 8% of high school pupils in United States were estimated to misuse prescription opioids, and 6.5% of high school seniors were considered to be daily or near-daily marijuana users (18). Similarly, a report from the European Monitoring Center for Drugs and Drug Addiction showed that the number of children who have ever used drugs is very low at age 11–12, but sharply increases to more than 40% by the age of 18 (19). Furthermore, as an example of situation in low- and middle-income countries, in Afghanistan, about 1.4% of all children were estimated to be associated with opioid use (20).

Alcohol and drug use often play an important role in injuries and incidents. Despite the lowest mortality rate being observed during adolescence, drug use still holds risk of death, disease, and injury. The leading causes of adolescent morbidity and mortality include unintentional injuries, described as car crashes and delinquent activities; intentional injuries such as homicide, bullying, and suicide; and reproductive health issues such as unplanned pregnancy. In people fatally injured in road traffic accidents, the prevalence of drug use ranges from 8.8% to 33.5 % (21), and of treatment-seeking pregnant women using opioids, 86% were seeking treatment for unplanned pregnancy and sexually transmitted infectious diseases (18, 22, 23).

As discussed in the section that follows, several risk factors are associated with drug use in adolescents.

1.2. Review of factors associated with adolescent drug use

Previous studies have highlighted several factors associated with adolescent drug use. Personal factors include sensation seeking, heritability, male gender, delinquency, low education levels, low socioeconomic status, low family affluence, absence of parents and parental monitoring, fewer close friends, and exposure to early life stress. Environmental factors include high availability of the substance, peer effect, and cultural norms (22, 24-34). In addition, macro-level variables include regulations, cultural discrimination, taxation of legal substances, and lifetime prevalence of the use of the substance in the area (35). The factors previously found to be significantly associated with adolescent drug use are discussed below.

Individual-level factors

Sex

Being male is one of the clearest factors influencing drug use. In Robin's study, conducted in three states in the Unites States, males were more likely to use drugs, with 1.3 to 1.9 times greater relative risk (36). In this study, this gender difference was the smallest in the youngest age group (18–24 years old). In another study targeting Hispanics in the United States, the proportion of people using drugs in both the previous year and over their lifetime was higher in males than in females in all the subgroups of Mexican American, Puerto Rican, and Cuban Americans involved in the study (37).

Age

Age, a basic demographic factor, is often used to adjust for other demographic factors. In a study that targeted US citizens aged 18 or older, the youngest age group of between 18 and 24 years old was found to have the highest rate of drug abuse and dependence compared to older age groups (36).

History of early onset of smoking

Having a history of socially accepted substance, especially tobacco, has been suggested as a factor influencing adolescent drug use (38). Of the socially accepted substances, through a study of the coexistence of legal and illegal substance use, tobacco showed a higher association with the use of illicit drugs compared to other legal substances such as alcohol (39). In Durant's study, cigarette use at or before age 11 was found to significantly increase the health risk behavior scale, which includes the use of drugs or other substances ($\beta = 2.04$, $p < 0.0001$; (40). In a study examining pupils in grades 5–12, pupils consuming one or more packets of tobacco were 10 to 30 times more likely to use illicit drugs compared those who have never smoked (41). In addition, in the study, the relationship between smoking and the use of illicit drugs was dose-responsive. Regarding pathways from tobacco to other drugs, smoking involves practicing and acquiring several skills, including smoking behavior, needed for using some forms of illicit drugs (38, 42).

Environmental factors

Parents' and environmental attitude toward substance

Environment and the effect of parents are also important. Family environment was found to influence vulnerability to drug use (43). In King's study, experiencing parental alcohol misuse during their lifetime was shown to increase the odds of children using alcohol (44). In a study in Iran, most participants in the survey blamed interaction with friends who were drug users as a cause of addiction (45). Additionally, peer attitudes toward drug use are associated with adolescents' drug use (46–49).

Household income

The effect of household income or poverty at household-level on drug use was identified as heterogeneous. In a cross-country study targeting mainly developed countries, household income was positively associated with legal and illegal drug use (50). On the other hand, in a study in the United States, higher odds of nicotine dependence (adjusted $OR = 1.88$, 95% CI [1.62, 2.18]) were observed in households whose annual income was equal to or less than $19,999 compared to people whose annual household income was equal to or more than $70,000 (51).

Neighborhood income

Not only household-level income but also neighborhood poverty drives drug use, as was found in a study conducted in the United States (52). Similarly, living in an urban poverty area has been reported to be associated with increased cocaine use (53), and in Latino groups, neighborhood poverty was positively related with alcohol and tobacco use (54). In a study of adolescents, those who moved to middle-class neighborhoods exhibited fewer signs of problem drinking and marijuana use compared with those who remained in disadvantaged neighborhoods (55).

Neighborhood income inequality

Living in an area characterized by large income inequality is a further predictor of substance use. Simetin introduced the concept of school homogeneity—which refers to schools consisting of pupils with homogeneous socioeconomic status (SES) levels separate from school-level SES or area-level SES—into a multilevel study targeting Croatian pupils, and found that attending heterogeneous schools plays a harmful role (OR = 1.876, SE = 0.258) for cannabis use (56).

Neighborhood disorder

Neighborhood disorder was found to induce illicit drug use. In a study on 2,100 neighborhoods in the United States, illicit drug use was observed to be 1.3 times more likely in the most disadvantaged neighborhood compared with the least disadvantaged neighborhood (57). Moreover, a study conducted in New York found an association between neighborhood disorder and intravenous drug use (58), and a study focusing on intravenous drug users determined that the proportion of arrests made in neighborhoods was associated with increased odds of continual heroin or cocaine use (59). In addition, the interaction between neighborhood disadvantage and other environmental factors was reported. Snedker showed that neighborhood disadvantage moderates the effect of deviant peers on adolescent marijuana use and, in fact, has a positive direct effect (60).

Accessibility of drugs

Finally, the neighborhood environment around drug use is a strong predictor, and accessibility defined by price affects substance use: a $1.10 increase in cigarette tax is estimated to reduce the prevalence of juvenile smoking by nearly one third (61).

Country-level factors

Per capita income of the country

According to the WHO, up to a level of purchasing power parity (PPP)–adjusted gross domestic product of $7,000, a close relationship was observed between alcohol abstention and economic level (62). In addition, Blecher pointed out the effects of the increased affordability of tobacco in fast-growing countries such as Vietnam and Costa Rica, where the relative price of tobacco has decreased (63).

Drug-use friendly culture

A study that focused on the predicting factor of drug use in previous month, adjusting for factors including rate of "new treatment clients per 100,000," "substitution usage per 100,000," "trafficking/dealing offense rate per 100,000," "possession for use offense rate per 100,000," "possession for use decriminalized," and "syringe exchange in pharmacies" across EU countries found that there was a significant random-intercept effect among countries in the model (64).

1.3. Importance of income inequality

Among the factors listed above, this study focused on social-level factors, especially income inequality because unlike individual specific factors, macro-level factors affect all individuals living in the region. In this sense, income inequality can be thought of as a public health concern rather than something an individual should address alone. Therefore, a review was conducted to identify studies linking income inequality and substance use.

1.4. Search terms and method, and overview of the results of previous studies

To identify factors associated with adolescent drug use, a comprehensive literature review was carried out. Literature available on Internet databases, including Medline, PsycINFO, PsycArticles, and CINAHL Plus, was searched for articles published from 1990 January to May 2015. Search terms were chosen from previous studies and classified as follows:

1. Gini, income inequality, income inequity, drug, substance, abuse, misuse, dependence,

drug use, substance use

2. Income distribution, drug, substance, abuse, misuse, dependence, drug use, substance use

The search was done in May 2015, and 106 articles were identified from search term group one and 122 articles from search term group two.

The Gini index, listed as "Gini" in group one, is a commonly used index of income distribution among households or individuals in a country or community. It is derived from a Lorenz curve plot: a cumulative plot of earned income against the cumulative plots of recipients, measuring the area between the Lorenz curve and a 45-degree hypothetical absolute equality line (65). A Gini index of 0 shows a perfectly equally distributed society, while 100 indicates a completely unequal state. For the term "drug," only substances used for leisure or nonmedical use, which are often illegal, were included. After excluding duplicates within each search result, which was done automatically by the EBSCO system, 71 and 84 articles were obtained, with some articles appearing on both lists.

After excluding letters, reviews, articles without any regressions or analysis, articles written in languages other than English, and articles that concerned neither substance abuse nor income inequality, 14 articles remained. In addition, five articles identified from citations were included in the review list. Figure 1 shows the overall flow and structure of the review. As this field is relatively new, only a limited amount of literature was available.

Four articles were identified that examined income inequality and substance use by international dataset. Of these, three were about either alcohol or tobacco. The last one involved several hard drugs, but the study site was limited, and the study was targeted at adults. Therefore, at the time, there were no international studies on income inequality and adolescent drug use behavior. In terms of income inequality and substance use among children or youth, two articles were found, one from international studies and one from the results of the literature search.

In terms of substance types and outcomes, studies were identified relating to analgesic overdose, any drug overdose, alcohol, tobacco, marijuana, opiates, cocaine, cannabis, ecstasy and amphetamines, drug related mortality, and drug use (66-78). As a measurement of income inequality, researchers used the Gini index, population earned 70% of total earnings, and 80:20 income distribution (74, 77).

Out of 11 studies, nine focused on adults, including the working-age population, and two focused on adolescents. Nine of the 11 studies showed at least some significant results linked with income inequality, while two reported that income inequality did not have significant effects on substance use.

1.5. Income inequality in previous research studies

In an ecological study, Pickett showed that a 80:20 ratio was significantly associated with the drug use indices created originally for the study, applying international country data (77). In a study focusing on adolescent substance use, significant effects of income inequality were also observed. In a study examining the possible relationship between adolescent tobacco use and macro-level factors in developing countries, higher income inequality was independently associated with adolescent smoking for both boys and girls (for boys, $OR = 1.04$, $p = 0.013$; for girls, $OR = 1.05$, $p < 0.001$; 70). In a study connecting income inequality with child drinking behavior, income inequality was significantly associated with the consumption of two to four alcoholic drinks per week among pupils aged 11 and 13 in high income inequality tertile countries (for 11 years old, $OR = 1.85$, 95% CI [1.07, 3.21]; for 13 years old, $OR = 1.96$, 95% CI [1.40, 2.74]; 68).

1.6. Analysis methods

Among all 11 studies, in one article a two-group comparison with a chi-squared test was applied (67), in one the bivariate relationship was examined using Pearson's correlation statistics, in one OLS estimation was used, and in one logistic regression was used (66). In the rest of the studies, multilevel analytical methods were used, with the generalized estimating equation method used in four studies, a modified GLS or random effect model used in one study, and a random intercept model used in three studies (68, 70, 71). All these models are based on the assumption that the independent variables and covariates affect adolescent drug use in the same way across the groups.

1.7. Summary

The literature review revealed that being male, especially of Hispanic origin; being younger, in one's twenties or in the 18–24 year group; taking up smoking early; household poverty, neighborhood disorder, and median income; and gross national income (GNI) and income inequality were risk factors for adolescent drug use. However, these results were based on single-level and random intercept models, and the contextual effect of the Gini index on adolescent drug use in a random slope, random intercept model had not yet been studied.

2. Hypothesis for Study 1

2.1. Gap suggested from previous studies, and research question

The literature review emphasized the lack of studies exploring the relationship between income inequality and substance use, especially in developing countries. In addition, there is a need to estimate the magnitude of the effect of income inequality on adolescent drug use in developing countries, separately from the effects of poverty on adolescent health behaviors. Culture, discrimination, the availability of drugs and their varieties, economic tendencies, and government attitudes toward drugs and adolescent health, as well as education, differ significantly among countries. Thus, some differences can be expected in the probability and likelihood of drug use among adolescents, even in the hypothetical case that income inequality was absolutely zero among all countries. However, based on the findings of the literature review, most studies used limited types of analysis methods, which might influence findings and weaken the analyses. Therefore, in this study, random slope and random intercept models were constructed, which relaxed the assumption of an equal effect across groups that was applied in the previous studies (70, 71).

The mechanism involved in how income inequality affects adolescent drug use behavior was predicted as follows: Higher income inequality causes parents to feel depressed and increases their stress levels, and they then tend to consume more tobacco to cope with the stress relating to the disparity of wealth at country level (79). Children, who grow up observing their parents, would thus possibly learn smoking behavior at an earlier life stage compared to others. Having started smoking earlier, they will then have a higher probability of progressing to using drugs (80).

2.2. Theories underpinning this research

Apart from the review results, two theories inform the research questions in this study. The first, the income inequality hypothesis, explains the context of the association of higher income inequality with poor individual health outcomes, while the second, the gateway drug theory, explains the mechanism that affects onset of drug use by acquisition of smoking behavior.

The income inequality hypothesis links income inequality and poor health outcomes (81-84). Schor proposed that high levels of domestic inequality promote a culture of social comparison. Wilkinson and Pickett elaborated this theory into substance use behavior, arguing that the existing social strata motivate people to use drugs or substances to reduce stress (79, 84).

Further, based on the gateway drug theory, also often called the stepping-stone theory, individuals who begin smoking or drinking (or often those who initially use cannabis or other soft drugs) will progress toward using harder drugs later in life (85-89). In this study, it was supposed that the onset of smoking at a young age is a direct cause of using drugs, based on this theory.

2.3. Research question

Based on the income inequality and gateway drug theories, the following models were constructed to delineate the pathway from income inequality to adolescent drug use: Income inequality, as expressed by the Gini index for respective countries, negatively affects parental mental health, as parents witness the harsh lives of poor people, which increases psychological stress and drives parents to use tobacco to reduce stress. Children view their parents as role models and thus learn to smoke at an early age; this acquisition of behavior then leads them to use drugs during adolescence.

In this study, the following question was examined: Does higher income inequality increase the probability of adolescent drug use in a simple Poisson regression model, and in a random slope-random intercept model, based on a cross-sectional dataset?

2.4. Research hypotheses regarding income inequality and adolescent drug use

Two hypotheses were set to enable the objective verification of the research questions defined above. Due to the scarcity of literature explaining the mechanisms affecting income inequality and drug use, the researcher introduced the stepping-stone hypothesis to fill the gap. Based on these theories, the following relationship from the analyses was supposed:

1. Countries with higher income inequality positively correlate with higher lifetime drug user prevalence
2. The effect of higher income inequality on adolescent drug use is mediated by the early onset of smoking and parental smoking behaviors. The Gini index becomes smaller or becomes nonsignificant when adding variables indicating parental smoking behavior and the early onset of smoking, respectively.

