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Aolin Wang and Onyebuchi A. Arah

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Aolin Wang[1,2*] aolinw@ucla.edu

Onyebuchi A. Arah[1-3] arah@ucla.edu

[1]Department of Epidemiology, Fielding School of Public Health, University of California, Los Angeles (UCLA), Los Angeles, California, USA

[2]California Center for Population Research (CCPR), Los Angeles, California, USA

[3]UCLA Center for Health Policy Research, Los Angeles, California, USA

[*]Corresponding author: Aolin Wang

Address: Department of Epidemiology, UCLA Fielding School of Public Health, 650 Charles E. Young Drive South, Los Angeles, CA 90095-1772, USA.

Email: aolinw@ucla.edu

Abstract

Using causal mediation analysis to account for multiple mediators and possible interactions between education and downstream behaviors, we examined health disparities in education and the contributions of pathways through social mediating factors and health behaviors. We analyzed the World Health Survey data on 164,743 participants aged 25 or older from 46 countries. G-computation algorithm implemented using Monte Carlo simulation of generalized linear mixed models was used to estimate natural and controlled direct effects, and mediated effects of 'lower educational attainment' compared to 'high school or beyond' (reference) education. Lower educational attainment had an overall negative impact on health (*b* ranging from –1.06 for secondary school completed to –4.05 for no formal education), the largest proportion of which was not mediated by social factors nor health behaviors. A substantial amount of the observed education-related health disparities would be eliminated if everyone had healthy behaviors — the proportion eliminated ranging from 48% for those that completed secondary school to 72% for those with no formal education. Simultaneously intervening on education, health behaviors and social factors will be more effective in reducing health disparities than intervening on education alone, since these mediating factors are important effect modifiers for the health effects of education.

Keywords: education, health behaviors, mediation analysis, pathway, interaction, heterogeneity

INTRODUCTION

The literature has persistently documented the relationship between lower socioeconomic status (SES) and poor health among affluent countries [1,2] and worldwide [3]. However, the mechanisms underlying education and health are not clear. Although different factors and pathways have been proposed to explain the socioeconomic inequalities in health [4–7], health behavior or lifestyle appeared to be the most popular factor. It is suggested that unhealthy behavior or lifestyle accounted for 50% of mortality in 1976 in the United States (U.S.), according to the Healthy People: The Surgeon-General's Report on Health Promotion and Disease Prevention in 1979 [8], highlighting the importance of studying these behavioral factors when explain the educational gradient in health.

Empirical evidence is abundant on the relations between low SES and health behaviors such as smoking, alcohol consumption, physical inactivity [9–11], or psychosocial factors [12,13], and between these behaviors and various health comes (Lantz et al. 1998; Institute of Medicine (US) Committee on Health and Behavior: Research; Practice; and Policy 2001; Adler and Newman 2002). Some studies also examined the direct impact of SES on health accounting for possible mediating pathways [1,4,9,10,13,15,16]. However, these studies were mainly from European countries and the U.S., results reflecting a global picture is lacking. Also, past studies using traditional analytical approaches such as the difference method [17] or linear path model [18] seldom considered the possible interactions between SES and downstream behaviors. The past decade has seen considerable growth of the literature on effect definition, identification, and estimation for causal mediation analysis under the potential outcome framework [19–22]. They have also been extended to complex settings involving multiple causally ordered mediators [23] and time-varying exposure

and mediators [24].

In this study, we examined (1) health disparities due to educational attainment, a commonly used SES measure that shapes future occupational opportunities and income [5], and (2) the contributions of possible mediating pathways through social factors and health behaviors. We partitioned the total effect of education on health into pathway effects while preserving the interaction between education and mediators (mechanistic perspective). We also examine two types of controlled direct effect that correspond to certain hypothetical public health interventions on social factors and health behaviors.

RESULTS

Among 231,274 participants aged 25 years or older, 164,743 (71.2%) participants from 46 countries had complete information on all covariates. Country-specific sample size and characteristics, and the characteristics of the excluded participants are presented in supplement (Table S1 and S2 respectively). The main reason for exclusion was missing information on at least one health behavior factor or health score. Excluded participants were slightly older, more likely to obtain education greater than high school, and be unemployed, unmarried, and physically inactive but less likely to have used alcohol. Distributions of other variables were similar to that among participants in the analytic sample.

Table 1 shows participant characteristics by educational attainment. As education increased, participants were younger, less likely to live in rural areas or be unemployed, more likely to have used alcohol and be physically inactive, and reported better health. More females and higher level of stress were seen among people with no formal education than the rest of the participants.

Table 2 displays the effect estimates comparing each of the four index education levels to the reference 'high school or beyond' category. Across all education levels, low educational attainment was associated with poorer health (TE ranging from -4.05 to -1.06). The impact of low education on health was negative through pathways involving social factors (NIE-A ranging from -0.54 to -0.18), pathway through health behaviors only (NIE-B ranging from -0.43 to -0.14), and pathways other than through social factors or health behaviors (NDE ranging from -3.08 to -0.74). Lower educational attainment was associated with poorer health when we either fixed all mediators at the desired reference levels (i.e. living in urban areas, being employed and married,

not currently smoking, never used alcohol, being physically active, and not feeling stressed) (CDE-00 ranging from -0.22 to -0.34), or fixed only health behaviors at the desired levels (CDE-X0 ranging from -1.12 to -0.55). One exception is that, after fixing all mediators at the aforementioned desired levels, 'no formal education' was not associated with health (CDE-00: -0.10, 95% CI: -0.40-0.19). For all types of effects, effect sizes became smaller as education level increased from "no formal education" to "secondary school completed".

Figure 1 depicts the proportion explained by each type of effect relative to the TE across different education levels. Indirect effect of education through social factors and their consequences made up 13.4% ~ 16.9% of the TE. Pathway involving health behaviors only accounted for 10.6% ~ 13.3% of the TE. The negative impact of lower education on health was mainly direct (i.e., via other pathways) (69.8% ~ 76.0%). The majority of the negative impact of lower educational attainment on health could be prevented if we could, by some hypothetical intervention, fix both social factors and health behaviors at the desired levels, especially for those with no formal education [proportion eliminated (CDE-00): 97.5%, proportion eliminated (CDE-00) ranging from 67.4% to 82.1% for other education levels]. A large portion of the health disparities due to education could be eliminated if hypothetical intervention was implemented to fix health behaviors at the desired levels [proportion eliminated (CDE-X0) ranging from 47.8% to 72.3%].

DISCUSSION

This large population-based global study found a widening gap in health status among participants with varying educational attainment compared to participants with high school or beyond education. Mechanistically, the major contribution of the negative impact of lower education on health was through pathways other than through social factors or health behaviors. Still, pathways through social factors or health behaviors accounted for more than one tenth of the health disparities due to education. A substantial amount of the observed health disparities would be eliminated if, in addition to increasing education, everyone had healthy behaviors and achieved the desired level of social factors via hypothetical interventions.

We found that health behaviors contributed to the education 'gradient' in health, though the former did not fully explain the latter. This is in line with one study that found a significant direct effect of education even adjusting for work and economic conditions, social-psychological resources, and health lifestyle [4], but not with the other, which found no educational impact after adjusting for income and health behaviors [10]. From a mechanistic perspective, only 11% to 13% of the educational disparity was attributed to the pathway from education to health behaviors and in turn to health. Direct comparison to the existing literature is difficult due to the different methods used in defining and estimating the pathway effects. Only one other study used causal mediation analysis to examine the mediating role of health behaviors in the relation between education and diabetes incidence [25]. Body mass index and physical activity appeared to be mediating such relationship but the mediation proportion cannot be calculated because some of the pathways operated in the opposite directions. The large portion of direct effect not explained in the natural decomposition could be attributed to other important pathways such as physical

and social environment, access to health care, psychosocial factors such as job control or social support [6,12,26].