3. Method

3.1. Data structure

The study relied on data from several secondary sources. The main body of secondary data, regarding pupils' health behaviors, included class and school identification variables from the Global School Health Survey (GSHS) dataset. As this dataset did not include country profiles, such as the aggregated level of economic information, several sources of official statistical data were imputed. The imputed data came mostly from the World Bank, the United Nations Development Program (UNDP), the United Nations University, and other gray literature for countries where no statistical data were found from international organizations' databases or websites.

3.2. Data sources

The main body of the data, collected in the Global School Health Survey (GSHS) project (90), carried out by the Centers for Disease Control and Prevention and the WHO, refers to secondary schools in 66 developing countries. In this study, due to data availability, only data sampled from 2003 to 2012 were included.

For country statistics data, the Gini index and per capita income (GNI per capita) were used. GNI per capita is an indicator of the per capita income of a country, in which the calculated total income earned by a nation is divided by the total number of people living there. GNI is often used as an economic index for developing countries. These data were derived from various public data sources, mostly from the World Bank, UNDP, and the Central Intelligence Agency (CIA) Factbook. To make it concordant within each country, the years of the data were set to the same years in which the survey was taken in the country.

3.3. Participants

The participants who completed the survey were all secondary school pupils aged from 11 to 16. Pupils younger than 11 and older than 16 were recorded as 11 and 16, respectively. For some countries surveyed in 2012 or later, new categories were created for pupils aged from 17 to 18 and older. In this study, however, all pupils recorded as 16 or older in any forms were categorized as "16 years old" for consistency with previous surveys. Age was categorized by year and treated as a continuous variable.

The overall demographic characteristics used in Study 1 are shown in Table 1. Participants were asked to report the number of times of any kinds of drugs they had ever used, if any, using surveys conducted between 2003 and 2008. In total, 45 countries were available for analysis in this study.

Table 2 shows the total of 45 countries' names, populations, and their proportions to the total.

3.4. Questionnaire and variables used in this study

The questionnaire was standardized; thus, all the countries shared the same questions. Participants could decide whether they wanted to answer optional questions, but as the optional questions and their answers were not published, they were not publicly accessible. This study, therefore, includes data from the standardized questions section of the survey.

For the analyses, the following variables, as described in Table 1, were used.

Lifetime drug use

The questionnaire, for the 2003–2008 surveys, asked participants how many times they had used each type of drug. The versions used in the surveys of 2009 and later asked participants their age of first use of any kind of drug (90). The questionnaire in this project does not define the types of the drugs. However, the users' guidebook and rationale of the items included recent articles focusing on illicit drug trade, cannabis, amphetamine-type stimulants, cocaine, opiates, and heroin as examples of research findings related to drug use.

For example, the questionnaire used in the survey conducted in the Seychelles in 2007 addressed lifetime drug use experiences as follows: "During your life, how many times have you used drugs such as marijuana, cannabis or hashish, *lapay,* steam, *studff,* joint, or *tyalas* [*lay*, *studff*, and *tyalas* are the names of drugs prevalent at their survey sites]?" The answer was recorded using a 4-point scale: "1: 0 times," "2: 1 or 2 times," "3: 3 to 9 times," and "4: 10 or more times" (91). The revision of the question can be seen in Algeria's survey, conducted in 2011: "How old were you when you first used drugs?" The answer was provided using a 7-point scale, per age: "1. I have never used drugs," "2. 7 years old or younger," "8 or 9 years old," "10 or 11 years old," "12 or 13 years old," "14 or 15 years old," or "16 years old or older"(90). The standardized questionnaire can be downloaded directly from the GSHS group websites (90).

Some countries used their own languages in the surveys, but information was not publicly accessible as to how each country represented translated each survey. In this study, the questions were transformed into dichotomous variables, converting to 0 if respondents answered that they have never used drugs in both versions, and 1 otherwise.

Age

Six alternative age groups were provided in the questionnaire, ranging from 11 years old to 16 years old.

Sex

Sex was collected in the questionnaire. Male was coded as 0, whereas female was coded as 1.

Household poverty

For the household poverty variable, since the survey did not ask respondents to describe household income or household belongings, their answer to the question about "frequency of hunger" was used as an indicator of the extent of household poverty. The original item was scored at 1 if the participants "feel hunger not at all" and 5 if they "feel hunger all the time." In this study, however, the variable was ordered so that 1 indicates the poorest situation and 5 the richest condition.

Early onset of smoking

Adolescent behavior around the early initiation of smoking was modeled. Our concept was that those who started smoking early in their lifetime may be more likely to progress to taking drugs, based on the stepping-stone theory. In the questionnaire, respondents were asked how old they were when they first used tobacco. The answers to the question were converted into a dichotomous variable—1 if their answers suggested using tobacco before age 13, and 0 otherwise. This category was based on the previous studies done by Henry Jackson on the relationship between early initiation of smoking (prior to 13 years old) and illicit drug use.

Parental smoking

Parental smoking status was also modeled, as parental behavior provides an example for children (66). In this study, the smoking behavior of parents was assumed to be affected by income inequality, based on the idea that parents may smoke as a strategy for coping with stress that comes from their awareness of existing social strata and inequality (68). Relating to tobacco use, the survey also asked who in the respondent's household smoked, using a multiple alternative question form.

Neighborhood characteristics variables

Although the dataset had a variable distinguishing each school, there was no information about school name, nor the names of cities, counties, or villages, except for the data provided by a few countries. This was mainly to protect respondents' privacy and security. To overcome limitation, respondents' answers grouped by schools as proxies for neighborhood characteristics were aggregated. In this study, three variables were created: neighborhood average income, neighborhood poverty variance, and neighborhood drug use.

Neighborhood average income

Average income was determined by aggregating the individual income variable. Therefore, it is 5 in the poorest neighborhoods, and 1 if all pupils within the same school are in the wealthiest category.

Neighborhood poverty variability

To substitute for neighborhood income inequality, this study focused on the variability of income-like variables in a certain area. This idea was derived from previous studies, where researchers accounted for the standard deviation or mean of socioeconomic measures for a pupil's school, compared with that calculated for all sample schools (56). The researcher further consulted other established income inequality indexes, such as Atkinson's index and the Theil index, where the entropy of household income among the groups or area is used as a marker of income inequality.

Moreover, several previous studies have shown that there are certain positive correlations between calorie intake and household income in low-income countries. From these studies, the answer to the "frequency of hunger" question in the questionnaire was considered to take the place of the indicator of calorie intake. Therefore, the Gini index was calculated from frequency of calorie intake for each group of pupils in the same school. The answer to the frequency of hunger was scored 1 if pupils answered "always [feel hunger]", and 5 if they answered "never [have felt hunger]", respectively. The neighborhood poverty variance was created by calculating the Gini index from the individuals' frequency of hunger within the same school. For the calculation, Stata's additional package called "ineqdeco (STB-48: sg104)," released by Stephen P. Jenkins, was used. It takes a 0 to 1 value: 0 if pupils within the same school have exactly the same wealth status, whereas larger values suggest greater inequality within the neighborhood.

Neighborhood drug use

"Neighborhood drug use" was aggregated from the individual lifetime drug use answer, indicating the prevalence of drug use within the same school.

Country-level variables

The following variables are country-level variables, where adolescents from the same country share the same value. As these variables could not be obtained from the GSHS data, both variables were taken from other sources and later imputed into the dataset.

The Gini index

The Gini index was obtained from official statistics such as those released by the World Bank and UNDP, and from gray literature published by governments. In this study, the Gini index was multiplied by 100 and is shown as a value from 0 to 100 so that the differences can be seen more easily.

Per capita income of the country

As a variable for social affluence, Gross National Income (GNI) per capita was used, which is adjusted for PPP (in the international dollar in 2005). As per capita income looked agglomerated when plotting with a scatter plot with the Gini index, the logged value of GNI per capita was used.

3.5. Statistical Modeling

In this study, the associations between income inequality and lifetime drug use throughout the countries were supposed to be different, and the probability of drug use at country level, where the Gini index was zero in all countries, was different with intercept for random slope. Throughout this study, neighborhood income inequality is referred as "neighborhood poverty variance," and country income inequality is expressed as "the Gini index."

First, a hierarchical model was created to assess the mediation effect of parental and adolescent early onset of smoking on lifetime drug use. For introducing the contextual effect into the model, a multilevel model was employed. Previous studies argue the use of the dummy variable in the case where the variables on area-level aspects other than income inequality were not used in the model, to represent area-specific characteristics (92). Another method involves using instrumental variables for adjusting endogenous variables (93). However, even this method cannot eliminate the endogeneity problem entirely (94). Furthermore, compared with fixed effect models, random effects models can compute with smaller standard errors, as random effect models also use information of between-group variation (95). As a multilevel model, a random intercept and random slope model at two levels were created. As a dependent variable, a dichotomous variable on lifetime drug use was used. For the independent variables, demographic variables—age, sex, and household poverty—and the log of per capita income, three neighborhood variables (neighborhood average income, neighborhood poverty variance, neighborhood drug use), the Gini index, the parental smoking variable, and the early onset of smoking indicator were included in the model. This model is based on the assumption that country-level factors cause a different probability of drug use when one unit is changed. A two-level model was created for all participants.

Next, a three-level model with both country and neighborhood random slope was created. In this model, it is assumed that not only country factors but also neighborhood characteristics have a variety of magnitude of effects across neighborhoods. To compare the effects of average income and income inequality, only the neighborhood average income and neighborhood poverty variance were modeled as a random slope. All the variances were set as equal, and all covariances were zero in the random effect parts. In these analyses, the missing values were not imputed, and list-wise deletion was applied.

Through the model for the study investigating lifetime drug use probability, age and household poverty were modeled as continuous variables. The variable for parental smoking status was aggregated to the continuous variable, taking 0 if neither parent smoked and 2 if both parents smoked.

For the statistical packages, Stata 12, 13, and 15 were used. For mapping country prevalence of lifetime drug use, shown in Figure 4, Geoda was used.

4. Results

4.1. Prevalence

Table 3 shows sample characteristics of the dataset used for this study. The survey was completed by 151,196 participants in 45 countries. The total proportion of pupils who had ever used drugs was 0.79%, and pupils' mean age was 14.19 years old. Sex was almost equally distributed; female pupils comprised 52.3% of the sample.

The Gini index values for all countries are graphed in Figure 2. Countries are arranged in order of per capita income, listed from poor to wealthy from left to right. Country-specific lifetime drug use prevalence was plotted against the Gini index. The linear fitted line and distribution of the plots show that higher income inequality was associated with a higher prevalence of drug use in these countries.

Figure 3 shows the box plot of the Gini index for each country, with significant variations in income inequality values. Here, countries are also arranged in order of per capita income, listed from poor to wealthy from left to right. Similarly, Figure 4 presents the lifetime drug use prevalence of each country, calculated based on the dataset and mapped. Again, prevalence varied widely across the sample countries. Darker colors represent higher prevalence of drug use. Because of the presence of many small island countries in the West

Pacific and the Caribbean, the number of countries that can be observed from the map is smaller than the actual number of countries.

4.2. Results from a simple regression

The results for scatter plots with fitted bivariate regression of lifetime drug use on the Gini index are shown in Figure 5. The results of regression of lifetime drug use probability with the Gini index in single level regression model, three-level regression model with random intercept for country and neighborhood, three-level regression model with random slope for country effects and random intercept for country and neighborhood, are shown in Table 4 at Model 1, 2, and 3, respectively. The results from Model 1 in Table 4 show that all three variables are independently and significantly associated. The Gini index, GNI, and household poverty are 0.036 ($p < 0.001$), –0.153 ($p < 0.001$), and 0.318 ($p < 0.001$). The positive slope for the Gini index and household poverty suggests that higher income inequality and lower household income are positively associated with probability of drug use. From the results of Model 2, the effect of the Gini index can be observed after adjusting for random intercept for both country and neighborhood. *P* values rise to 0.035, but income inequality remains significant.

The coefficient for the Gini index also does not change a great deal, increasing by only 0.003 from Model 1 to Model 2, while per capita income is no longer significant. After adding random slopes for both income inequality and per capita income in Model 3, assuming both the Gini index and GNI (1) affected adolescent drug use differently in each country, (2) random slopes for them were significant, and (3) fixed effect for them were not significant.

Based on the results of the preliminary analysis, a possible independent association between the Gini index and lifetime drug use was observed. This gave some plausibility to studying the relationship between these two factors. The following analyses were carried out by adjusting for all individual, neighborhood, and country-level characteristics.

4.3. Results from the multi-level model

Table 5 reports the result of a series of regression results in a hierarchical regression model. Models were based on the assumption that all factors affected adolescent drug use in the same way across the countries and that there would be no difference between the countries when all variables had been set to the same value.

In addition, the following was observed from the effects of adding each variable in this table: In Model 2, higher neighborhood average income, higher neighborhood poverty variance, and higher drug use in the neighborhood were all significantly related to higher probability of drug use. In Model 3, the log of per capita income was positive ($\beta = 0.035$, $p < 0.001$), suggesting living in wealthier country increases the possibility of drug use. In Model 4, adding the Gini index decreased the coefficient of per capita income, suggesting a positive relationship between income inequality and the Gini index.

In Model 5, after adding the parental smoking variable, the probability of using drugs attributable to the Gini index increased, which may indicate that parental smoking may decrease the probability of lifetime drug use, unlike the hypothesized model. The *p* value indicates that parental smoking is significantly associated with lifetime drug use. Similarly, the incremental probability of drug use at country level when the Gini index increased a single unit decreased when adding adolescent early smoking initiation before age 13 in Model 6. In Model 6, all variables except per capita income were significant to drug use probability.

Table 6 shows the results of the two-level random slopes, random intercept model for country-level factors, analyzed for all samples. None of the country-level fixed effects were significant (for the Gini index, coefficient = 0.005, $p = 0.554$; for per capita income, coefficient = 0.133, $p = 0.065$). In addition, random effects for both the Gini index and per capita income were insignificant.

Table 7 shows the results of the three-level random intercept with both country- and neighborhood-level random slopes. Here, only the random slopes of the country intercept (estimated *SE* = 0.264, 95% CI [0.17, 0.42]) and the neighborhood average income were significant (estimated *SE* = 0.013, 95% CI [0.010, 0.017]). The fixed effect of neither the Gini index nor GNI were significant.

5. Discussion

5.1. Summary of findings

This study examined whether income inequality is positively associated with the probability of adolescent drug use. The analysis showed significant results only on the single level. In the random slope and random intercept model, the effect of the Gini index on adolescent drug use was not significant after adjusting for individual and environmental variables.

5.2. Discussion of Hypothesis 1

According to the first hypothesis, higher income inequality increases lifetime drug use in a country. As shown in Table 5, the Gini index significantly and positively correlates with adolescent drug use probability ($\beta = 0.005$, $p < 0.001$). In the next series of models, after adjusting for all individual-level factors, the Gini index value is positively associated with probability of drug use. For the random intercept models and random slope models, the Gini index values are not significant.

In Le's study, in contrast, the hazard ratio of income Gini on participants having consumed 12 drinks during the past 12 months was equal to or larger than 1.00, although it was not significant (69). The positive association between the Gini index and substance use behavior seems plausible. For the random intercept model, previous studies have found that the hazard ratio of income Gini on the fixed effect part was significantly larger than 1.0, regardless of gender (70). While our results in the random intercept models also showed the Gini index slightly larger than 0 which is equivalent with hazard ratio larger than 1, the researcher cannot determine the hazardous effect of the Gini index, as the Gini index were not significant.

For the multilevel models, if the variance of the Gini index in level two, after adjusting for other variables, was large enough, then a clearer relationship between income inequality and lifetime drug use could be expected. In this study, the effect of the Gini index on lifetime drug use in a multi-level model, shown in Tables 6 and 7, is not significant, possibly because of the limited variance for the Gini index. As the Gini index is not significantly associated in the random intercept and random slope model (although this is significant in Table 5), it might be interpreted that the Gini index is not associated with drug use.

In Li's study, even in the random-intercept model, Gini was significantly associated with tobacco use among teenage participants in 63 low- and middle-income countries (70). Our results, however, are not consistent with Li's study. The discrepancy in the results may be caused by the difference in the kind of drugs focused on in the two studies. While Li's study targeted only tobacco use, this study included all drugs, from cannabis to amphetamines. Given that the coefficient of Gini is small, at 1 in 10 compared with GNI, which is another macro-level factor, the absolute effect of Gini on adolescent drug use is relatively small. As smoking is legal and the prevalence of tobacco is high, Li's study was able to significantly capture the small increase in the number of adolescents using tobacco, attributable to increased income inequality, which our study could not.

An additional interpretation of the results might point to further complex, unobservable factors that may confuse the relationship between the Gini index and lifetime drug use. Although the results were inconsistent throughout the model, overall there seemed to be a positive and significant relationship between the Gini index and lifetime drug use probability. For those models that did not show significance in this study, ideally more studies should be carried out using numbers or samples from a greater variety of origins, and including more details about the site and country (median income, population, norms, etc.). Moreover, Table 7 shows a non-significant value for the neighborhood characteristics random slope, but this might be due to the attempt to share the limited numbers of variances with too many random slopes with many levels. For a better assessment with neighborhood characteristics, more models should be created, and each variable's coefficient and variance component changes should be compared between models.

For the effect of country-level income inequality on drug use, which was not significant, several factors can be considered. First, several fast-growing countries have been reported to have sharply dropped the relative-to-income price of drugs, as their economies have matured in a short time and people's purchasing power has also increased (63). In these countries, as the price of drugs decreases and drugs become more affordable, the number of people using drugs may also increase, especially among low-income people and adolescents. Second, the effect of incremental neighborhood-level factors on drug use probability was stronger than country-level factors, unlike in previous studies conducted in the United States (96). This might suggest that the effect of the neighborhood on individual health is stronger in low- and middle-income countries than in developed countries. The reason and factors are unclear, but one possibility is the social cohesion at neighborhood level might differ between developed countries and low- and middle-income countries.

5.3. Discussion of Hypothesis 2

The second hypothesis was that early onset of smoking and parental smoking have a mediating effect on the relationship between the Gini index and substance use prevalence. The early onset of smoking was expected to show a positive correlation with lifetime drug use, as well as with parental smoking and the Gini index. After adding early onset of smoking to the model in Table 5, the coefficient for the Gini index decreased from 0.011 to 0.005, suggesting that part of the association between the Gini index and lifetime drug use is explained by early onset of smoking. This is consistent with our hypothesis. This positive association was shown again in Model 6 in Table 5, which is likewise consistent with our hypothesis. The hypothesis was also supported, as discussed above, by the decrease in the parental smoking coefficient from Model 5 to Model 6, and the decrease in the Gini index coefficient from Model 5 to Model 6. Moreover, the early onset of smoking value consistently remained positive throughout the rest of the analyses, which could indicate that similar mediation effects could be seen in the rest of the analyses, consistent with the hypothesis.

In contrast, the random slopes for both the Gini index and GNI per capita were not significant. Although a random slope model was not constructed in previous studies, the fixed part of the random slope in the random intercept model was fairly robust. In this sense, the results are comparable to the Gini coefficients in a random intercept model created by Li, who studied adolescent smoking behavior in 61 developing countries and reported a weak but significant odds ratio for female pupils (for both sexes, *OR* for Gini = 1.05, 95% CI [1.03, 1.07]; (70). The logged value for 1.05 produced 0.04, which was interpreted as converged coefficients, suggesting that the magnitude of estimation of Gini, after adjusting for covariates, was plausible.

From these factors, it could be possible to assume a mediation effect for parental smoking on the relationship between income inequality and lifetime drug use, as is shown in Table 5 in Model 5 to 6. However, as the relationship between the Gini index and drug use was not shown in previous analyses, the mediation effect of the Gini index was not clear in this study.

5.4. Strengths

This study is the first to examine country-level income inequality and drug use among adolescents in more than 40 low- and middle-income countries. In addition, this is the first study to evaluate the effects of income inequality on drug use by using a random slope model and assessing the effect of income inequality. Furthermore, in this study, throughout the several models, the Gini index appeared significant only in Table 5, where the Gini index was regressed in a single-level Poisson model. The significant Gini index effect, shown in the multilevel and stratified models, was consistent with the results from one of the previous studies (68).

5.5. Limitations

5.5.1. Omitting variable problem

Country-, culture-, and region-specific factors

One of the fatal problems of this study is that country-level, community-level, and individual-level unobservable factors for drug use were not considered. At a country level (or at a state or province level), one confounding factor would be laws and other regulations, which vary from country to country. For example, in Malaysia, possessing five grams or more of cocaine is punishable by death in terms of the Dangerous Drugs Act of 1952 (97). On the other hand, Guatemala recently proposed legalizing the production of marijuana and poppies for medical use due to the heavy burden of maintaining jails (98). These differences in regulation may affect drug accessibility. For example, in Le's study, a beer tax of higher than 1.9% correlated significantly and protectively with reduced female symptoms of alcohol dependence (*OR* = 0.72; 95% CI [0.54, 0.96]), and more than 3.35 cent per drink was protective for both males and females (for males, *OR* = 0.72; 95% CI [0.58, 0.89]; for females, OR = 0.61; 95% CI [0.47, 0.79]; (69). In addition, decriminalization of drugs in Portugal in 2001 increased the prevalence of drug use among 6th, 8th, and 10th grade pupils (99). However, another study questioned the effectiveness of legal regulation (100). In this study, as the data include countries where the common language is not English, a limitation existed in that the researcher could not include information on regulation in each sample country.

At the community level, the extent of discrimination against drug use is one of the community-level unobservable characteristics. Other social and cultural norms may also suppress drug use probability in some areas. For example, in Henderson's study, restrictive drinking norms and education specific to restrictive drinking norms were associated protectively with alcohol use (66). Nandi also observed that there was an association between police activity within an area and a decrease in accidental overdose deaths in New York City (73). Moreover, among individual personality characteristics, sensation seeking is another strong predictor that could not be captured in this survey (101, 102).

For a future study, the researcher would like to highlight several points about the differences in drug types. While cocaine, crack and amphetamines are typically bought through dealers or obtained at shops, marijuana, opium, betel nuts and other “natural” drugs can sometimes be obtained in nature or in cultivated fields. This can lead to significant differences in accessibility and extent of surveillance of adults. “Natural” drugs are not only easier to access in some cases but also tend to be the most commonly used and the most culturally accepted drugs. For example, in Iran, some people openly admit to using opium because it is perceived as culturally acceptable (103). In these situations, although residents may control the scenarios in which the drug is used, the drug itself is easy to obtain. Therefore, the chances of children using the drug may be greater than for those drugs that are not customarily used on certain occasions. Additionally, due to these specific and local problems, further studies are needed to obtain more precise information about the sampling sites and their local traditions and circumstances.

To overcome these problems, the researcher aggregated the respondents' answers by school(s), and attempted to adjust for school- and community-level norms and availability of drugs. However, because this is based on the respondents' self-reporting, it may affect the accuracy of the portrayal of school-level prevalence of drug use and community-level drug availability. It is possible that the pupils of particular schools did not align with the average SES in the neighborhood, or that the classrooms within each school chosen to participate had profiles that differ from the average characteristics of the school. However, the aggregations of the data and estimation fairly reflect the current situation perceived by respondent pupils.

5.5.2. Lack of severity measures

This dataset could capture only the status of the issue at one point in time, and only among respondents of up to 16 years of age (some respondents may have been older than 16, but most were teenagers). Adolescence is a life stage characterized by the exploration of deviant activities. Therefore, even if some pupils have used drugs, they may not continue to do so, and they may not develop drug abuse or dependence symptoms. Indeed, the researcher has observed that in developed countries, pupils in junior and senior high school often try marijuana or inhalants a few times but remain "clean" afterward, not using any drugs. Consequently, they have no problems associated with using drugs in their thirties or forties, or later in their lives. Nevertheless, as being associated with drugs at least once may dramatically increase the probability of heavy or continuous drug use, or of restarting the use of illicit drugs in later life, the researcher attempted to use this measure to estimate the magnitude of the problem associated with drug use during the adolescent period.

5.5.3. Selection bias

The characteristics of the sample also is problematic. GSHS surveys are conducted in secondary school classrooms; thus, those who have dropped out or who do not attend school are not included. However, these adolescents might be living in more poverty or have problems at home, which might be risk factors of drug use (104).

5.6. Conclusion

This study hypothesized the increased probability of drug use with higher income inequality, and the mediation effect of the Gini index and parental and adolescent smoking. From the result of the multilevel model, the effect of higher income inequality on increasing probability of drug use was not observed. Therefore, the main effect was not observed, and the second hypothesis was not supported.

This study focused on data related to higher neighborhood-level income inequality rather than country-level income inequality in low-and middle-income countries, which may imply unobserved factors at neighborhood-level that are peculiar to low- and middle-income countries, such as stronger effects of social capital than in developed countries. Further studies are desired to investigate neighborhood-level factors to estimate more accurate effects of country-level income inequality.

Study 2: Does higher income inequality drive adolescents to use drugs earlier?

1. Introduction

1.1. Epidemiology, importance, and mechanisms of severe morbidity of early initiation of drug use

Age at first use of illicit drugs may vary. In Europe, most people who have ever used drugs tried them after the age of 11 or 12 (19). Early initiation of drug use has a serious effect both on adolescent mortality and morbidity, and on adolescents' families and work achievements. In a study focused on young adults and adolescents, early initiation of drug use was reported to be related to motor vehicle accidents and injuries; less frequent use of condoms, leading to unplanned pregnancy; and low employment retention rate (17). Early initiation of cannabis use was also reported as relating to the early onset of psychosis symptoms (105).

1.2. Factors associated with early onset of drug use

Several studies have examined the link between stress and earlier use of psychoactive substances (106), and research has suggested several factors related to the early onset of drug or substance use. In a study examining the relationship between drinking for the first time at or before age 14 and unhealthy alcohol use behaviors, researchers controlled for parental and peer alcohol use, as well as parental attitudes toward drinking (107). In a study using NHANES data on early onset smoking behaviors in users with drug use progression and other risky health behaviors, the early onset of regular smoking was significantly associated with illicit drug use (108). Furthermore, a longitudinal survey study focused on the cannabis use initiation process among high school pupils found that social anxiety ($\beta = -0.3405$, $p = 0.0336$), alcohol use ($\beta = 0.5821$, $p < 0.0001$), perceived peer use ($\beta = 0.25$, $p = 0.0198$), and depression ($\beta = -0.3601$, $p = 0.0125$) were all significant in the logistics analysis (109). A study of from 9 to 13-year-old adolescents also found that restless sleep experiences significantly predicted onset age for alcohol or cannabis use (110).

Moreover, in a study using longitudinal birth cohort data, conducted in Christchurch, New Zealand, the relationship between early cannabis use and tobacco use was examined. A frequency of tobacco consumption of more than 10 times per day showed a high proportion of co-existence with cannabis use among 18-year-old participants, with 25.4% of non-smokers reporting cannabis use, and 81.4% of all self-reported cannabis users being smokers; 60.1% smoked fewer than 10 cigarettes a day (111). In addition, according to a study of demographic factors for early onset of cannabis use, subjects' level of education (equal to or less than high school completion), income (less than $30,000), and history of using drugs were all statistically significantly different from the control group.

Other factors have also been pointed out, such as maturity or heritable influences (112). Adolescents with earlier pubertal periods were likewise observed to associate with substances at an earlier age. Furthermore, country-specific factors may contribute to variations in first age of drug use. In Lawrinson's study targeting eight countries, the mean first age of opiate use in Chinese participants (M_{age} = 27.2, SD = 6.8) was apparently later than in other countries such as Iran (M_{age} = 19.8, SD = 5.0) and Poland (M_{age} = 18, SD = 3.5; 113).

2. Hypothesis of Study 2

2.1. Research gap

Per the previous studies, the timing of first use of drugs is accelerated by factors such as having experienced an unpleasant life event, the timing or amount of intake of a substance such as tobacco or alcohol, social anxiety, and lower household income. As psychological distress, alcohol use, and tobacco use are often caused by income inequality, the accelerated onset timing of illicit drug use may be caused by higher income inequality. Nevertheless, overall few studies have been conducted on income inequality and onset age of any kind of drug use, especially in low- and middle-income countries, possibly due to a relatively low prevalence of adolescent drug use and/or a poor awareness of the issue in these countries or areas. Thus, there is a need to study the links between income inequality and onset timing for drug use.