Health behaviors and social factors may be less important mechanistic mediators in the current study sample, but they were important effect modifier, as can be seen in the discrepancy between natural and controlled direct effects. Such discrepancy could be attributable to the presence of interaction between education and mediators in affecting health and the fact that these social factors and health behaviors were not completely deterministic by educational attainment. Detailed explanation can be found in the supplement (Section 4 and Table S3).

From a public health intervention perspective, 48% to 72% of the educational gradient in health can be prevented by setting health behaviors at the desired level. Using the difference method, the British Whitehall II studies reported that health behaviors assessed at baseline explained 42%, 29%, and 61% of the socioeconomic gradient (measured by occupational grade) in all-cause, CVD, and non-cancer/non-CVD mortality whereas the repeated assessments of these behaviors during follow-up explained 72%, 45%, and 94% respectively [16]. In a later analysis of the Whitehall II study in comparison to the French GAZEL study, health behaviors were found to attenuate the association of SES with mortality by 75% in the former but only by 19% in the later [9]. Using data from the National Health and Nutrition Examination Survey, researchers found that in the low-income group, health behaviors attenuated the risk of all-cause and CVD/diabetes mortality by 30% and 21%, respectively [15]. In a study analyzing data from the National Health Interview Survey, the effect of education on mortality was reduced by 30% when controlling for exercise, smoking, drinking, seat belt use, and use of preventive care [13].

Our study is not easily comparable to the above studies because of the different behavioral factors included, health outcomes, and measures of SES. Some scholars did point out that different measures of SES are not interchangeable [27,28] and there is variation in the SES-health association because of the choice of measure [29]. It is also possible that the causal chain from SES to health/mortality via health behaviors played out differently due to the difference in social patterning of unhealthy behaviors between countries [9]. Nevertheless, our study showed that health behaviors played an important role, especially among the least educated. Under hypothetical intervention of fixing the health behaviors at the desired level, the health disparity gap by education narrowed as educational attainment increased. People with no formal education would potentially benefit most from interventions that promote healthy behaviors in terms of narrowing the educational gradient in health.

To the best of our knowledge, this is the first study to quantify the contribution of underlying pathways that explained educational disparities in health across countries and continents using causal inference technique. The use of standardized global health data allowed for pooling data from multiple high-, middle-, and low-income countries and examining a global picture. We used causal mediation analysis tool that incorporated nonlinear relationships, which is crucial in the presence of exposure-mediator interaction. We presented results from both mechanistic and interventional perspectives that shed light on the well-established yet mysterious relationship between education and health. The hierarchical nature of the data was accounted for by using multilevel generalized linear models. Apart from partitioning the impact of education on health into pathway-specific effects, we also examined the remaining health disparities due to education under hypothetical intervention of either setting health behaviors singly or combined with social

factors at the desired levels.

Several methodological limitations need to be addressed. We assumed that educational attainment preceded mediators and health status, though they were measured at the same time. Educational attainment, unlike income [30], is less likely to be influenced by mid-life health conditions. Sensitivity analysis that restricted analysis to participants aged 40 and older (N=91,728) revealed similar patterns but slightly larger estimates. Nevertheless, we cannot rule out the possibility that some of the health behaviors such as smoking had occurred by late adolescence [31] and could affect educational attainment [32]. Repeated measurements on behaviors were not available, which could explain a significantly greater part of the SES-mortality association compared to baseline-only assessments [16]. Due to missing information on health behaviors and health status, we lost participants from 24 countries, most of which were countries from the European Region. We also did not include fruit and vegetable consumption in our analysis due to vast missing values. We did not impose directionality between different social factors nor between different health behaviors; rather, we hypothesized variables within each of these two constructs were related by their upstream determinants as depicted in our DAG. Despite the use of causal inference techniques, our result could still be subject to uncontrolled confounding between health behaviors and health status and measurement error biases. The results of CDEs should be interpreted with caution. They correspond to an ideal scenario that might never happen: you cannot force people to be married or have no stress. Therefore, they can be an overestimation of the educational disparities in health that could be eliminated by such joint interventions on health behaviors and social factors. In future studies, we will explore different intervention scenarios and the combinations of them in reducing health disparities by

education.

This study provides evidence on the contribution of underlying pathways that explained educational gradient in health. Mechanistically, the impact of education on health was mainly not through the studied behavioral and social mediators. Yet, if the population could achieve the desired levels for health behaviors by certain interventions, a large portion of educational disparities in health could be eliminated, especially among those with no formal education. Our study highlights the need for continuing efforts on health behavior interventions among the less educated as countries throughout the world continue to achieve universal primary education or universal secondary education [33].

METHODS

Study sample and variables

We used data from the World Health Survey (WHS) conducted by the WHO in 70 high-, middle-, and low-income countries from 2002 to 2004. The study design and methods of the WHS have been documented in detail elsewhere [3,34] and in the supplement (Section 1). This study is based on a secondary analysis of the publicly available WHS data and does not involve direct contact of participants, experiments on humans, nor the use of human tissue samples.

Outcome

The health state measures has been extensively tested [35] and have showed good consistency and reliability [3]. Individual participants reported their perceived difficulties based on two 5-point Likert scale questions for each of the eight health state domains: mobility, self-care, pain and discomfort, cognition, interpersonal activities, vision, sleep and energy, and affect [34]. Similar to a previous study [3], we performed factor analysis, and used principal component and regression scoring methods to obtain factor scores. The factor score was rescaled with 0 indicating worst health and 100 indicating best health.

Exposure

Individual educational attainment was measured as the highest level of education a person completed. There are five categories: “no formal schooling”, “less than primary school”, “primary school completed”, “secondary school completed”, and “high school or beyond”. For individuals with missing educational attainment but reporting 0 years of schooling, we assigned “no formal schooling” as their educational attainment (N=37). These categories were made to be

applicable to all countries regardless of the type of educational system via a mapping algorithm to record educational categories other than those specified above [36].

Mediators

Social factors included residence (living in rural areas versus urban or semi-urban area), unemployment (currently not employed versus employed), and marital status (currently not married versus married).

Individual health behaviors included smoking (currently smoke versus not), alcohol drinking (ever versus never), physical inactivity (having <3 times of vigorous physical activity per week versus having ≥3 times) and stress. Participants were asked "How often have you felt that you were unable to control the important things in your life" and "How often have you found that you could not cope with all the things that you had to do". Answers based on 5-point Likert scale (ranging from "1-never" to "5-very often") were aggregated and then log transformed (using log base 2) and re-centered so that higher scores indicated more stress while 0 represented no stress (score ranging from 0 to 2.3).

Confounders

Potential contextual confounders were WHO region and country level wealth, measured by gross domestic product per capita (in current US$) in 2003 that were obtained from the United Nations (UN) database [37]. Individual level predisposing factors are age and sex.