2.2. Research question

The purpose of this study was to assess the relationship between the age of onset of drug use and the Gini index of the adolescent's country. To my knowledge, no other study has determined the effect of income inequality on adolescent age at initial drug use by using a population representative dataset from low- and middle-income countries. In this study, the question whether living in countries with higher income inequality is associated with earlier onset age of drug use was examined.

2.3. Research hypothesis

From the question above, the following hypothesis was formulated:

The hazard ratio of onset of drug use for higher income inequality country groups is higher than that for lower income inequality country groups.

3. Methods

3.1. Data preparation

To retrospectively observe the drug use onset of adolescents, data from the GSHS dataset (90) used in Study 1 were used again, but for this study, the researcher used the updated versions of the questionnaire released in 2009. While the previous questionnaire requested that respondents report the total number of times they used any kinds of drugs, the new questionnaire requested that respondents report their ages at first use of drugs, according to age category. Based on these answers, the onset age of drug use was converted into continuous age and combined with the data of pupils who had not used drugs yet, using age as a unit of time.

3.2. Models and estimation for Study 2

A continuous-time and a discrete-time model were used in this study.

Continuous-time model

First, the proportional-hazard (PH) assumption was checked, which focused on the stable relationship between risks and exposure during the whole observation time. Subsequently, each independent or covariate variable was regressed using the Cox proportional-hazard regression model, weighted with a sampling weight per the sample size of each country. The model was weighted simply to reduce the inflation of hazard ratio for specific factors. It was not weighted for the random intercept model and shared frailty model, as it was technically unavailable. In addition, because the early onset of smoking, neighborhood average income, neighborhood poverty variance, neighborhood drug use prevalence, Gini index, and per capita income varied in relation to the increment in age variable, an adjusted Cox proportional-hazard model was created as a confirmation (as shown in Appendix1a and 1b).

As the structure of the data nested in country was not considered in a single-level Cox model, two additional models adjusting for country were created. The first was a shared frailty model, which adjusts for elements that share the same characteristics. In this model, the data relating to pupils within the same country were adjusted. The second model was a two-level random intercept Cox proportional-hazard model, where the hazard ratio for the Gini index was checked.

Discrete-time model

As the survey requested the onset age of drug use by age group category, the data could only distinguish that the pupils began using drugs during a certain age period rather than at an exact age. Therefore, the survival time in this dataset might be sufficient to treat as discrete time rather than as a continuous time span. For this reason, a discrete-time model was also considered. The answer to the onset age of drug use was categorized so that both the answer to "age" and the answer to “onset age” fit in the same category. The hazard ratio for the Gini index to lifetime drug use was assessed by log-log model with random effects by country.

In the above analyses, the missing values were not imputed, and listwise deletion was applied. For the statistical packages, Stata 12, 13, and 15 were used.

4. Results

4.1. Sample characteristics

The sample characteristics are shown in Table 9. After excluding missing variables by listwise deletion, 75,591 samples remained. Out of the sample, 5,854 (7.74% of the sample) pupils had ever used any kind of drugs. The mean age of adolescents at survey was 14.4 years, while the mean onset age of drug use among pupils who had ever used drugs in their lifetime was 10.56 years. Per capita income was slightly higher than in the Study 1 sample, but other variables on sex, age, household poverty, parental smoking status, neighborhood characteristics and the Gini index were largely similar.

4.2. Cox proportional-hazard model and proportional-hazard assumption test results

The value of rho showed coefficients of the fitted slopes of scaled Schoenfeld residuals for each covariate against rank of failure time (114-116). The positive value for the slope means that the residuals increased as time (t) increased, and vice versa for the negative slope. The chi-squared test results for rho indicated whether the slope was zero or not. As the proportional-hazards test shows, the assumption was made that the variance should be homogeneous across risk sets; *p* value smaller than 0.05 implies that the proportional-hazard assumption is violated for the covariates (114).

Among the nine variables tested for the PH assumption, tabulated in Table 10, four variables (neighborhood average income, neighborhood poverty variance, Gini index, and log of per capita income) show a p value smaller than 0.05, which means that those variables violate the PH assumption. However, as the dataset was cross-sectional survey data, all these variables were measured only at one time point. Thus, the result of the test was ignored in the study.

For the purposes of a robustness check, the proportional-hazard regression was also regressed, splitting each point for a different relationship within Gini quartiles, for each of the four variables. The results are shown in Appendix 1b. The data in Appendix 1a were adjusted only for early onset of smoking, which the researcher thought to be a logically plausible time-varying factor. The results of the analysis of the data in Appendix 1a show that the inflation of the variable was not adjusted in 1a; it was fully adjusted in 1b after including all four variables.

Table 11 shows the results of the single-level Cox proportional-hazard regression. In terms of the Gini index, significantly higher hazard ratios were observed among adolescents living in more unequal countries (HR = 0.976, $p < 0.001$). For per capita income, living in countries with lower GNI showed a comparable hazard effect (HR = 0.896, $p < 0.001$).

4.3. Result of the models, adjusting for country effect

Tables 12 and 13 show the results of the models, considering the effect of being in the same country. Table 12 shows the results of the shared frailty model, while Table 13 shows the results of the Cox proportional-hazard model with country random intercept. The protective effect of Gini toward drug use remains after adjusting for country-level random intercept.

4.4. Discrete-time analysis

Table 14 shows the results of the discrete time analysis in the random effect log-log model. Adolescents from more unequal countries showed a significant hazard ratio. Compared with the continuous-time model, the log likelihood value from the previous model presented a considerable decrease, which might suggest a better model fit in the discrete-time model.

5. Discussion

5.1. Summary of findings

This study examined the relationship between higher country-level income inequality and adolescents' onset age of drug use. The researcher hypothesized that higher income inequality accelerates the first use of drugs in single- and multilevel models. Results from the single-level regression in Table 11 show that higher income inequality was associated with a later onset of drug use. This protective relationship did not change in the multilevel model, which is a shared frailty model or random intercept model. Age and variable for age at first use were modeled as serial time in the first models, then recategorized to determine the effect of the Gini index in the random intercept log-log model, but the tendency for income inequality remained unchanged.

5.2. Discussion of hypothesis

The results of the study show that the hypothesis was not supported. From the results in Table 11, where single-level Cox regression was performed, the hazard ratio for higher income inequality was significantly lower, indicating that the findings are contrary to the hypothesis. However, the positive coefficient for the Gini index was not significant under the different assumption about data structure in Tables 12 and 13, possibly due to the countries comprising

Southeast Asian countries and China, where the Gini index was relatively higher and the extent of drug use was limited. According to the World Drug Report, in 2014, one of the major drugs used in Southeast Asia and China was amphetamines (20). Along with amphetamines and other hard drugs, intravenous drug use is common in Eastern Europe as well. Compared to other drugs and substances such as cannabis and inhalants, age at first use of amphetamines tends to be higher. The results in Tables 12 and 13 reflect the differences across these countries and cultures and are therefore not significant, while the prior results are significant. However, the protective relationship was largely accounted for by the coexistence of higher mean GNI in higher income inequality countries. As there were no studies focusing on the relationship between the Gini index and substance use, it was impossible to compare the coefficient or the effect.

Based on the results, the incremental effect of the Gini index revealed the opposite: values were positive and significant toward the probability of using any kind of drugs at the next unit of time. Similarly, in all the models from Tables 11–13, the results were inconsistent. The tables, however, show inconsistent results regarding the effect of income inequality on age of first drug use. In Table 11, which lists results on the relationship between the Gini index and the hazard level for the onset of drug use with single-level Cox regression, the hazard ratio of the Gini index is smaller than 1, indicating living in unequal countries has a protective effect. On the other hand, in Table 12, where income inequality and age at first drug use was modeled in Cox regression, assuming shared vulnerability among countries, the hazard ratio of the Gini index was more than 1, which is the opposite of the result of Table 11. Likewise, comparing multilevel models, the Table 12 continuous time model and Table 13 count-time model, shows an inconsistent hazard ratio of the Gini index.

The inconsistency of the Gini index between models may be due to the small coefficients of the Gini index compared with other variables of the models such as GNI. Given that GNI holds large coefficients, as much as 10 times larger than those of the Gini index, it is possible that this caused a fluctuation of the Gini index's signs into the opposite direction from the true signs. The conflicts in Tables 11–13 may have arisen because by introducing the assumption of country-specific difference, expressed as "shared frailty" in Table 12, the effects of the characteristics of a country with a relatively large population would be stabilized, and therefore the hazard ratios in the most unequal countries were adjusted into larger ratios. Another possible reason might be the relatively weaker relationships between the Gini index and the prevalence of adolescent drug users compared with other determinants such as dispensable income, availability of drugs, and parental behaviors toward substance use, which showed significance throughout the models.

For statistical significance, only Table 11 was significant for all groups. Among these tables, the Gini index was significant for onset age of drug use in all country groups in Table 13. Moreover, through the tables, neighborhood poverty variance, drug use prevalence, and initiation of smoking in earlier age showed relatively higher coefficients than others. This may suggest earlier initiation of drug use is affected by neighborhood condition, as well as adolescents' experience, with possible influence from interventions at school- or neighborhood-level and prevention of early tobacco usage. Based on the discussions above, the hypothesis, which is that higher country-level income inequality accelerates first drug use, was not supported.

For the effect of the Gini index, which was not significant, it is possible that the conflict with the hypothesis derives from the composition of the countries, or from education at school. For example, in the United States, about $75.7 million was used for youth violence prevention activities, including campaigns related to alcohol and other drug abuse (117). However, low- and middle-income countries may not be able to disburse budget on preventive campaigns and education, and as a result, these preventive activities depend on schools or areas. Thus, in schools or countries where pupils did not receive any preventive education, one may observe accelerated onset of drug use in comparison to areas where preventative education was offered. Nevertheless, as there were no clear reasons that could be observed, nothing can be concluded as an actual factor.

5.3. Strengths

This study found a significant fixed effect of country-level income inequality on adolescent drug use, although the effect had disappeared in the random-effect model adjusted for various individual-specific fixed effects. Compared with country-specific environmental factors, which are the Gini index and per capita income, the neighborhood-level variables consisted of average income, income inequality, and drug prevalence, which were all significant variables at fixed effects and had larger absolute values of coefficient on adolescent drug use.

Compared with previous studies, this study succeeded in determining the effects of country-level economic factors on starting age of drug use. Furthermore, while other studies focused mostly on high-income countries, or within-country or city sites, this study showed results from low- and middle-income countries.

5.4. Limitations

Several factors remain unclear. First, the uneven distribution of the proportion of pupils who used drugs, or began using drugs, before age 7, where higher prevalence was observed among poorer countries, was not assessed in terms of its direct factors from this model. As a future study, information about participants' neighborhoods—such as population density, monetary mean income, and adult drug use prevalence—is necessary to adjust and stratify the models. Second, as some of my models could not converge due to having fewer units of time points, a study on data with finer time-point units would capture the hazard at each age increase more accurately.

Moreover, as this survey is based on retrospective self-administered questionnaires, recall bias should exist. This effect would be uneven among participants, as people using drugs are often reported having cognitive impairment (118). In addition, as discussed in the summary findings, this study found a much younger onset age of drug use compared with previous studies. As a future study, it would be useful to combine datasets of developing countries and developed countries, as well as the relationship between mean onset age and macro-level factors, while stratifying other demographic variables (such as gender and relative wealth quintile within the neighborhood and individual homes).

Lastly, for this study, information about the types of drugs used, presented in Study 1, was not collected. While some drugs, such as opium and marijuana, were often observed as being used for daily use purposes such us as pain killers, other types of drugs such as MDMA are used in a different context and by people with different characteristics. Therefore, groups started using marijuana at age of eight and another group started using MDMA at age of 15, for example, are considered different groups regarding the context of usage, but this study cannot distinguish the differences between them.

5.5. Conclusion

This study hypothesized that higher income inequality correlates with earlier onset of drug use. Based on the single-level and multi-level survival analysis with fluctuated hazard ratios, the hypothesis was not supported. This may have been caused by the compositional effect of different sources of drugs in different settings and the possible effect of differences of the extent of preventive education.

Nevertheless, this study makes a valuable contribution to the body of research on the topic, as it is one of the first to assess the effect of income inequality on onset of drug use in low- and middle-income countries. Among the predictors, neighborhood poverty variance, neighborhood drug prevalence, and early onset of smoking are some of the strongest, suggesting the need for intervention at neighborhood level, with emphasis on preventive education regarding drugs as well as smoking for children.

Conclusion

This thesis presented the results of a pooled cross-sectional analysis of a health survey targeting secondary school pupils, conducted in 45 low- and middle-income countries, and examined the relationship between country-level income inequality and the probability of adolescent drug use, considering possible pathways and age at first use of drugs.

The first study hypothesized that higher country-level income inequality is associated with adolescent lifetime drug use probability, and the relationship is mediated by parental smoking behavior and adolescent early initiation of smoking. Based on the results, there was no clear relationship between income inequality and adolescent drug use in a multilevel model. As the main effect was unclear, the mediation effect of parental and adolescent smoking was not confirmed. In Study 2, whether higher income inequality is associated with initiation of drug use at earlier age was tested. As effect of income inequality on age at first use of drug was inconsistent in a multilevel model, the effect was unclear, and therefore the hypothesis was not supported.

The conflict between the results and hypotheses possibly stemmed from the limitations of the data available. There are stronger variables relating to income inequality that also considerably increase adolescent stress levels, more strongly than income inequality or other country-level variables. Additionally, although income inequality showed a significant effect, the coefficient was tiny compared to other variables, such as neighborhood drug use prevalence and early onset of drug use.

When integrating the results from Studies 1 and 2, the hazardous effect of income inequality on adolescent drug remains unclear, which may have been caused by the mitigating effect of the attrition of adolescents who are not attending secondary schools.

However, this study showed a far stronger relationship between neighborhood factors and adolescent drug use than between country-level factors and adolescent drug use through the analysis of data from low-and middle-income countries. The stronger effect of neighborhood factors suggests not only differences in the structure but also in the extent of the effect of country-level policy, compared with high-income countries.

Conducting further research that includes additional variables regarding both individual history and environmental, cultural, and regional characteristics—together with these study results—may help clarify the pathways along which income inequality affects and interacts with substance use tendencies.

Acknowledgements

This research would not have been possible without the work of the WHO and CIDI GSHS survey team and all the researchers, teachers, and personnel involved in collecting the data in each country included in the dataset. Thank you for your efforts.

I further would like to thank several people for their support during the completion of this research: I am grateful to Andrew Stickley, who cheered me on and inspired me, shared his insights on child mental health, and taught me useful models that show children can be affected by their parents. I am also grateful for Ms. Takano, who often spent her precious time listening to my thoughts on my project and shared her insights, information on the latest research on illicit drugs, and her own work. Her comments were invaluable in making a breakthrough in the discussion of this paper. I also would like to thank Professors Kawakami and Diez-Roux, my supervisors, for their support and advice, particularly on statistical analysis.

Furthermore, I would like to thank the University of Tokyo for its generous 2014 Short Study Abroad Scholarships, which allowed me to partially fund this thesis project.

Finally, I would like to thank my family and friends for their support during my doctoral studies.

Table 1. Variable descriptions

Variables	Description
Lifetime drug use	Whether the respondents have used any sort of drugs in their lifetime
Onset age of drug use	Age at first drug use
Observation period	Total observation period, starting from 7 to either onset age of drug use for ever drug users, and age at answering survey for non-drug users
Age	Age at survey
Sex	Sex
Household poverty	Household poverty, substituted by frequency of feeling hunger
Young onset of smoking	Young onset of smoking younger than 13 year's old
Parental smoking	Number of parents/guardians who smoke
Neighborhood average income	A substitute for neighborhood income, calculated as mean income of respondents by each school
Neighborhood poverty variance	A substitute for neighborhood income inequality, calculated as the Gini index aggregated from Household poverty survey answers
Neighborhood drug use	Neighborhood drug use environment, calculated as prevalence of students' drug use by each school
The Gini index	Country's income inequality measurement, from official statistics such as World Bank, United Nations Development Programme (UNDP), and gray literature from governments, (Gini index × 100)
Log of per capita income	Country's per capita income, from official statistics such as World Bank, United Nations Development Programme (UNDP), and gray literature from governments

Table 2. Countries used in the study 1

(N= 151,196)

Country	Frequency	Percent
Algeria	3,922	2.59
Antigua Barbuda	1,162	0.77
Argentina	1,866	1.23
Barbados	1,532	1.01
Benin	2,521	1.67
Botswana	2,128	1.41
British Virgin	1,610	1.06
Cayman	1,242	0.82
Chile	7,076	4.68
China	8,753	5.79
Colombia	9,652	6.38
Cook Islands	1,195	0.79
Costa Rica	2,630	1.74
Ecuador	5,198	3.44
Grenada	1,425	0.94
Guyana	1,172	0.78
Indonesia	3,080	2.04
Iraq	1,841	1.22
Jamaica	1,505	1.00
Kenya	3,269	2.16
Kiribati	1,474	0.97
Kuwait	2,225	1.47
Macedonia	1,965	1.30
Malaysia	24,621	16.28
Mauritania	1,708	1.13
Mauritius	2,074	1.37
Morocco	2,549	1.69
Myanmar	2,778	1.84
Occupied Palestian Territory	12,802	8.47
Peru	2,769	1.83
Philippine	5,553	3.67
Saint Lucia	1,226	0.81
Saint Vincent	1,205	0.80
Samoa	1,689	1.12
Senegal	3,052	2.02
Seychelles	1,220	0.81
Solomon Islands	1,118	0.74
Suriname	1,631	1.08
Tanzania	2,042	1.35
Thailand	2,734	1.81
Tonga	1,976	1.31
Trinidad Tobago	2,735	1.81
Uganda	2,915	1.93
Uruguay	3,319	2.20
Vanuatu	1,037	0.69
Total	151,196	100

Table 3. Variables for study 1

Variable	Number	Frequency	Percentage	Mean	SD	Min	Max
Lifetime drug use	151,196	11,925	7.89%	0.079	0.27	0	1
Age	151,196			14.188	1.27	11	16
Sex (Female)	151,196	79,066	52.29%	1.523	0.499	1	2
Household poverty	151,196			1.817	1.037	1	5
Young onset of smoking	151,196	25,895	17.13%	0.171	0.377	0	1
Parental smoking	151,196			0.437	0.686	0	2
Either one of them is smoking	151,196	46,584	30.81%				
Both of parents are smoking	151,196	7,189	4.75%				
Neighborhood average poverty level	151,196			1.812	0.385	1	4
Neighborhood poverty variance	151,196			0.252	0.044	0	0.343
Neighborhood drug prevalence	151,196			0.076	0.083	0	1
The Gini index	151,196			44.945	7.231	23	65.8
Log of per capita income	151,196			8,983	11,815	790	88,170

(N = 151,196)

Table 4. Simple regression model

	Model1			Model2			Model3		
Fixed-effects Parameters	Coefficient	SE	P-value	Coefficient	SE	P-value	Coefficient	SE	P-value
Household poverty	0.318	0.007	<0.001	0.224	0.008	<0.001	0.018	0.001	<0.001
The Gini index	0.036	0.001	<0.001	0.039	0.019	0.035	0.003	0.002	0.091
Log of per capita income	-0.153	0.009	<0.001	0.046	0.135	0.733	-0.005	0.012	0.687
Constant	-3.308	0.085	<0.001	-5.053	1.386	<0.001	0.003	0.127	0.982
Random-effects Parameters				Estimate	SE	95 % CI	Estimate	SE	95 % CI
The Gini index random slope							0.0014	0.0018	0.0001 - 0.0181
Log of per capita income random slope							0.00000005	0.00000014	2.66×10^{-10} - 9.52×10^{-6}
Country intercept				1.015	0.105	0.83 - 1.24	0.07	0.08	0.007 - 0.616
Neighborhood intercept				0.696	0.02	0.66 - 0.74	0.059	0.001	0.056 - 0.062
Log likelihood	-57884.709			-50958.411			-21313.961		

Table 5. Single-level multiple variable regression result

	Model 1			Model 2			Model 3		
	Coefficient	SE	P-value	Coefficient	SE	P-value	Coefficient	SE	P-value
Age	0.171	0.006	<0.001	0.173	0.006	<0.001	0.174	0.006	<0.001
Sex (Female)	-0.499	0.016	<0.001	-0.484	0.016	<0.001	-0.486	0.016	<0.001
Household poverty	0.254	0.006	<0.001	0.163	0.007	<0.001	0.163	0.007	<0.001
Young onset of smoking									
Parental smoking									
Neighborhood average income				-0.367	0.018	<0.001	-0.33	0.021	<0.001
Neighborhood poverty variance				1.326	0.165	<0.001	1.246	0.167	<0.001
Neighborhood drug use				6.653	0.058	<0.001	6.629	0.058	<0.001
The Gini index									
Log of per capita income							0.035	0.009	<0.001
Constant	-5.168	0.091	<0.001	-4.986	0.102	<0.001	-5.353	0.138	<0.001
Log likelihood	-57518.273			-51671.37			-51663.552		

	Model 4			Model 5			Model 6		
	Coefficient	SE	P-value	Coefficient	SE	P-value	Coefficient	SE	P-value
Age	0.173	0.006	<0.001	0.218	0.007	<0.001	0.214	0.007	<0.001
Sex (Female)	-0.489	0.016	<0.001	-0.573	0.018	<0.001	-0.435	0.018	<0.001
Household poverty	0.162	0.007	<0.001	0.166	0.008	<0.001	0.148	0.008	<0.001
Young onset of smoking							1.219	0.018	<0.001
Parental smoking				0.282	0.011	<0.001	0.198	0.011	<0.001
Neighborhood average income	-0.297	0.021	<0.001	-0.393	0.024	<0.001	-0.3	0.025	<0.001
Neighborhood poverty variance	1.601	0.174	<0.001	1.909	0.199	<0.001	2.018	0.203	<0.001
Neighborhood drug use	6.543	0.059	<0.001	6.965	0.067	<0.001	6.34	0.072	<0.001
The Gini index	0.009	0.001	<0.001	0.011	0.001	<0.001	0.005	0.001	<0.001
Log of per capita income	0.029	0.009	0.002	0.02	0.011	0.081	-0.018	0.012	0.13
Constant	-5.848	0.153	<0.001	-6.508	0.176	<0.001	-6.512	0.183	<0.001
Log likelihood	-51636.066			-40777.297			-38588.249		

Table 6. 2-level random slope-, random intercept model (Country-level)

(N=151,196)

Fixed-effects Parameters	Coefficient	SE	P-value
Age	0.234	0.009	<0.001
Sex (Female)	-0.726	0.02	<0.001
Young onset of smoking	1.658	0.023	<0.001
Household poverty	0.202	0.01	<0.001
Parental smoking	0.431	0.015	<0.001
Neighborhood average income	-0.165	0.051	0.001
Neighborhood poverty variance	1.573	0.329	<0.001
Neighborhood drug prevalence	8.537	0.155	<0.001
The Gini index	0.005	0.009	0.554
Log of per capita income	0.133	0.072	0.065
Constant	-7.222	0.774	<0.001
Random-effects Parameters	**Estimate**	**SE**	**95 % CI**
The Gini index random slope	1.13×10^{-8}	0.0002	n.a.
Log of per capita income random slope	4.01×10^{-8}	0.001	n.a.
Country intercept	0.513	0.06	0.408 - 0.646
Log likelihood		-37530.613	

Table 7. Result of three-level random slope, random intercept model

(N=151,196)

Fixed-effects Parameters	Coefficien	SE	P-value
Age	0.198	0.008	<0.001
Sex (Female)	-0.588	0.018	<0.001
Household poverty	0.153	0.008	<0.001
Young onset of smoking	1.277	0.035	<0.001
Parental smoking	0.331	0.013	<0.001
Neighborhood average income	-0.03	0.059	0.616
Neighborhood poverty variance	1.808	0.376	<0.001
Neighborhood drug prevalence	6.586	0.179	<0.001
The Gini index	0.006	0.009	0.517
Log of per capita income	0.133	0.075	0.075
Constant	-7.254	0.791	<0.001
Random-effects Parameters	**Estimate**	**SE**	**95% CI**
The Gini index random slope	$1.76 \times 10^{-}$	$1.36 \times 10^{-}$	n.a.
Log of per capita income random slope	$1.54 \times 10^{-}$	$1.02 \times 10^{-}$	n.a.
Country intercept	0.264	0.062	0.17 - 0.42
Neighborhood average income random slope	0.013	0.002	0.010 - 0.017
Neighborhood poverty variance random slope	3.04×10^{-9}	0.00005	n.a.
Neighborhood intercept	$7.35 \times 10^{-}$	$5.59 \times 10^{-}$	n.a.
Log likelihood		-39465.824	

Table 8. Countries used in the study 2

(N=75,591)

Country	Frequency	Percent
Algeria	3,922	5.19
Antigua Barbuda	1,162	1.54
Barbados	1,532	2.03
Benin	2,521	3.34
British Virgin	1,610	2.13
Cook Islands	1,195	1.58
Costa Rica	2,630	3.48
Iraq	1,841	2.44
Jamaica	1,505	1.99
Kiribati	1,474	1.95
Kuwait	2,225	2.94
Malaysia	24,621	32.57
Mauritania	1,708	2.26
Mauritius	2,074	2.74
Morocco	2,549	3.37
Occupied Palestian Territory	12,802	16.94
Peru	2,769	3.66
Samoa	1,689	2.23
Solomon Islands	1,118	1.48
Suriname	1,631	2.16
Tonga	1,976	2.61
Vanuatu	1,037	1.37
Total	75,591	100

Table 9. Variables for study2

(N=75,591)

Variable	Number	Frequency	Percentage	Mean	SD	Min	Max
Lifetime drug use	75,591	5,854	7.74%			0	1
Onset age of drug use	5,854			10.563	3.085	7	16
Age	75,591			14.371	1.227	11	16
Sex (Female)	75,591	39,302	51.99%			1	2
Household poverty	75,591			1.917	1.078	1	5
Young onset of smoking	75,591	12,143	16.06%			0	1
Parental smoking	75,591					0	2
Either one of them is smoking	75,591	24,158	31.96%				
Both of parents are smoking	75,591	3,297	4.36%				
Neighborhood average income	75,591			1.915	0.354	1.122	3.341
Neighborhood poverty variance	75,591			0.264	0.038	0.099	0.343
Neighborhood drug prevalence	75,591			0.073	0.09	0	0.622
The Gini index	75,591			42.489	5.885	23	52.9
Log of per capita income	75,591			10,156	14,660	1430	88,170

Table 10. Proportional-Hazard assumption test for variables used in the analysis

(N=75,591)

	ϱ	χ^2	P-value
Sex (Female)	0.011	0.74	0.39
Household poverty	-0.008	0.39	0.531
Young onset of smoking	0.018	1.93	0.165
Parental smoking	-0.015	1.24	0.266
Neighborhood average income	-0.05	14.88	0.0001
Neighborhood poverty variance	-0.058	18.94	<0.001
Neighborhood drug prevalence	0.021	2.54	0.111
The Gini index	0.038	7.89	0.005
Log of per capita income	0.046	12.58	0.0004

Table 11. Result of single-level Cox proportional hazard regression

(N=75,591

	Hazard Ratio	95% CI	P-value
Sex (Female)	0.625	0.592 - 0.660	<0.001
Household poverty	1.167	1.141 - 1.195	<0.001
Young onset of smoke	3.906	3.702 - 4.120	<0.001
Parental smoking	1.209	1.173 - 1.245	<0.001
Neighborhood average income	0.546	0.501 - 0.595	<0.001
Neighborhood poverty variance	4.220	2.191 - 8.125	<0.001
Neighborhood drug prevalence	2705.707	2124.0 - 3446.7	<0.001
The Gini index	0.976	0.972 - 0.980	<0.001
Log of per capita income	0.896	0.868 - 0.926	<0.001
Log of pseudo likelihood		-59334.043	

Table 12. Result of single-level Cox proportional hazard regression with shared frailty for country

(n=75,591)