Conceptual framework and effect decomposition

We used a directed acyclic graph (DAG) [38] to represent our assumptions about the data

generating process (Figure 2). We restricted our sample to participants aged 25 and older and, assumed that educational attainment preceded participants residence, employment and marital status, health behaviors including current smoking status, alcohol use, physical activity status and stress level, and the present health status measured at the time of the survey, despite the cross-sectional nature of the WHS data set. Also, social factors were assumed to precede health behaviors, which preceded current health status.

In the presence of two causally ordered mediators, total effect (TE) of education on health can be decomposed into a natural direct effect (NDE) of education that is not through any of the two mediator sets, a natural indirect effect through social factors and their consequences (NIE-A), and a natural indirect effect through health behaviors only (NIE-B) (Supplementary Figure S1). We also examined two types of controlled direct effect: (i) one that captured the direct effect of education had we fixed both social factors and health behaviors at their reference levels (CDE-00), and (ii) one that captured the direct effect of education while fixing only health behaviors at the reference levels but not fixing social factors (i.e., allowing them to respond to education) (CDE-X0). Effect definitions under the potential outcome (counterfactual) framework were listed in Supplementary Table S4. We invoked the stable unit treatment value assumption (SUTVA) [39,40], and assumptions of general consistency, positivity, and conditional exchangeability (no uncontrolled confounding) [23]. Details for the conditional exchangeability assumption are listed in the supplement (Section 2).

Statistical analysis

We used appropriate descriptive statistics to summarize the characteristics of the participants by their educational attainment. We adopted a fully parametric approach, implemented via Monte

Carlo simulation, to obtain marginal estimates for each effect. Detailed steps can be found elsewhere [41] and in the supplement (Section 3). Briefly, we estimated parameters for predicting each mediator and the outcome using multilevel generalized linear models with random intercept for country. Then we created an education intervention variable, simulated the potential mediators and outcomes sequentially based on the corresponding counterfactual definitions. Finally, we ran a marginal structural model to obtain a marginal estimate for each type of effect and used non-parametric bootstrap to obtain standard errors and 95% confidence intervals. All analyses were conducted in SAS 9.4 (SAS Institute Inc., Cary, North Carolina, USA).

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Authors' contributions

AW conceived this study, performed all analyses, and wrote the manuscript. OAA participated in study conception, provided guidance on analysis and interpretation of the result, edited the final manuscript, and supervised the study.

Competing Interest

None declared.

FIGURES AND LEGENDS

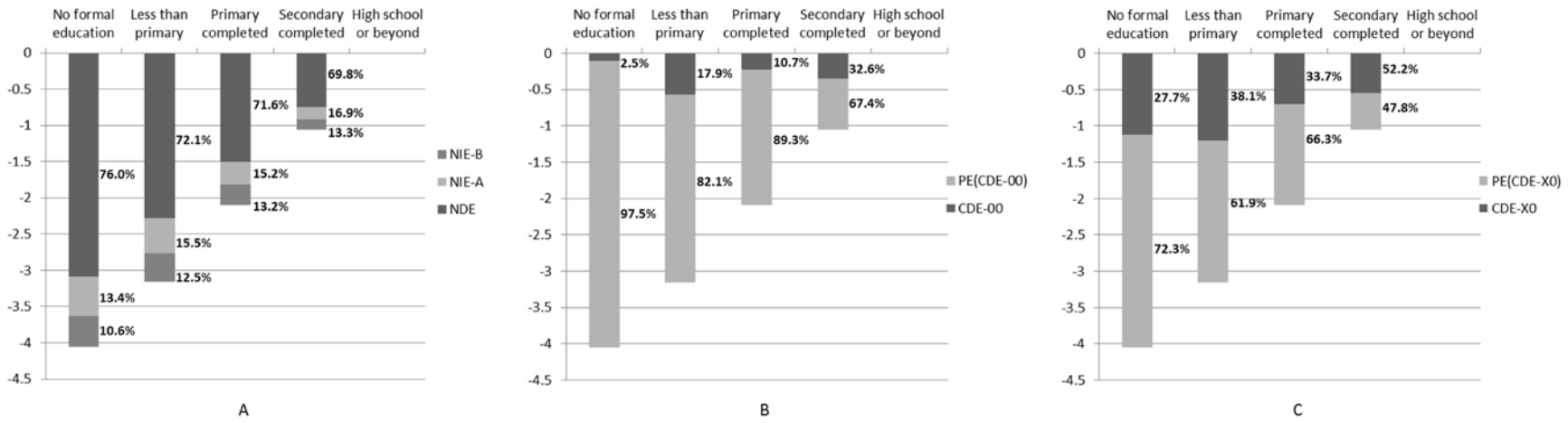

Figure 1. Effect decomposition and proportion explained by each pathway.

Legends: A: natural decomposition; B and C: decomposition involving controlled direct effect. NDE: natural direct effect; NIE-A: natural indirect effect that is through social mediating factors and their consequences; NIE-B: natural indirect effect that is through health behavioral mediators only; CDE-00: controlled direct effect while fixing all mediators at the reference level (i.e. living in urban areas, being employed and married, not currently smoking, never used alcohol, being physically active, and not feeling stressed); CDE-X0: controlled direct effect while fixing only health behavioral mediators at the reference level (i.e. not currently smoking, never used alcohol, being physically active, not feeling stressed); PE(CDE-00) and PE(CDE-X0): the corresponding complement of total effect, also called “portion eliminated” (PE).