	Hazard Ratio	95% CI	P-value
Sex (Female)	0.593	0.562-0.626	<0.001
Household poverty	1.164	1.137-1.191	<0.001
Young onset of smoke	3.871	3.667-4.087	<0.001
Parental smoking	1.308	1.262-1.356	<0.001
Neighborhood average income	1.095	0.960-1.248	0.176
Neighborhood poverty variance	21.098	8.028-55.446	<0.001
Neighborhood drug use	125.421	83.831-187.646	<0.001
The Gini index	1.004	0.978-1.031	0.741
Log of per capita income	1.045	0.851-1.281	0.673
Frailty Parameter	Estimate	SE	95 % CI
θ	0.216	0.066	0.150-0.281
Log likelihood		-58964.537	

Table 13. Result from two level survival regression model with random intercept for country

(N=75,591)

Fixed-effect Parameters	Hazard Ratio	95% CI	P-value
Sex (Female)	0.634	0.585-0.687	<0.001
Household poverty	1.108	1.069-1.149	<0.001
Young onset of smoke	3.249	2.996-3.523	<0.001
Parental smoking	1.405	1.338-1.475	<0.001
Neighborhood average income	0.993	0.875-1.128	0.919
Neighborhood poverty variance	15.342	5.784-40.692	<0.001
Neighborhood drug prevalence	55.639	36.98-83.72	<0.001
The Gini index	0.981	0.976-0.987	<0.001
Log of per capita income	0.954	0.906-1.004	0.07
Constant	0.01	0.005-0.020	<0.001
Random-effect Parameters	**Estimate**	**95 % CI**	
Country intercept	3.839	3.412-4.320	
Log likelihood		-39281.513	

Table 14. Result from complementary log-log model with random effects for country

(N=75,591)

	Hazard Ratio	95% CI	P-value
Individual-level			
Age Interval			
≤11 years' old	(reference)		
12 - 13 years' old	0.033	0.030 - 0.036	<0.001
14 - 15 years' old	0.017	0.016 - 0.019	<0.001
16 years' old	0.025	0.023 - 0028	<0.001
Sex (Female)	0.575	0.537 - 0.615	<0.001
Household poverty	1.161	1.129 - 1.195	<0.001
Young onset of smoke	3.757	3.506 - 4.026	<0.001
Parental smoking	1.298	1.240 - 1.358	<0.001
Neighborhood average income	1.004	0.854 - 1.180	0.786
Neighborhood poverty variance	6.235	1.866 - 20.829	0.001
Neighborhood drug use	527.4	301.4 - 922.9	<0.001
The Gini index	1.029	0.999 - 1.061	0.057
Log of per capita income	1.063	0.851 - 1.327	0.592
Constant	0.095	0.007 - 1.270	0.075
Random-effects Parameters	Estimate	95 % CI	
ln (σ_v)	0.243	0.129 – 0.457	
σ_v	1.673	1.433 – 1.963	
ϱ	1.137	1.076 – 1.243	
Log likelihood		-9796.4807	