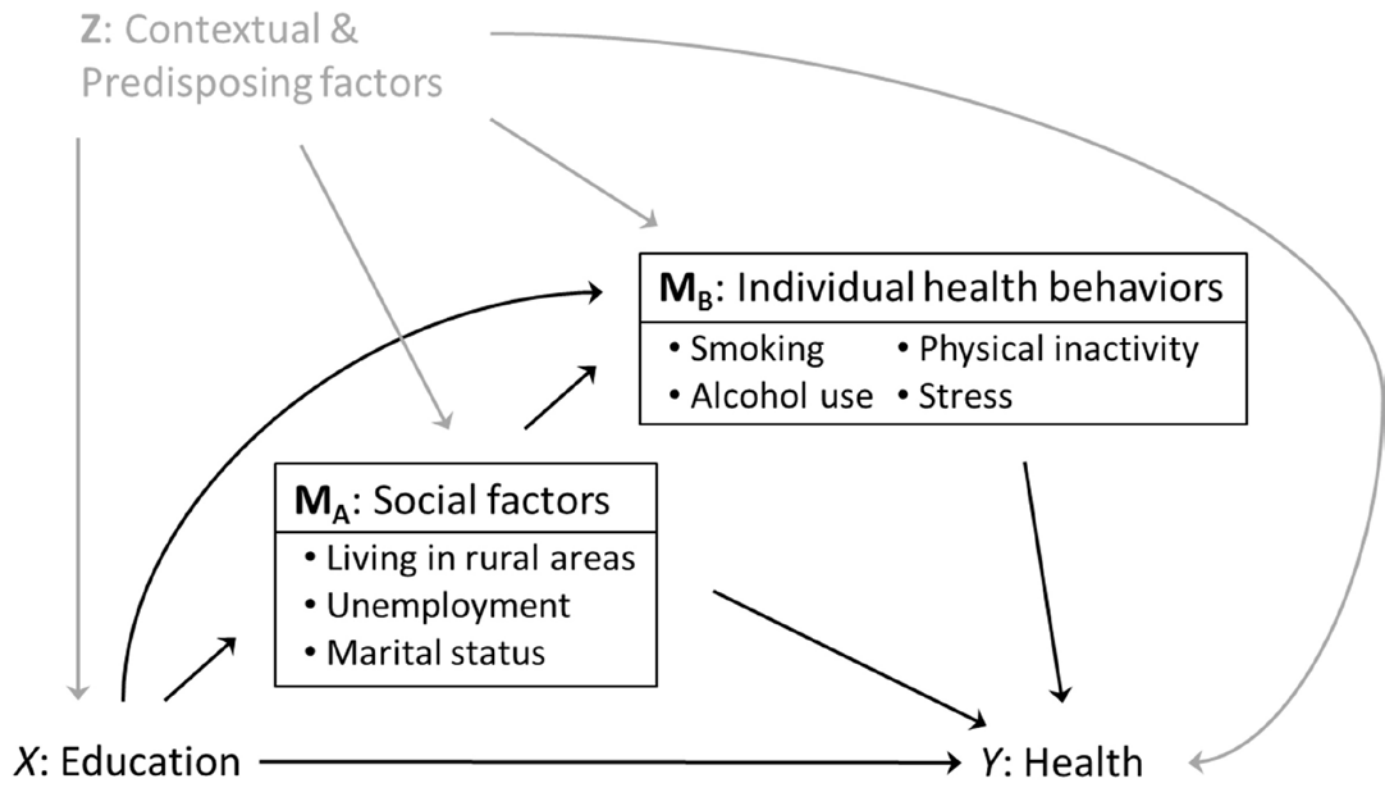

Figure 2. Graphical representation of hypothesized data generating process.

Legends: *X*: a single exposure *X*, $\mathbf{M_A}$ and $\mathbf{M_B}$: two sets of causally ordered mediators, *Y*: an outcome, and **Z**: a set of confounders sufficient for confounding control. Arrows represent theorized causal relations. When only mediator $\mathbf{M_B}$ is of interest, $\mathbf{M_A}$ is sometimes called “endogenous confounders” or “intermediate confounders” as they are consequences of *X*.

TABLES

Table 1 Participant characteristics by educational attainment, World Health Survey 2002-2004.

Characteristics	No formal education	Less than primary school	Primary school completed	Secondary school completed	High school or beyond	All
Total, N (%)	35973 (21.8)	20958 (12.7)	32018 (19.4)	40663 (24.7)	35131 (21.3)	164743 (100)
Age, mean (SD)	47.9 (16.1)	46.7 (15.8)	45.6 (15.6)	43.3 (14.3)	41.8 (12.8)	44.8 (15.0)
Females, N (%)	22784 (63.3)	11107 (53.0)	16847 (52.6)	21923 (53.9)	18609 (53.0)	91270 (55.4)
Social factors						
Living in rural areas, N (%)	28093 (78.1)	14213 (67.8)	16739 (52.3)	13965 (34.3)	8833 (25.1)	81843 (49.7)
Unemployment, N (%)	17005 (47.3)	8960 (42.8)	14116 (44.1)	18653 (45.9)	10711 (30.5)	69445 (42.2)
Not Married, N (%)	10213 (28.4)	7523 (35.9)	10394 (32.5)	12962 (31.9)	11249 (32.0)	52341 (31.8)
Individual health behaviors						
Currently smoking, N (%)	9438 (26.2)	5893 (28.1)	8187 (25.6)	10297 (25.3)	9006 (25.6)	42821 (26.0)
Alcohol use, N (%)	8045 (22.4)	8201 (39.1)	12479 (39.0)	18511 (45.5)	18396 (52.4)	65632 (39.8)
Physical inactivity, N (%)	22961 (63.8)	13722 (65.5)	22112 (69.1)	30374 (74.7)	26889 (76.5)	116058 (70.5)
Stress (log transformed), mean (SD)	1.2 (0.7)	1.0 (0.8)	1.0 (0.7)	0.8 (0.7)	0.9 (0.7)	1.0 (0.7)
Health score, mean (SD)	80.8 (18.1)	84.3 (15.8)	86.4 (14.8)	89.1 (12.7)	89.6 (12.0)	86.3 (15.1)

Table 2 Marginal effect estimate (95% Confidence Interval)[a] for educational attainment on health using g-computation formula[b], World Health Survey 2002-2004.

	No formal education	**Less than primary school**	**Primary school completed**	**Secondary school completed**	**High school or beyond**
Total effect	-4.05 (-4.24, -3.85)	-3.15 (-3.35, -2.95)	-2.09 (-2.24, -1.94)	-1.06 (-1.19, -0.92)	Reference
Natural direct effect	-3.08 (-3.31, -2.85)	-2.28 (-2.49, -2.06)	-1.50 (-1.65, -1.34)	-0.74 (-0.87, -0.61)	Reference
Natural indirect effect-A	-0.54 (-0.68, -0.41)	-0.49 (-0.60, -0.37)	-0.32 (-0.38, -0.26)	-0.18 (-0.21, -0.15)	Reference
Natural indirect effect-B	-0.43 (-0.49, -0.37)	-0.39 (-0.45, -0.34)	-0.28 (-0.31, -0.24)	-0.14 (-0.16, -0.12)	Reference
Controlled direct effect-00	-0.10 (-0.40, 0.19)	-0.56 (-0.88, -0.24)	-0.22 (-0.46, 0.02)	-0.34 (-0.57, -0.12)	Reference
Controlled direct effect-X0	-1.12 (-1.38, -0.86)	-1.20 (-1.46, -0.94)	-0.70 (-0.91, -0.50)	-0.55 (-0.75, -0.35)	Reference

[a] Wald type confidence intervals (CIs) were calculated as: point estimate ± 1.96 × SD, where SD was the standard deviation of the 200 point estimates from 200 bootstrapped samples.

[b] g-computation formula approach was domestic product per capita. implemented via Monte Carlo simulation, accounting for confounding due to age, gender, WHO region and country level wealth, measured by gross

Supplementary file

Title:

Education and health in 46 countries: modeling the mediating role of social factors and health behaviors

Aolin Wang[1,2*] aolinw@ucla.edu

Onyebuchi A. Arah[1-3] arah@ucla.edu

[1]Department of Epidemiology, Fielding School of Public Health, University of California, Los Angeles (UCLA), Los Angeles, California, USA

[2]California Center for Population Research (CCPR), Los Angeles, California, USA

[3]UCLA Center for Health Policy Research, Los Angeles, California, USA

[*]Corresponding author: Aolin Wang

Address: Department of Epidemiology, UCLA Fielding School of Public Health, 650 Charles E. Young Drive South, Los Angeles, CA 90095-1772, USA.

Email: aolinw@ucla.edu

Contents

1. Description of the World Health Survey (WHS) data set

Within each country, samples were probabilistically selected with every individual being assigned to a known non-zero selection probability. These samples were nationally representative except in China, Comoros, Congo, Côte d'Ivoire, India, and the Russian Federation, where the survey was carried out in geographically limited regions. This study included participants from 17 countries in the African region, 10 in the European region, six in the Americas, five in the South-East Asia region, five in the western Pacific region, and three in the Eastern Mediterranean region (Table S1). All respondents were interviewed face-to-face with the standardized WHS survey, which included questions regarding demographic, socioeconomic, and behavioral factors.

To obtain the health state measures, we performed factor analysis using polychoric correlations to account for the covariance structure of the responses to individual questions. Similar to a previous study [1], we chose one factor solution based on the high eigenvalue of the first factor (8.92, 73% as a cumulative percentage of the variance explained) and the high communalities of the original variables (between 0.36 and 0.70). Then, we used the principal component method for factor extraction and the regression scoring method to obtain the factor scores. The factor score was rescaled with 0 indicating worst health and 100 indicating best health.