Figures

Figure 1. Chart of the articles screened

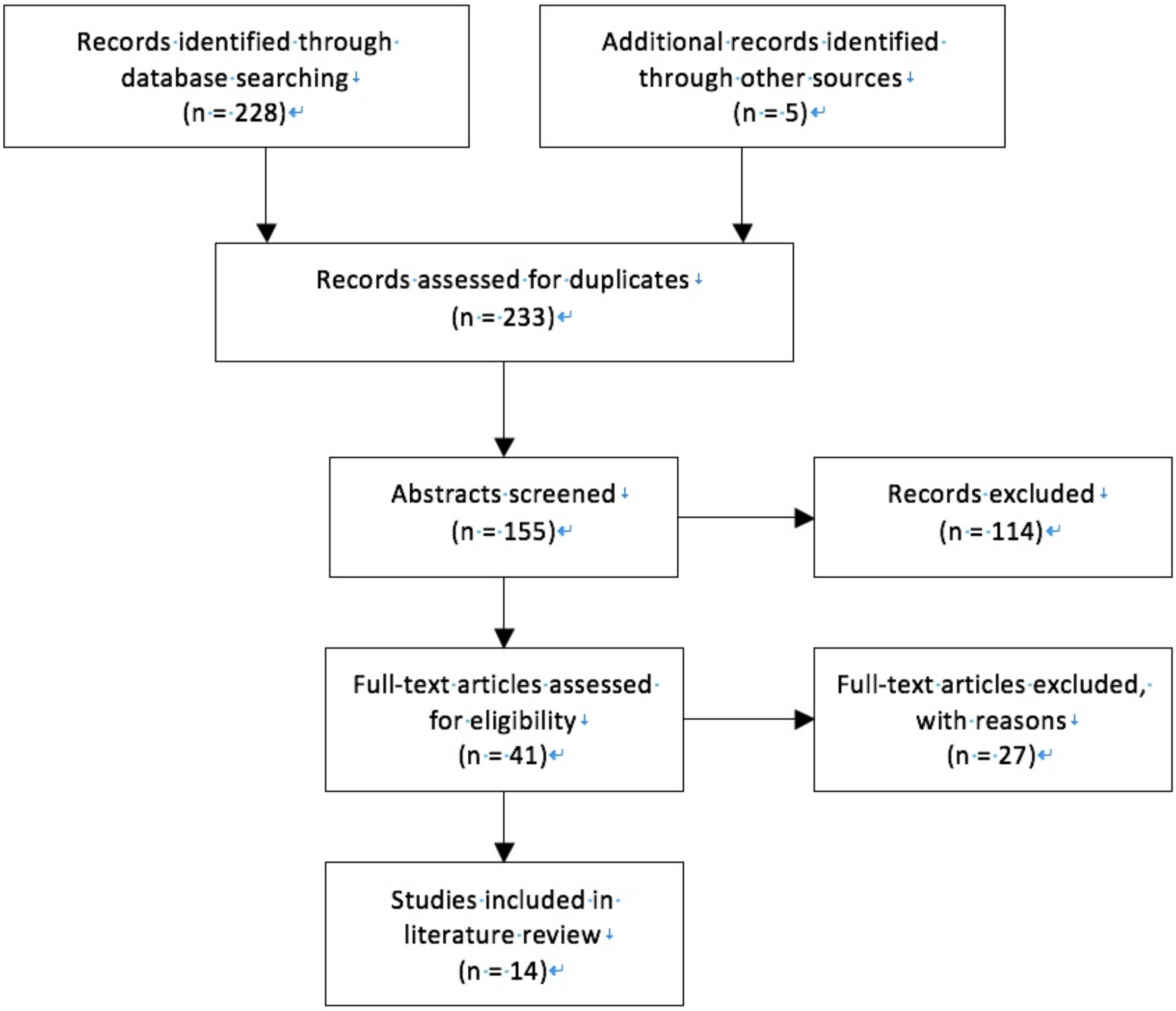


Figure 2. Box plot of the Gini index for all sample countries

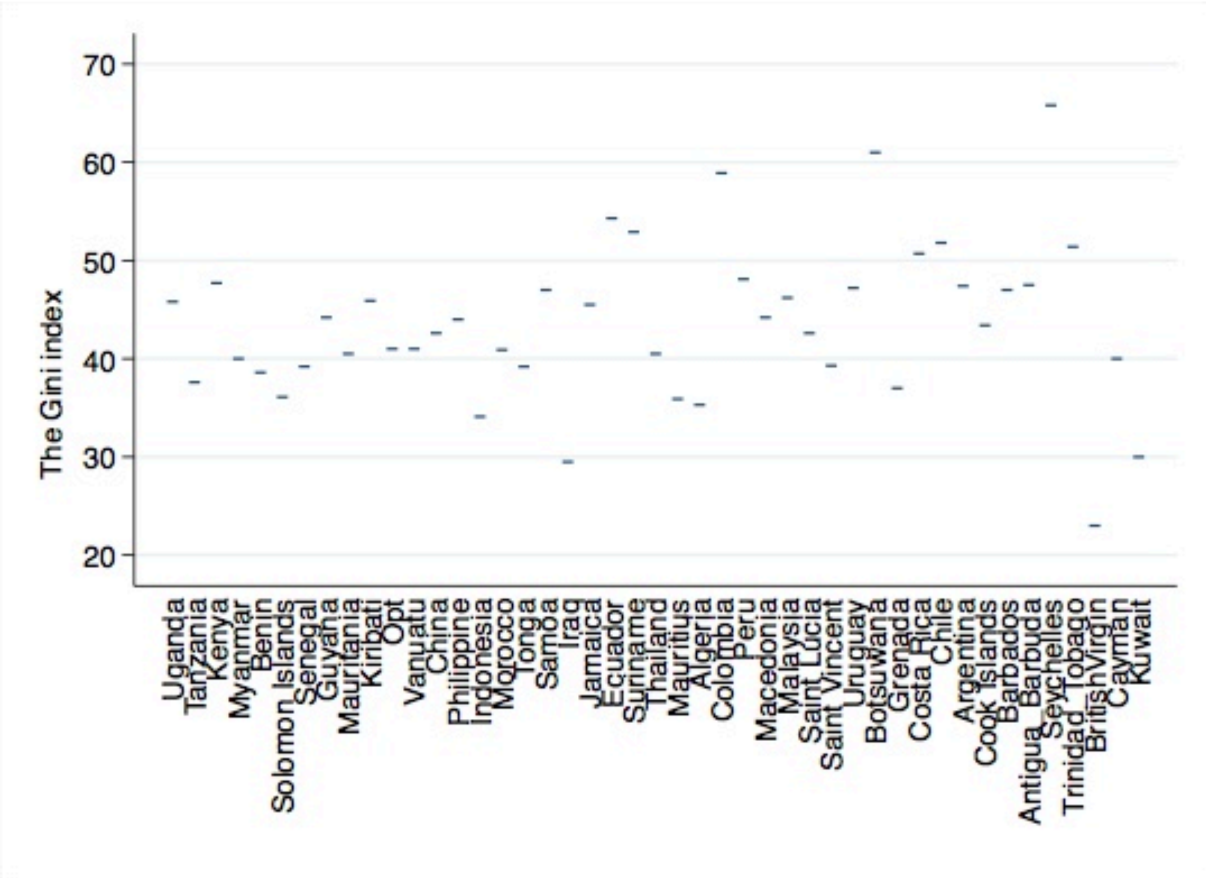


Figure 3. Box plot of lifetime drug use prevalence of all sample countries

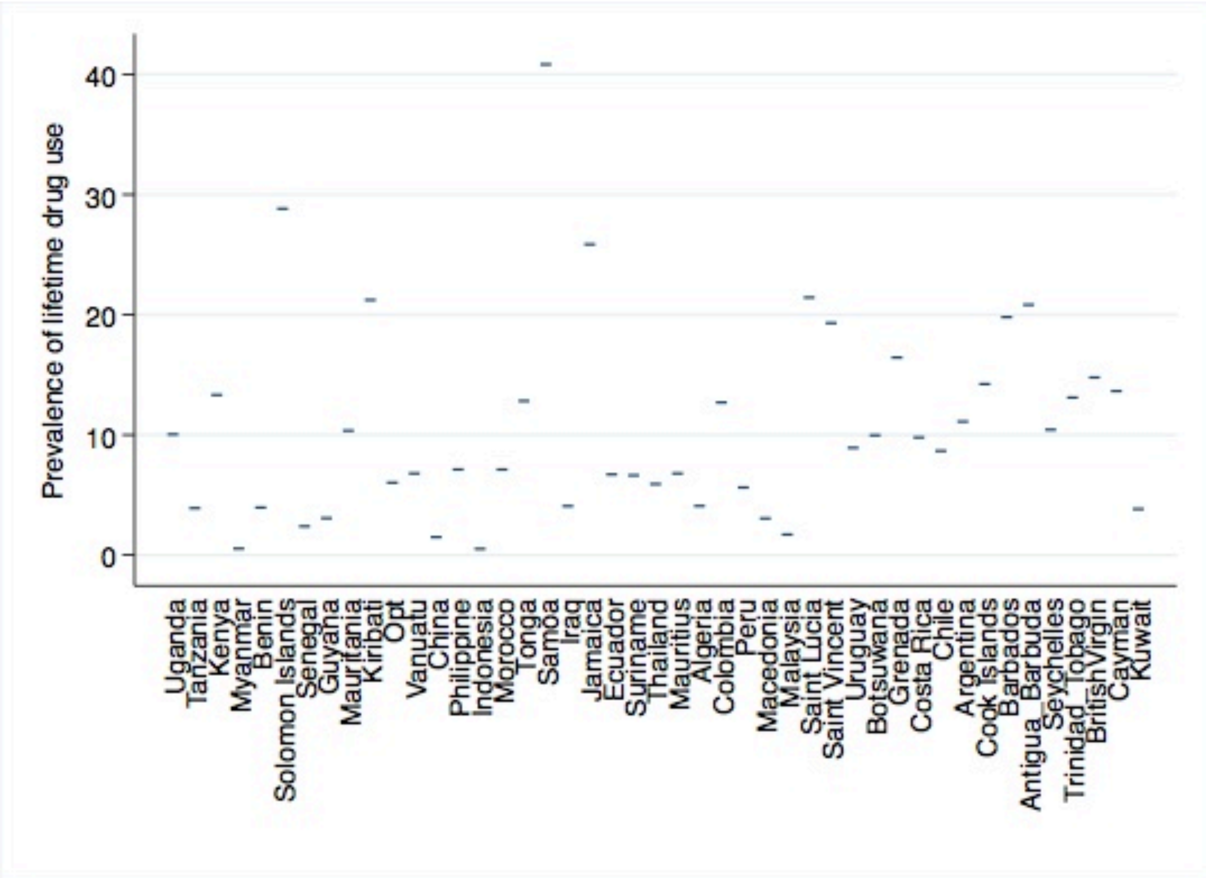
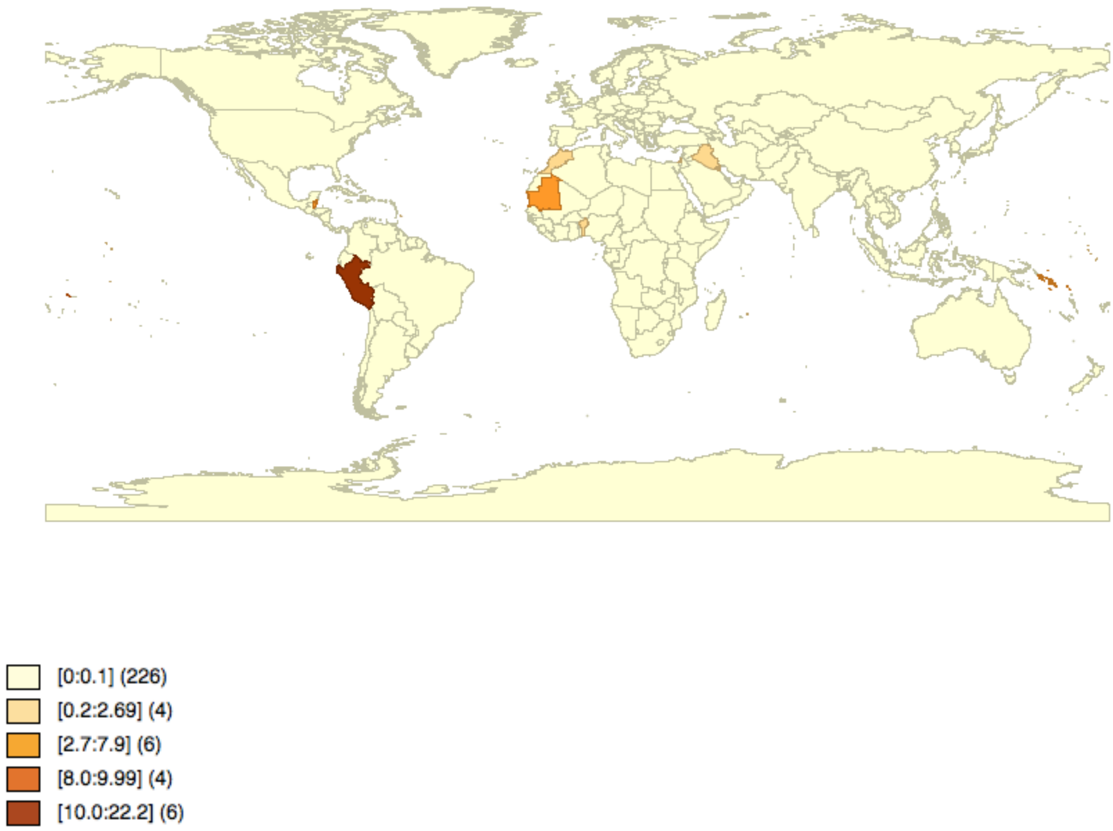
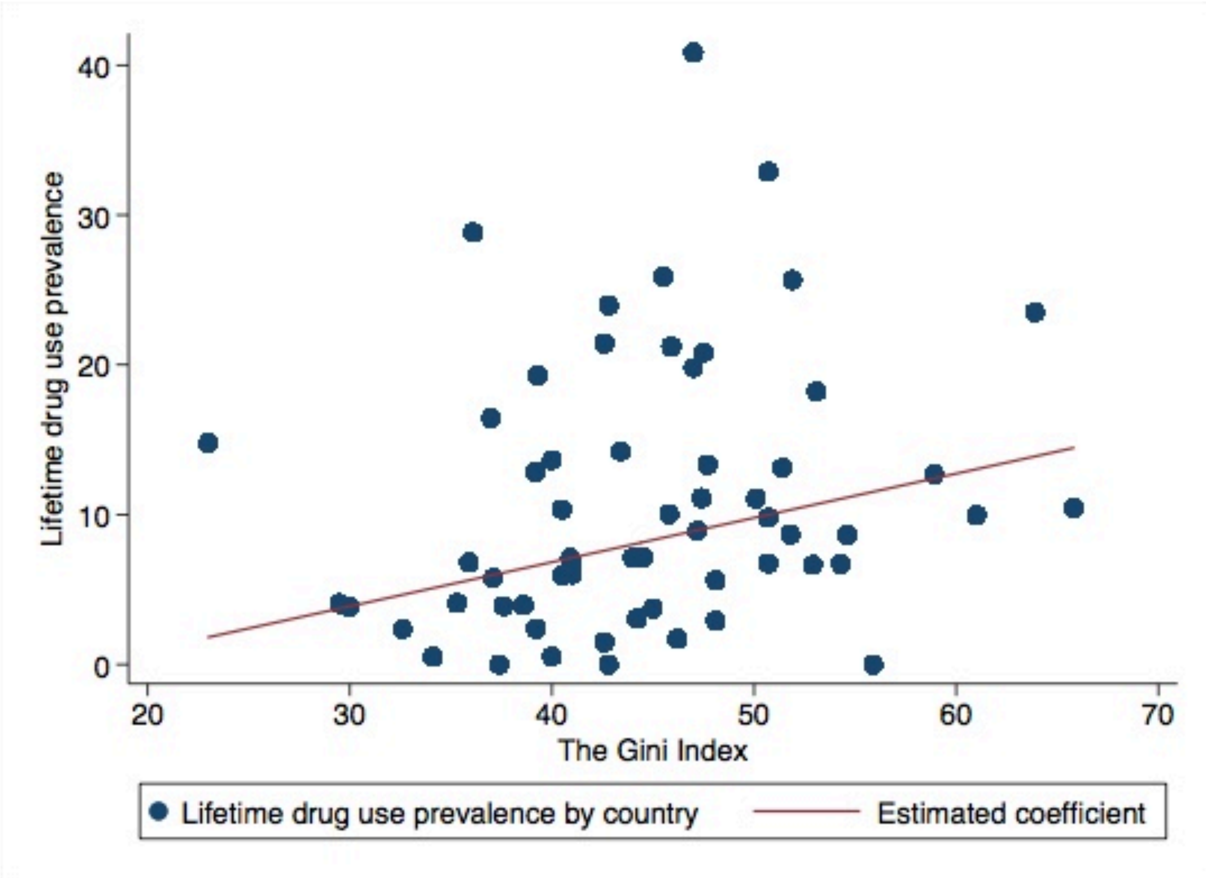


Figure 4. Map of lifetime drug use prevalence in sample countries



¶Darker color shows higher prevalence of drug use in the country

Figure 5. Scatter plots of the Gini index with lifetime drug use prevalence of sample countries



¶The straight line shows estimated coefficient of the lifetime drug use probability regressed on the Gini index

Appendix

Appendix 1 a. Result of single-level Cox proportional hazard regression adjusting for time-dependent covariates

	Hazard Ratio	SE	P-value
Sex	0.477	0.023	<0.001
Household poverty	1.257	0.025	<0.001
Parental smoking	1.299	0.034	<0.001
Neighborhood average income	1.118	0.071	0.078
Neighborhood poverty variance	237214	128166	<0.001
Neighborhood drug prevalence	4231	715	<0.001
The Gini index	0.919	0.003	<0.001
Log of per capita income	0.972	0.022	0.221
Time- varying covariates			
Young onset of smoking	1.154	0.005	<0.001
Log of pseudo- likelihood	-35068.623		

Appendix 1 b. Result of single-level Cox proportional hazard regression adjusting for time-dependent covariates

	Hazard Ratio	SE	P-value
Sex	0.574	0.016	<0.001
Household poverty	1.207	0.014	<0.001
Parental smoking	1.262	0.019	<0.001
Time- varying covariates			
Young onset of smoking	1.133	0.003	<0.001
Neighborhood average income	1.026	0.004	<0.001
Neighborhood poverty variance	1.482	0.045	<0.001
Neighborhood drug prevalence	1.950	0.020	<0.001
The Gini index	0.995	0.000	<0.001
Log of per capita income	1.004	0.001	0.019
Log of pseudo- likelihood	-127173.9		

Reference

1. WorldHealthOrganization. Abuse (drug, alcohol, chemical, substance or psychoactive substance) [cited 2018 Februrary 19th]. Available from: http://www.who.int/substance_abuse/terminology/abuse/en.

2. Abuse S. Emergency department trends from The Drug Abuse Warning Network, Final estimates 1994–2001. 2002.

3. USDHHS. Healthy people 2010: Office of Disease Prevention and Health Promotion, US Department of Health and Human Services; 2000.

4. Stiglitz JE. Macroeconomic fluctuations, inequality, and human development. Journal of Human Development and Capabilities. 2012;13(1):31-58.

5. Marmot MG, Stansfeld S, Patel C, North F, Head J, White I, et al. Health inequalities among British civil servants: the Whitehall II study. The Lancet. 1991;337(8754):1387-93.

6. Wilkinson RG. Income distribution and life expectancy. BMJ: British Medical Journal. 1992;304(6820):165.

7. Kennedy BP, Kawachi I, Prothrow-Stith D. Income distribution and mortality:

cross sectional ecological study of the Robin Hood index in the United States. Bmj. 1996;312(7037):1004-7 0959-8138.

8. Wilkinson R. Unhealthy Societies: The Afflictions of Inequality. 1996.

9. Wilkinson RG. Unhealthy societies: from inequality to well-being: Routledge; 1996.

10. Macintyre S, Ellaway A, Cummins S. Place effects on health: how can we conceptualise, operationalise and measure them? Social science & medicine. 2002;55(1):125-39.

11. Kawachi I, Kennedy BP. The health of nations: why inequality is harmful to your health. 2002.

12. Gilens M. Inequality and democratic responsiveness. Public Opinion Quarterly. 2005;69(5):778-96.

13. Runciman WG. Relative deprivation & social justice: Study attitudes social inequality in 20th century England. 1966.

14. Yitzhaki S. Relative deprivation and the Gini coefficient. The quarterly journal of economics. 1979:321-4.

15. Wilkinson RG. The impact of inequality: How to make sick societies healthier: The New Press; 2005.

16. The Economic Impact of Illicit Drug Use on American Society., Center NDI; 2011.

17. Li J, OMalley P, Bachman J, Schulenberg J, Miech R. Monitoring future national survey results on drug use 1975-2013. Michigan: The National Institute on Drug Abuse, The National Institutes of Health. 2013:85.

18. Connery HS AB, Rodolico JM. Adolescent substance use and unplanned pregnancy: strategies for risk reduction. Obstetrics and gynecology clinics of North America. 2014;41(2):191-203.

19. Hartnoll R. Drugs in focus; Measuring prevalence and incidence of drug use2002. Available from: http://www.emcdda.europa.eu/system/files/publications/171/Dif03en_63222.pdf.

20. United Nations Office on Drugs and Crime; World Drug Report 2014. In: UNODC, editor: United Nations; 2014.

21. World Health Organization. Drug use and road safety: a policy brief. 2016.

22. Kandel DB, Davies M, Karus D, Yamaguchi K. The Consequences in Young Adulthood of Adolescent Drug Involvement: An Overview. Archives of General Psychiatry. 1986;43(8):746-54.

23. Heil SH, Jones HE, Arria A, Kaltenbach K, Coyle M, Fischer G, et al. Unintended pregnancy in opioid-abusing women. Journal of substance abuse treatment. 2011;40(2):199-202.

24. Fergusson DM, Boden JM, Horwood LJ. The developmental antecedents of illicit drug use: evidence from a 25-year longitudinal study. Drug and alcohol dependence. 2008;96(1):165-77.

25. Tarter RE, Vanyukov M, Kirisci L, Reynolds M, Clark DB. Predictors of marijuana use in adolescents before and after licit drug use: examination of the gateway hypothesis. American Journal of Psychiatry. 2006.

26. Redonnet B, Chollet A, Fombonne E, Bowes L, Melchior M. Tobacco, alcohol, cannabis and other illegal drug use among young adults: the socioeconomic context. Drug and alcohol dependence. 2012;121(3):231-9.

27. Farrell AD, White KS. Peer influences and drug use among urban adolescents:

Family structure and parent–adolescent relationship as protective factors. Journal of consulting and clinical psychology. 1998;66(2):248.

28. Chilcoat HD, Anthony JC. Impact of parent monitoring on initiation of drug use through late childhood. Journal of the American Academy of Child & Adolescent Psychiatry. 1996;35(1):91-100.

29. Olivares EL, Kendler KS, Neale MC, Gillespie NA. The Genetic and Environmental Association Between Parental Monitoring and Risk of Cannabis, Stimulants, and Cocaine Initiation in a Sample of Male Twins: Does Parenting Matter? Twin Research and Human Genetics. 2016;19(04):297-305.

30. Robin RW, Chester B, Rasmussen JK, Jaranson JM, Goldman D. Prevalence, characteristics, and impact of childhood sexual abuse in a Southwestern American Indian tribe. Child abuse & neglect. 1997;21(8):769-87.

31. Enoch M-A, Hodgkinson CA, Yuan Q, Shen P-H, Goldman D, Roy A. The influence of GABRA2, childhood trauma, and their interaction on alcohol, heroin, and cocaine dependence. Biological psychiatry. 2010;67(1):20-7.

32. Bogt TF, Looze M, Molcho M, Godeau E, Hublet A, Kokkevi A, et al. Do

societal wealth, family affluence and gender account for trends in adolescent cannabis use? A 30 country cross-national study. Addiction. 2014;109(2):273-83.

33. Kokkevi A, Gabhainn SN, Spyropoulou M, HBSC RBFGot. Early initiation of cannabis use: a cross-national European perspective. Journal of Adolescent Health. 2006;39(5):712-9.

34. Maddahian E, Newcomb MD, Bentler P. Adolescent drug use and intention to use drugs: Concurrent and longitudinal analyses of four ethnic groups. Addictive behaviors. 1988;13(2):191-5.

35. Ter Bogt T, Schmid H, Nic Gabhainn S, Fotiou A, Vollebergh W. Economic and cultural correlates of cannabis use among mid-adolescents in 31 countries. Addiction. 2006;101(2):241-51.

36. Robins LN, Przybeck TR. Age of onset of drug use as a factor in drug and other disorders. NIDA Res Monogr. 1985;56:178-92.

37. Amaro H, Whitaker R, Coffman G, Heeren T. Acculturation and marijuana and cocaine use: findings from HHANES 1982-84. American Journal of Public Health. 1990;80(Suppl):54-60.

38. Fleming R, Leventhal H, Glynn K, Ershler J. The role of cigarettes in the initiation and progression of early substance use. Addictive Behaviors. 1989;14(3):261-72.

39. Single E, Kandel D, Faust R. Patterns of multiple drug use in high school. Journal of Health and Social Behavior. 1974:344-57.

40. DuRant RH, Smith JA, Kreiter SR, Krowchuk DP. The relationship between early age of onset of initial substance use and engaging in multiple health risk behaviors among young adolescents. Archives of pediatrics & adolescent medicine. 1999;153(3):286-91.