2. Effect decomposition, definition, and empirical analogs

Let Y denote one's health state, X the educational attainment, $\mathbf{M_A}$ the social factors – the first set of mediators of interest, $\mathbf{M_B}$ the individual health behaviors – the second set of mediators of interest, and $\mathbf{Z}$ the set of covariates not affected by the exposure but which are assumed to be sufficient for confounding control for effects estimation. Let $Y(x, \mathbf{M_A}(x), \mathbf{M_B}(x, \mathbf{M_A}(x)))$

represent the potential Y had X been set to x, $\mathbf{M_A}$ been set to the natural value under $X=x$, $\mathbf{M_B}$ been set to the natural value under $X=x$ and $\mathbf{M_A} = \mathbf{M_A}(x)$. Let x denote any one of the four index education level: "no formal education", "less than primary school", "primary school completed", and "secondary school completed", and x^* the reference level: "high school or beyond", which were the two values of the exposure we wish to compare. Let $\mathbf{m_a^*}$ and $\mathbf{m_b^*}$ denote the reference values for $\mathbf{M_A}$ and $\mathbf{M_B}$ used in controlled direct effects. We consider factors in $\mathbf{M_A}$ and $\mathbf{M_B}$ jointly as a construct without further specifying the causal direction between factors in the same set. Effect definitions under the potential outcome (counterfactual) framework were listed in Table S4 (left column).

Under the assumptions listed below in Section 3, each effect can be expressed in terms of their empirical analogs (Table S4, right column). For a specific effect, each half of the empirical analog used to estimate the expected potential outcome under different exposure and mediator assignment is recognized as an extension of the g-computation formula [2] or the mediation formula [3] to multiple-mediator settings.

3. Assumptions for identification

To estimate the effects defined above using the observational data, we assumed stable unit treatment value assumption (SUTVA) [4,5]. general consistency, conditional exchangeability (no uncontrolled confounding), and positivity [6]. The conditional exchangeability assumption for natural effects included: (i) no uncontrolled confounding of the (X, $\mathbf{M_A}$, $\mathbf{M_B}$) – Y, X – $\mathbf{M_A}$, or (X, $\mathbf{M_A}$) – $\mathbf{M_B}$ relations given covariate set $\mathbf{Z}$, and (ii) no members of the covariate set $\mathbf{Z}$ are affected by X *or* $\mathbf{M_A}$. To identify controlled direct effect, we assumed no uncontrolled confounding of the

(X, $\mathbf{M_A}$, $\mathbf{M_B}$) – Y relationship given $\mathbf{Z}$ (CDE-00) and of the (X, $\mathbf{M_B}$) – Y relationship given $\mathbf{Z}$ (CDE-X0) respectively.

There are other ways to decompose the total effect into components representing natural direct and indirect effects [6]. The current decomposition was also discussed in the intermediate-confounding context [7,8] and has the advantage of circumventing the need for specifying an additional sensitivity parameter. This parameter represents the conditional correlation between $\mathbf{M_A}(x)$ and $\mathbf{M_A}(x^*)$ given $\mathbf{Z}$ and cannot be obtained from the observed data. Each potential outcome expression (half of the effect definition) listed in Table S1 (left column) follows the form of $Y(x_1, \mathbf{M_A}(x_2), \mathbf{M_B}(x_3, \mathbf{M_A}(x_4)))$ and for all listed expressions, we have $x_2 = x_4$ and thus is a special case [6].

4. Description of the g-computation steps

We implemented the parametric g-formula algorithm in the three steps described here. First, we used multilevel generalized linear models with random intercept for country for each of the social factors and individual health behaviors and health score to account for the clustering within country (PROC MIXED procedure for stress and health score and PROC GLIMMIX procedure for the other variables in SAS). For each prediction model, confounders including an age-squared term and preceding factors for the corresponding outcome are included based on Figure 1. Bivariate interaction terms between education and all individual level factors were included as covariates in prediction models if the terms were significant at the $P<0.15$ level. Second, we created five copies of the original sample and assigned each copy the following education level: “no formal education”, “less than primary school”, “primary school completed”,

"secondary school completed", or "high school and beyond". The pooled data set contained five synthetic cohorts under different education interventions ($X^{INT}=x^{INT}$). We then simulated potential variables for (i) social factors, (ii) health behaviors, and (iii) health sequentially using both the fixed effect estimates and the random intercept value for each country obtained from the first step. Use no formal education as index intervention as an example. According to the counterfactual definitions presented in Table S4, we simulated:

(i) each potential social factor had we assign everyone no formal education [$\mathbf{M_A}(x)$], or high school or beyond education [$\mathbf{M_A}(x^*)$], or under the specific education intervention for their own cohort [$\mathbf{M_A}(x^{INT})$, i.e. combinations of $\mathbf{M_A}(x)$ and $\mathbf{M_A}(x^*)$];

(ii) potential health behavior variables under different education intervention and potential social factor assignments: $\mathbf{M_B}(x^{INT}, \mathbf{M_A}(x^{INT}))$, $\mathbf{M_B}(x^*, \mathbf{M_A}(x^*))$, $\mathbf{M_B}(x^*, \mathbf{M_A}(x^{INT}))$, and $\mathbf{M_B}(x^{INT}, \mathbf{M_A}(x))$; and

(iii) potential health status under education intervention, potential social factor from (i) and potential health behaviors from (ii): $Y(x^{INT}, \mathbf{M_A}(x^{INT}), \mathbf{M_B}(x^{INT}, \mathbf{M_A}(x^{INT})))$ (TE), $Y(x^{INT}, \mathbf{M_A}(x^*), \mathbf{M_B}(x^*, \mathbf{M_A}(x^*)))$ (NDE), $Y(x, \mathbf{M_A}(x^{INT}), \mathbf{M_B}(x^*, \mathbf{M_A}(x^{INT})))$ (NIE-A), $Y(x, \mathbf{M_A}(x), \mathbf{M_B}(x^{INT}, \mathbf{M_A}(x)))$ (NIE-B), $Y(x^{INT}, \mathbf{M_A}=\mathbf{m_a}, \mathbf{M_B}=\mathbf{m_b})$ (CDE-00), $Y(x^{INT}, \mathbf{M_A}(x^{INT}), \mathbf{M_B}=\mathbf{m_b})$.

To reduce Monte Carlo simulation error, the simulation was done on a dataset 200 times the size of the original (obtained via resampling with replacement), but the parameter estimation were based on the original sample size. For continuous stress and health score, the simulated value was bounded within the observed values ($0 \leq \text{stress} \leq 2.32$ and $0 \leq \text{health} \leq 99.9$). The final step involved regressing each potential health variable from (iii) on education intervention to obtain the point estimate for the corresponding marginal effect.

We repeated the above three steps on 200 bootstrapped samples taken at random with replacement from the original data by country. The Wald type 95% confidence interval (CI) was calculated as: point estimate ± 1.96 × SD, where SD was the standard deviation of the 200 resultant point estimates from the final regression in the third step.

5. Explanation for the discrepancy between natural and controlled direct effects

In our study, interaction was present between education and each mediator in affecting health. In this case, the three types of DEs examined in the current study can differ because they captured the direct impact of education on health under different assignments of the mediators. The NDE evaluated the education effect had the distribution of the social factors and health behaviors for all participants achieved the same distributions as those among participants with high school or beyond education. In other words, it quantified the remaining health disparity due to education had all participants achieved the same living status and behave the same way as people with high school or beyond education did in terms of residence, employment, marriage, smoking, alcohol drinking, physical activity, and stress level. On the other hand, the CDE-00 evaluated the remaining health disparity due to education had everyone lived in urban areas, been employed and married, never smoked nor used alcohol, and been physically active and not stressed. Similarly, the CDE-X0 quantified the remaining education effect had everyone never smoked nor used alcohol, and been physically active and not stressed. Multiple values of CDE-00 and CDE-X0 were possible, depending on the value we set the mediators. The presence of such education-mediator interaction highlights the need for health behavior interventions in addition to the effort in increasing education, in that these behavioral factors not only mediate the

education impact but also moderate the strength of such impact. Health gap by education will exacerbate in the presence of unhealthy behaviors (supplement Table S3).

Another reason for such difference was that these social factors and health behaviors were not completely deterministic by educational attainment: the mediator assignments were quite different for natural versus controlled direct effects. Consider unemployment as an example: despite the lower rates seen among the most educated, the unemployment rate was far from zero (data not shown), an ideal scenario that was evaluated in the CDE-00. Also, the most educated were not the ones that had the healthiest profiles; they drank alcohol more and were more physically inactive. Some of the positive impact of reducing smoking rates or stress may be offset by the negative impact of more alcohol use and being physically inactive and thus the NDE differed from the two CDEs.

Supplementary Tables

Table S1 Country-specific sample size, percent female, mean age, and national 2003 GDP per capita (GDP/c), World Health Surveys 2002-2004.

Country	Initial sample size	N missing health score	N missing education information	N missing demographics	N missing health behaviors	Final sample size	Female (%)	Mean age	GDP/c (current USD)
African Region (AFR)									
Burkina Faso	3607	91	0	4	25	3486	50.7	41.4	332
Chad	3628	364	0	43	281	2991	51.8	41.8	292
Comoros	1411	55	0	82	21	1262	57.0	47.5	569
Congo	1937	414	11	247	540	1212	52.4	40.0	1039
Côte d'Ivoire	2402	248	13	86	117	2027	42.0	40.3	905
Ethiopia	3775	442	2	5	254	3115	51.1	41.9	117
Ghana	3302	114	34	25	96	3047	55.7	45.1	603
Kenya	3449	47	0	5	65	3332	57.9	42.6	504
Malawi	3761	126	1	16	39	3519	56.9	42.3	262
Mali	3176	2450	15	541	646	514	43.7	46.2	376
Mauritania	3011	295	5	114	604	2108	61.7	43.2	527
Mauritius	3385	302	0	2	24	3066	52.7	45.2	4830
Namibia	3284	1201	3	205	255	2016	59.3	42.6	2489
Senegal	2542	553	9	609	769	1247	48.2	42.9	643
South Africa	1876	331	1	39	89	1444	53.1	41.8	3739
Swaziland	2396	870	8	786	897	1390	54.0	43.8	1704
Zambia	2847	333	0	2	15	2490	53.5	41.2	399
Zimbabwe	3020	117	0	45	3020	0	64.8	43.1	529
Region of the Americas (AMR)									
Brazil	4209	548	0	139	4209	0	56.8	45.6	3039
Dominican Republic	3758	61	1	5	67	3638	53.2	45.8	2210
Ecuador	3869	326	7	97	1855	1801	55.7	45.0	2442
Guatemala	3836	143	173	100	105	3351	61.1	44.6	1817
Mexico	32129	0	0	0	0	32129	57.5	45.1	6601
Paraguay	4062	45	0	1	30	3993	54.6	44.9	1159
Uruguay	2680	22	0	3	17	2640	51.8	48.7	3622
Eastern Mediterranean Region (EMR)									

Table S1 Country-specific sample size, percent female, mean age, and national 2003 GDP per capita (GDP/c), World Health Surveys 2002-2004.

Country	Initial sample size	N missing health score	N missing education information	N missing demographics	N missing health behaviors	Final sample size	Female (%)	Mean age	GDP/c (current USD)
Morocco	4184	4184	0	257	233	0	58.3	44.9	1684
Pakistan	5030	192	1	29	546	4315	45.3	41.6	597
Tunisia	4213	344	0	27	495	3430	54.9	45.9	2788
United Arab Emirates	984	65	3	0	64	863	47.8	40.3	36906
European Region (EUR)									
Austria	940	940	0	17	940	0	62.5	48.0	32019
Belgium	875	875	0	107	875	0	56.2	48.8	30675
Bosnia and Herzegovina	917	386	0	1	5	526	58.3	50.1	2182
Croatia	932	20	0	1	11	902	59.9	54.1	7857
Czech Republic	828	90	1	5	11	729	55.6	51.3	9732
Denmark	959	959	1	0	959	0	53.0	52.2	40517
Estonia	928	41	0	3	10	876	63.7	52.3	7333
Finland	944	944	0	1	944	0	55.3	55.1	32814
France	889	889	0	34	889	0	60.6	46.6	29657
Georgia	2441	16	0	64	12	2352	57.9	52.2	874
Germany	1147	1147	1	35	1147	0	59.9	53.2	29864
Greece	916	916	0	2	916	0	50.1	53.8	18269
Hungary	1262	315	1	4	1262	0	59.4	53.0	8355
Ireland	866	866	5	113	866	0	56.0	48.5	40759
Israel	1075	1075	6	12	1075	0	58.1	48.3	19407
Italy	907	907	0	7	907	0	58.2	51.1	27135
Kazakhstan	4111	105	0	2	3	4001	65.8	43.3	2091
Latvia	763	72	0	1	763	0	68.3	54.6	5632
Luxembourg	620	620	0	3	620	0	50.8	48.3	65088
Netherlands	825	825	0	825	825	0	70.3	51.3	35385
Norway	872	872	2	872	872	0	50.8	50.9	50165
Portugal	911	911	0	0	911	0	62.5	54.4	15802
Russian Federation	4070	278	21	10	180	3605	64.6	54.0	2970
Slovakia	1922	680	573	598	613	1170	63.9	43.8	6307
Slovenia	512	30	1	512	4	0	54.3	50.9	14914

Table S1 Country-specific sample size, percent female, mean age, and national 2003 GDP per capita (GDP/c), World Health Surveys 2002-2004.

Country	Initial sample size	N missing health score	N missing education information	N missing demographics	N missing health behaviors	Final sample size	Female (%)	Mean age	GDP/c (current USD)
Spain	5959	187	0	5	31	5741	59.1	54.9	21583
Sweden	908	908	0	21	908	0	58.7	53.9	37030
Turkey	9678	344	7649	9678	9678	0	56.3	45.3	4595
Ukraine	2517	205	0	234	74	2048	65.3	50.8	1088
United Kingdom	1069	1069	0	79	1069	0	62.9	53.8	32561
South-East Asia Region (SEAR)									
Bangladesh	4528	821	1	9	49	3666	52.2	42.6	427
India	8140	1640	56	76	369	6238	51.7	43.0	541
Myanmar	4996	4	0	0	3	4989	57.3	44.6	200
Nepal	6979	49	0	2	29	6900	56.3	43.3	264
Sri Lanka	5642	710	0	375	369	4303	54.0	44.9	968
Western Pacific Region (WPR)									
Australia	3316	3316	75	3316	3316	0	58.0	49.7	28017
China	3674	54	0	5	3	3614	51.4	47.2	1267
Lao People's Democratic Republic	4060	86	9	3	50	3919	52.7	41.8	358
Malaysia	5250	203	4	20	66	4996	56.8	44.2	4607
Philippines	8380	110	0	9	58	8207	54.6	42.6	1016
Viet Nam	2983	1428	0	8	26	1535	55.5	43.4	475

Table S2 Characteristics of 66,531 participants excluded from the main analyses due to missing values in one or more of the variables, World Health Survey 2002-2004.