41. Torabi MR, Bailey WJ, Majd-Jabbari M. Cigarette smoking as a predictor of alcohol and other drug use by children and adolescents: evidence of the "gateway drug effect". Journal of school health. 1993;63(7):302-6.

42. Lindsay GB, Rainey J. Psychosocial and pharmacologic explanations of nicotine's "gateway drug" function. Journal of School Health. 1997;67(4):123-6.

43. Tsuang MT, Lyons MJ, Meyer JM, Doyle T, Eisen SA, Goldberg J, et al. Co-occurrence of abuse of different drugs in men: the role of drug-specific and shared

vulnerabilities. Archives of general psychiatry. 1998;55(11):967-72.

44. King SM, Keyes M, Malone SM, Elkins I, Legrand LN, Iacono WG, et al. Parental alcohol dependence and the transmission of adolescent behavioral disinhibition: a study of adoptive and non-adoptive families. Addiction. 2009;104(4):578-86.

45. Raeisei A, Sarani H, Arbabisarjou A, Mojahed A. The Most Common Reasons and Incentives of Tendency to Addiction in Prisons and Rehabilitation Centres of Zahedan (Iran). Global journal of health science. 2015;7(4):329.

46. L. Flom SRFBJRCP. Peer norms regarding drug use and drug selling among household youth in a low-income'drug supermarket'urban neighborhood. Drugs: education, prevention and policy. 2001;8(3):219-32.

47. Kandel DB, Davies M. Decline in the use of illicit drugs by high school students in New York State: a comparison with national data. American journal of public health. 1991;81(8):1064-7.

48. McBride AA, Joe GW, Simpson DD. Prediction of long-term alcohol use, drug use, and criminality among inhalant users. Hispanic Journal of Behavioral

Sciences. 1991;13(3):315-23.

49. Urberg KA, Değirmencioğlu SM, Pilgrim C. Close friend and group influence on adolescent cigarette smoking and alcohol use. Developmental psychology. 1997;33(5):834.

50. Degenhardt L, Chiu W-T, Sampson N, Kessler RC, Anthony JC, Angermeyer M, et al. Toward a global view of alcohol, tobacco, cannabis, and cocaine use: findings from the WHO World Mental Health Surveys. PLoS medicine. 2008;5(7):e141.

51. Sareen J, Afifi TO, McMillan KA, Asmundson GJG. Relationship Between Household Income and Mental Disorders. Arch Gen Psychiatry. 2011;68(4):419-27.

52. Williams CT, Latkin CA. Neighborhood socioeconomic status, personal network attributes, and use of heroin and cocaine. American journal of preventive medicine. 2007;32(6):S203-S10.

53. Brownsberger WN. Prevalence of frequent cocaine use in urban poverty areas. Contemporary Drug Problems. 1997;24(2):349-71.

54. Kulis S, Marsiglia FF, Sicotte D, Nieri T. Neighborhood effects on youth substance use in a southwestern city. Sociological Perspectives. 2007;50(2):273-301.

55. de Souza Briggs X. Moving up versus moving out: Neighborhood effects in housing mobility programs. Housing policy debate. 1997;8(1):195-234.

56. Simetin IP, Kern J, Kuzman M, Pförtner T-K. Inequalities in Croatian pupils' risk behaviors associated to socioeconomic environment at school and area level: A multilevel approach. Social science & medicine. 2013;98:154-61.

57. Saxe L, Kadushin C, Beveridge A, Livert D, Tighe E, Rindskopf D, et al. The visibility of illicit drugs: implications for community-based drug control strategies. American Journal of Public Health. 2001;91(12):1987-94.

58. Galea S, Ahern J, Vlahov D. Contextual determinants of drug use risk behavior: a theoretic framework. Journal of Urban Health. 2003;80(3).

59. Schroeder JR, Latkin CA, Hoover DR, Curry AD, Knowlton AR, Celentano DD. Illicit drug use in one's social network and in one's neighborhood predicts individual heroin and cocaine use. Annals of epidemiology. 2001;11(6):389-94.

60. Snedker KA, Herting JR, Walton E. Contextual effects and adolescent substance use: Exploring the role of neighborhoods. Social Science Quarterly. 2009;90(5):1272-97.

61. Kleiman MAR. Drugs and drug policy: The case for a slow fix. Issues in

Science and Technology. 1998;15(1):45-52.

62. WHO Expert Committee on Problems Related to Alcohol Consumption: Second Report: World Health Organization; 2007.

63. Blecher EH, Van Walbeek CP. An international analysis of cigarette affordability. Tobacco Control. 2004;13(4):339-46.

64. Vuolo M. National-level drug policy and young people's illicit drug use: A multilevel analysis of the European Union. Drug and alcohol dependence. 2013;131(1):149-56.

65. World Bank Website: Available from: http://www.worldbank.org/.

66. Henderson C, Liu X, Roux AVD, Link BG, Hasin D. The effects of US state income inequality and alcohol policies on symptoms of depression and alcohol dependence. Social science & medicine. 2004;58(3):565-75.

67. Cerdá M, Ransome Y, Keyes KM, Koenen KC, Tardiff K, Vlahov D, et al. Revisiting the role of the urban environment in substance use: the case of analgesic overdose fatalities. American journal of public health. 2013;103(12):2252-60.

68. Elgar FJ, Roberts C, Parry-Langdon N, Boyce W. Income inequality and

alcohol use: a multilevel analysis of drinking and drunkenness in adolescents in 34 countries. The European Journal of Public Health. 2005;15(3):245-50.

69. Lê F, Ahern J, Galea S. Neighborhood education inequality and drinking behavior. Drug and alcohol dependence. 2010;112(1):18-26.

70. Li DX, Guindon GE. Income, income inequality and youth smoking in low- and middle-income countries. Addiction. 2013;108(4):799-808.

71. Quon EC, McGrath JJ. Community, family, and subjective socioeconomic status: Relative status and adolescent health. Health Psychology. 2015;34(6):591.

72. Galea S, Ahern J, Tracy M, Vlahov D. Neighborhood income and income distribution and the use of cigarettes, alcohol, and marijuana. American journal of preventive medicine. 2007;32(6):S195-S202.

73. Nandi A, Galea S, Ahern J, Bucciarelli A, Vlahov D, Tardiff K. What explains the association between neighborhood-level income inequality and the risk of fatal overdose in New York City? Social science & medicine. 2006;63(3):662-74.

74. Galea S, Ahern J, Vlahov D, Coffin PO, Fuller C, Leon AC, et al. Income distribution and risk of fatal drug overdose in New York City neighborhoods. Drug and

alcohol dependence. 2003;70(2):139-48.

75. Galea S, Ahern J, Tracy M, Rudenstine S, Vlahov D. Education inequality and use of cigarettes, alcohol, and marijuana. Drug and alcohol dependence. 2007;90:S4-S15.

76. Fraser C, Jackson H, Judd F, Komiti A, Robins G, Murray G, et al. Changing places: the impact of rural restructuring on mental health in Australia. Health & place. 2005;11(2):157-71.

77. Pickett KE, Wilkinson RG. Inequality: an underacknowledged source of mental illness and distress. The British Journal of Psychiatry. 2010;197(6):426-8.

78. Gunnell D, Middleton N, Whitley E, Dorling D, Frankel S. Why are suicide rates rising in young men but falling in the elderly?—a time-series analysis of trends in England and Wales 1950–1998. Social science & medicine. 2003;57(4):595-611.

79. Wilkinson RG, Pickett KE. Income inequality and social dysfunction. Annual Review of Sociology. 2009:493-511.

80. Chen C-Y, Storr CL, Anthony JC. Early-onset drug use and risk for drug dependence problems. Addictive behaviors. 2009;34(3):319-22.

81. Kawachi I, Kennedy BP. Income inequality and health: pathways and mechanisms. Health services research. 1999;34:215.

82. Kennedy BP, Kawachi I, Glass R, Prothrow-Stith D. Income distribution, socioeconomic status, and self rated health in the United States: multilevel analysis. Bmj. 1998;317(7163):917-21.

83. Subramanian S, Kawachi I. Income inequality and health: what have we learned so far? Epidemiologic reviews. 2004;26(1):78-91.

84. Wilkinson RG, Pickett KE. The problems of relative deprivation: why some societies do better than others. Social science & medicine. 2007;65(9):1965-78.

85. Fergusson DM, Boden JM, Horwood LJ. Cannabis use and other illicit drug use: testing the cannabis gateway hypothesis. Addiction. 2006;101(4):556-69.

86. Kandel D. Stages in adolescent involvement in drug use. Science. 1975;190(4217):912-4.

87. Kandel DB, Yamaguchi K, Chen K. Stages of progression in drug involvement from adolescence to adulthood: further evidence for the gateway theory. Journal of studies on alcohol. 1992;53(5):447-57.

88. Yamaguchi K, Kandel DB. Patterns of drug use from adolescence to young adulthood: II. Sequences of progression. American Journal of Public Health. 1984;74(7):668-72.

89. Yamaguchi K, Kandel DB. Patterns of drug use from adolescence to young adulthood: III. Predictors of progression. American Journal of Public Health. 1984;74(7):673-81.

90. Global School-based Student Health Survey (GSHS) Available from:
http://www.cdc.gov/gshs/ (CDC)
http://www.who.int/chp/gshs/en/ (WHO).

91. Aurelie M. Lasserre BV, Pascal Povet. 2007 Seychelles. Global School-based Student Health Survey: Full report. In: Ministry of Health and Social Development RoS, University of Lausanne, Center for Disease Control and prevention, World Health Organization, editor. 2008.

92. Mellor JM, Milyo J. Is exposure to income inequality a public health concern? Lagged effects of income inequality on individual and population health. Health services research. 2003;38(1p1):137-51.

93. Spencer N, Fielding A. An instrumental variable consistent estimation procedure to overcome the problem of endogenous variables in multilevel models. Multilevel Modelling Newsletter. 2000.

94. Oakes JM. The (mis) estimation of neighborhood effects: causal inference for a practicable social epidemiology. Social science & medicine. 2004;58(10):1929-52.

95. Allison PD. Fixed effects regression models: SAGE publications; 2009.

96. Blakely TA, Lochner K, Kawachi I. Metropolitan area income inequality and self-rated health—a multi-level study. Social science & medicine. 2002;54(1):65-77.

97. ACT 234 Dangerous DRUGS ACT 1952 (REVISED 1980). Sect. 39A (1980).

98. Graham D. Guatemala may weigh softer drug punishments in liberalization push. Reuters. 2014 October 16.

99. Hughes CE, Stevens A. What can we learn from the Portuguese decriminalization of illicit drugs? The British Journal of Criminology. 2010;50(6):999-1022.

100. Travis A. Eleven countries studied, one inescapable conclusion–the drug laws don't work. The Guardian. 2014;30.

101. Martin CA, Kelly TH, Rayens MK, Brogli BR, Brenzel A, Smith WJ, et al. Sensation seeking, puberty, and nicotine, alcohol, and marijuana use in adolescence. Journal of the American academy of child & adolescent psychiatry. 2002;41(12):1495-502.

102. Newcomb MD, Felix-Ortiz M. Multiple protective and risk factors for drug use and abuse: cross-sectional and prospective findings. Journal of personality and social psychology. 1992;63(2):280.

103. Momtazi S, Rawson RA. Substance abuse among Iranian high school students. Current opinion in psychiatry. 2010;23(3):221.

104. Oetting ER, Beauvais F. Adolescent drug use: Findings of national and local surveys. Journal of consulting and clinical psychology. 1990;58(4):385.

105. Bagot KS, Milin R, Kaminer Y. Adolescent initiation of cannabis use and early-onset psychosis. Substance abuse. 2015;36(4):524-33.

106. Sartor CE, Jackson KM, McCutcheon VV, Duncan AE, Grant JD, Werner KB, et al. Progression from First Drink, First Intoxication, and Regular Drinking to Alcohol Use Disorder: A Comparison of African American and European American Youth.

Alcoholism: Clinical and Experimental Research. 2016.

107. Rothman EF, Edwards EM, Heeren T, Hingson RW. Adverse childhood experiences predict earlier age of drinking onset: results from a representative US sample of current or former drinkers. Pediatrics. 2008;122(2):e298-e304.

108. Hanna EZ, Yi H-y, Dufour MC, Whitmore CC. The relationship of early-onset regular smoking to alcohol use, depression, illicit drug use, and other risky behaviors during early adolescence: results from the youth supplement to the third national health and nutrition examination survey. Journal of substance abuse. 2001;13(3):265-82.

109. Schmits E, Mathys C, Quertemont E. A longitudinal study of cannabis use initiation among high school students: Effects of social anxiety, expectancies, peers and alcohol. Journal of adolescence. 2015;41:43-52.

110. Hasler BP, Kirisci L, Clark DB. Restless sleep and variable sleep timing during late childhood accelerate the onset of alcohol and other drug involvement. Journal of Studies on Alcohol and Drugs. 2016;77(4):649-55.

111. Badiani A, Boden JM, De Pirro S, Fergusson DM, Horwood LJ, Harold GT. Tobacco smoking and cannabis use in a longitudinal birth cohort: Evidence of

reciprocal causal relationships. Drug and alcohol dependence. 2015;150:69-76.

112. Lynskey MT, Heath AC, Bucholz KK, Slutske WS, Madden PA, Nelson EC, et al. Escalation of drug use in early-onset cannabis users vs co-twin controls. Jama. 2003;289(4):427-33.

113. Lawrinson P, Ali R, Buavirat A, Chiamwongpaet S, Dvoryak S, Habrat B, et al. Key findings from the WHO collaborative study on substitution therapy for opioid dependence and HIV/AIDS. Addiction. 2008;103(9):1484-92.

114. Grambsch PM, Therneau TM. Proportional hazards tests and diagnostics based on weighted residuals. Biometrika. 1994;81(3):515-26.

115. Kleinbaum DG, Klein M. Survival analysis: a self-learning text: Springer Science & Business Media; 2006.

116. Schoenfeld D. Chi-squared goodness-of-fit tests for the proportional hazards regression model. Biometrika. 1980;67(1):145-53.

117. Year F. Substance abuse and mental health services administration. 2009.

118. Barker MJ, Greenwood KM, Jackson M, Crowe SF. Cognitive effects of long-term benzodiazepine use. CNS drugs. 2004;18(1):37-48.