Characteristics	Sample size	Descriptive statistics
Total, N (%)		
Age, mean (SD)	66237	46.7 (15.6)
Females, N (%)	66474	37961 (57.1)
Educational attainment	57835	
No formal education		14595 (25.2)
Less than primary school		5593 (9.7)
Primary school completed		10882 (18.8)
Secondary school completed		11044 (19.1)
High school and beyond		15721 (27.2)
Social factors		
Living in rural areas, N (%)	59677	27165 (45.5)
Unemployment, N (%)	61638	33309 (54)
Not Married, N (%)	55639	20798 (37.4)
Individual health behaviors		
Currently smoking, N (%)	45080	10857 (24.1)
Alcohol use, N (%)	43458	14159 (32.6)
Physical inactivity, N (%)	40637	31416 (77.3)
Stress (log transformed), mean (SD)	42956	0.9 (0.8)

Table S3 below shows the parameter estimates from a regular linear mixed model for health score, conditional on education, social factors, health behaviors and stress, and covariates while allowing for bivariate product terms between education level and every mediator and individual level confounders. The result presented below cannot be directly compared to the marginal CDE-00 presented in the main text because those effects are marginalized over covariates, representing the population average. Due to the presence of interaction between education and sex, conditional estimates were presented for males and females separately.

Table S3 Conditional controlled direct effect estimate (95% confidence interval) for educational attainment on health using linear mixed model with random intercept for country[a], World Health Survey 2002-2004.

	No formal education	**Less than primary school**	**Primary school completed**	**Secondary school completed**	**High school or beyond**
Males					
Conditional CDE-00[b]	0.24 (-0.38, 0.86)	-0.76 (-1.46, -0.07)	-0.47 (-1.07, 0.13)	-0.92 (-1.47, -0.36)	Reference
Conditional CDE-01[c]	-4.22 (-4.80, -3.63)	-2.86 (-3.53, -2.20)	-3.38 (-3.94, -2.83)	-3.34 (-3.84, -2.84)	Reference
Females					Reference
Conditional CDE-00	-0.03 (-0.67, 0.61)	-1.28 (-2.00, -0.55)	-0.29 (-0.92, 0.34)	-0.49 (-1.09, 0.10)	Reference
Conditional CDE-01	-4.49 (-5.18, -3.80)	-3.38 (-4.19, -2.57)	-3.21 (-3.89, -2.52)	-2.92 (-3.54, -2.30)	Reference

[a] Model included bivariate product terms between education level and every mediator and individual level confounder.
[b] Conditional CDE-00 represents the controlled direct effect when fixing both social factors and health behaviors at reference levels (i.e. living in urban areas, being employed and married, not smoking, never used alcohol, being physically active and not stressed) for 45 year-old participants.
[c] Conditional CDE-01 represents the controlled direct effect when fixing social factors at reference levels (i.e. living in urban areas and being employed and married) but health behaviors at index levels (i.e., smoking, ever used alcohol, being physically inactive and having 1-unit increase in stress score) for 45 year-old participants.

Table S4 Effect definition and empirical analogs, applied to World Health Survey 2002-2004[a].

Effect	Counterfactual definition	Empirical analog[b]
TE	$\mathrm{E}\{Y(x, \mathbf{M_A}(x), \mathbf{M_B}(x, \mathbf{M_A}(x))) - Y(x^*, \mathbf{M_A}(x^*), \mathbf{M_B}(x^*, \mathbf{M_A}(x^*)))\}$	$\sum_{\mathbf{z}}\sum_{\mathbf{m_a}}\sum_{\mathbf{m_b}}\{E(Y\|x,\mathbf{m_a},\mathbf{m_b},\mathbf{z})P(\mathbf{m_b}\|x,\mathbf{m_a},\mathbf{z})P(\mathbf{m_a}\|x,\mathbf{z}) - E(Y\|x^*,\mathbf{m_a},\mathbf{m_b},\mathbf{z})P(\mathbf{m_b}\|x^*,\mathbf{m_a},\mathbf{z})P(\mathbf{m_a}\|x^*,\mathbf{z})\}P(\mathbf{z})$
NDE	$\mathrm{E}\{Y(x, \mathbf{M_A}(x^*), \mathbf{M_B}(x^*, \mathbf{M_A}(x^*))) - Y(x^*, \mathbf{M_A}(x^*), \mathbf{M_B}(x^*, \mathbf{M_A}(x^*)))\}$	$\sum_{\mathbf{z}}\sum_{\mathbf{m_a}}\sum_{\mathbf{m_b}}\{E(Y\|x,\mathbf{m_a},\mathbf{m_b},\mathbf{z}) - E(Y\|x^*,\mathbf{m_a},\mathbf{m_b},\mathbf{z})\}P(\mathbf{m_b}\|x^*,\mathbf{m_a},\mathbf{z})P(\mathbf{m_a}\|x^*,\mathbf{z})P(\mathbf{z})$
NIE-A	$\mathrm{E}\{Y(x, \mathbf{M_A}(x), \mathbf{M_B}(x^*, \mathbf{M_A}(x))) - Y(x, \mathbf{M_A}(x^*), \mathbf{M_B}(x^*, \mathbf{M_A}(x^*)))\}$	$\sum_{\mathbf{z}}\sum_{\mathbf{m_a}}\sum_{\mathbf{m_b}} E(Y\|x,\mathbf{m_a},\mathbf{m_b},\mathbf{z})P(\mathbf{m_b}\|x^*,\mathbf{m_a},\mathbf{z})\{P(\mathbf{m_a}\|x,\mathbf{z}) - P(\mathbf{m_a}\|x^*,\mathbf{z})\}P(\mathbf{z})$
NIE-B	$\mathrm{E}\{Y(x, \mathbf{M_A}(x), \mathbf{M_B}(x, \mathbf{M_A}(x))) - Y(x, \mathbf{M_A}(x), \mathbf{M_B}(x^*, \mathbf{M_A}(x)))\}$	$\sum_{\mathbf{z}}\sum_{\mathbf{m_a}}\sum_{\mathbf{m_b}} E(Y\|x,\mathbf{m_a},\mathbf{m_b},\mathbf{z})\{P(\mathbf{m_b}\|x,\mathbf{m_a},\mathbf{z}) - P(\mathbf{m_b}\|x^*,\mathbf{m_a},\mathbf{z})\}P(\mathbf{m_a}\|x,\mathbf{z})P(\mathbf{z})$
CDE-00[c]	$\mathrm{E}\{Y(x, \mathbf{M_A}=\mathbf{m_a}^*, \mathbf{M_B}=\mathbf{m_b}^*) - Y(x^*, \mathbf{M_A}=\mathbf{m_a}^*, \mathbf{M_B}=\mathbf{m_b}^*)\}$	$\sum_{\mathbf{z}}\{E(Y\|x,\mathbf{m_a}^*,\mathbf{m_b}^*,\mathbf{z}) - E(Y\|x^*,\mathbf{m_a}^*,\mathbf{m_b}^*,\mathbf{z})\}P(\mathbf{z})$
CDE-X0[d]	$\mathrm{E}\{Y(x, \mathbf{M_A}(x), \mathbf{M_B}=\mathbf{m_b}^*) - Y(x^*, \mathbf{M_A}(x^*), \mathbf{M_B}=\mathbf{m_b}^*)\}$	$\sum_{\mathbf{z}}\sum_{\mathbf{m_a}}\{E(Y\|x,\mathbf{m_a},\mathbf{m_b}^*,\mathbf{z})P(\mathbf{m_a}\|x,\mathbf{z}) - E(Y\|x^*,\mathbf{m_a},\mathbf{m_b}^*,\mathbf{z})P(\mathbf{m_a}\|x^*,\mathbf{z})\}P(\mathbf{z})$

[a] Y: health score, X: educational attainment (x represents each index level of education and x^* represents the reference level of education – high school or beyond), $\mathbf{M_A}$: social factors including residence, unemployment, and being unmarried, $\mathbf{M_B}$: individual health behaviors including smoking, alcohol use, physical inactivity, and stress), $\boldsymbol{Z}$: age, sex, country level gross domestic product per capita (in current US$) in 2003, and WHO region.

[b] We use $E(Y|x, \mathbf{m_a}, \mathbf{m_b}, \mathbf{z})$ as a shorthand for $E(Y|X = x, \mathbf{M_A} = \mathbf{m_a}, \mathbf{M_B} = \mathbf{m_b}, \mathbf{Z} = \mathbf{z})$, $P(\mathbf{m_b}|x, \mathbf{m_a}, \mathbf{z})$ as a shorthand for $P(\mathbf{M_B} = \mathbf{m_b}|X = x, \mathbf{M_A} = \mathbf{m_a}, \mathbf{Z} = \mathbf{z})$ and $P(\mathbf{m_a}|x, \mathbf{z})$ as a shorthand for $P(\mathbf{M_A} = \mathbf{m_a}|X = x, \mathbf{Z} = \mathbf{z})$. Summations are replaced by integrals and the probability functions by appropriate density functions for continuous variables (e.g. stress).

[c] CDE-00 represents the controlled direct effect of education on health when participants lived in urban area, being employed and married, did not smoke nor drink alcohol, being physically active and having no stress ($\mathbf{m_a}^*$ and $\mathbf{m_b}^*$ equal to zero).

[d] CDE-X0 represents the controlled direct effect of education on health when participants did not smoke nor drink alcohol, being physically active and having no stress ($\mathbf{m_b}^*$ equals to zero).

Supplementary Figure

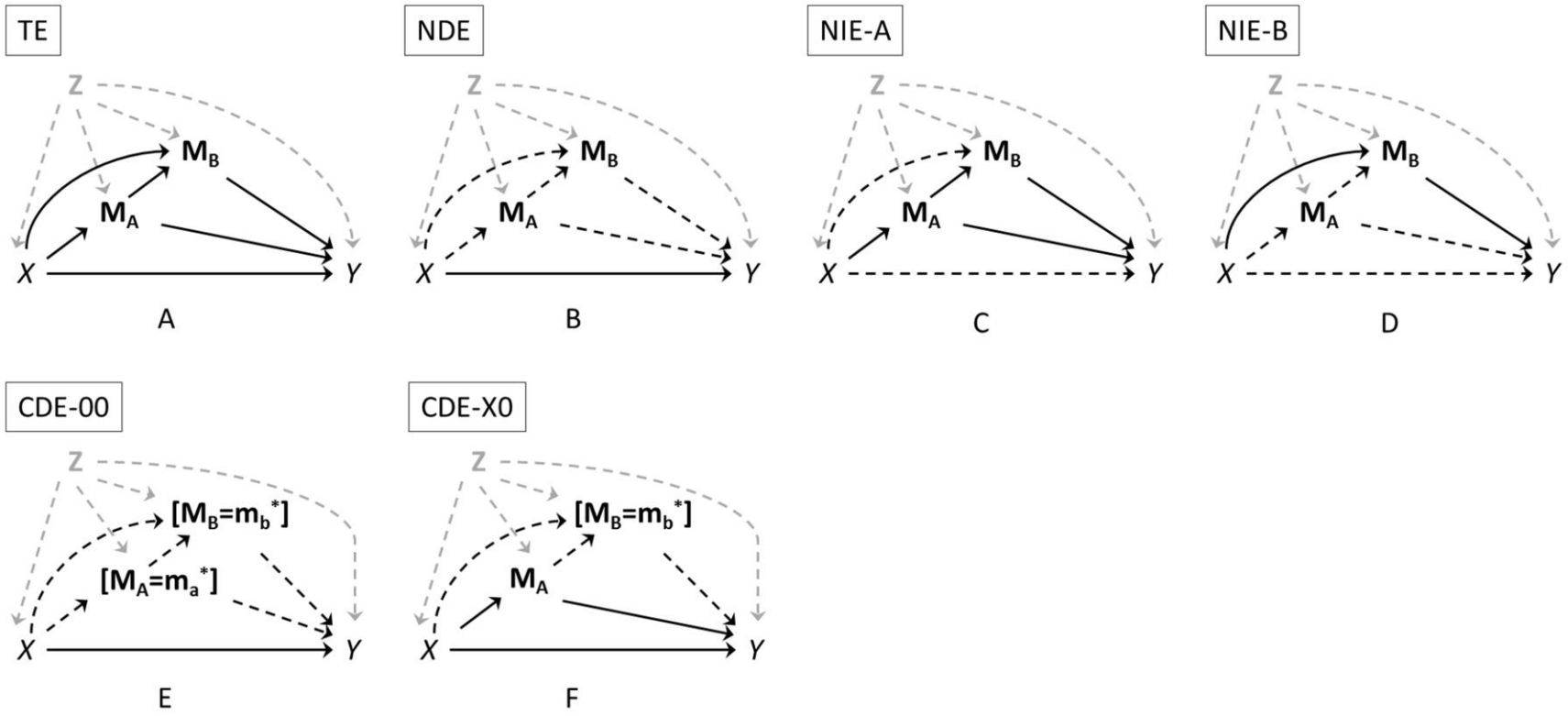

Figure S1. Graphical representations for different types of effect of interest.

Legends: *X*: educational attainment, $\mathbf{M_A}$: social factors including residence, unemployment, and marital status; $\mathbf{M_B}$: individual health behaviors including smoking, alcohol use, physical inactivity, and stress; *Y*: individual health; and **Z**: contextual and predisposing factors including WHO region, country level wealth and individual age and sex; TE: total effect; NDE: natural direct effect; NIE-A: natural indirect effect that is through $\mathbf{M_A}$ and its consequences; NIE-B: natural indirect effect that is through $\mathbf{M_B}$ only; CDE-00: controlled direct effect while fixing $\mathbf{M_A}=\mathbf{m_a}^*$ and $\mathbf{M_B}=\mathbf{m_b}^*$; CDE-X0: controlled direct effect while fixing only $\mathbf{M_B}=\mathbf{m_b}^*$ and allowing $\mathbf{M_A}$ to respond to *X*. Black solid lines represent the corresponding effect of *X* on *Y*. NDE, NIE-A, and NIE-B add up to TE.

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