

On the Intergenerational Transmission of Health Inequality

Donne Will,¹ Fuzhou Wang^{2,*}

1. Group of Ethics and Humanity, Division of Society and Politics, The BASE, Chapel Hill, NC 27510, USA

2. Group of Neuropharmacology and Neurophysiology, Division of Neuroscience, The BASE, Chapel Hill, NC 27510, USA

*: All corresponding should be sent to Dr. Fuzhou Wang.

Authors' Contact: Donne Will, Ph.D., E-mail: donne.will@basehq.org; Fuzhou Wang, M.D., Ph.D., E-mail: fred.wang@basehq.org.

DOI: <https://doi.org/10.15354/si.21.re262>

The authors declare no competing interest.

Cumulating evidence from social science has indicated the intergenerational transmission of inequality is majorly derived from the economic imbalance. In line with this, the same thing happens in health, and emerging evidence has been documenting its transmissible property. No matter the genetic or non-genetic causes, health inequality inevitably plays its role in contributing to the underlying health-associated despoliation in life. Each individual shows an eventual health state where equality and inequality reach a time-dependent temporary condition in which the balancing point fluctuates back and forth. To promote the overall health status, it is crucial to promote and optimize the positive health characteristics to get equilibrium between positive and negative. This review discussed the underlying mechanisms of intergenerational transmission of health inequality by focusing on different types of contributors to the inequality and providing prospective insights into the potentially beneficial strategies that can optimize overall individual health.

Keywords: Inequality; Intergenerational transmission; Health; Epigenetics; Equilibrium

Science Insights, 2021 December 28; Vol. 39, No. 5, pp.407-418.

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Introduction

CASE #1: A 55-year-old Asian female, visiting her daughter here in the USA for six months, was a former farmer in her original country. Tuberculosis (TB) test was positive, and she had liver cirrhosis. She underwent TIPS and TB treatment for four months. Three months post-TIPS, the patient complained of difficulty swallowing and passing through the esophagogastroduodenoscopy, so esophageal carcinoma was suspected. Given the high risk of biopsy, the patient received palliative stenting of the esophagus. The patient's family history indicated that her oldest daughter has HBV infection, her

younger son had HBV infection and TB, and her younger daughter had TB with treatment completed. This patient had low health consciousness caused by poor economic conditions, which caused her to be unaware of the whole process of disease development. As a result, she lost the opportunity of effective treatment until the end-stage of the disease. This is a typical case of intergenerational transmission of "economic-health" inequality.

Inequality plagues the world everywhere (1). When everyone expects equality, it is actually just a utopian idealized theoretical form. Just like "Yin-Yang", there is always a shift between equality and inequality, and the balance between the two

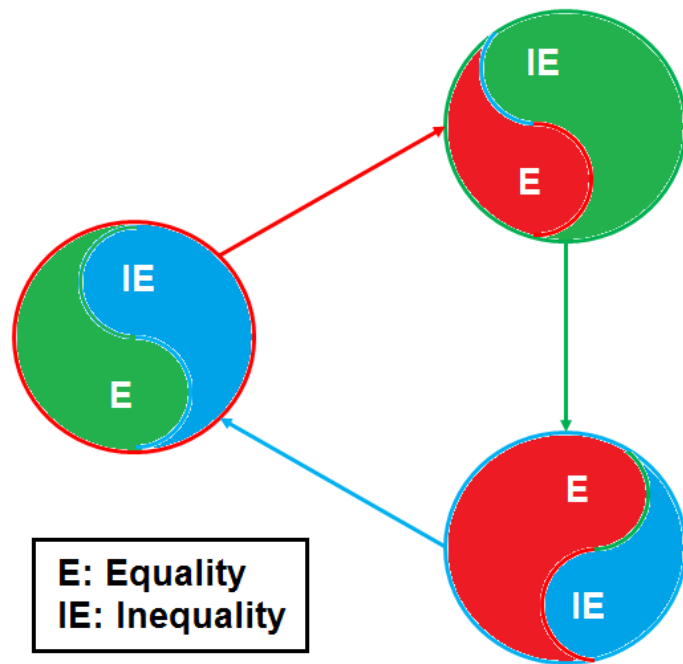


Figure 1. The Equilibrium between Equality and Inequality.

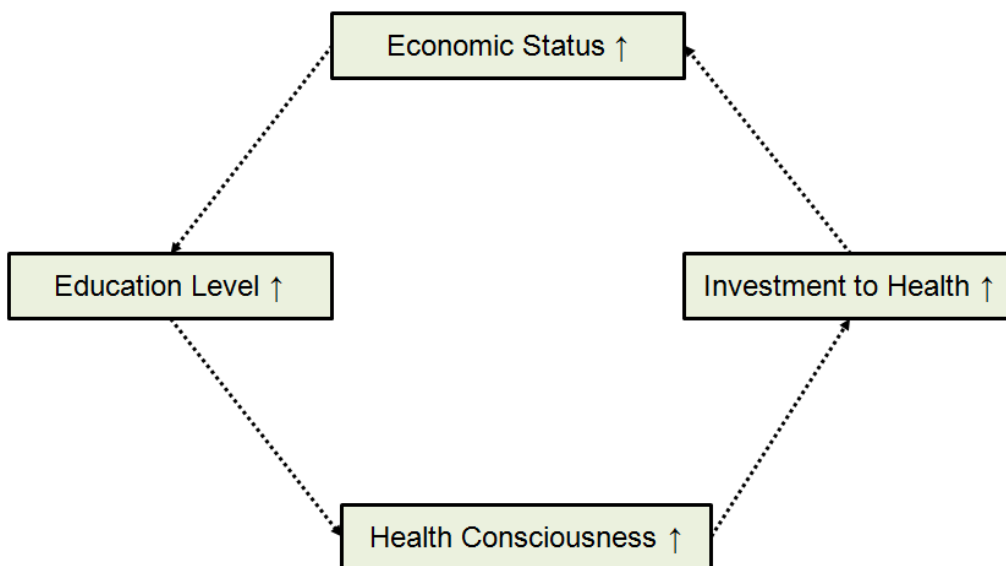


Figure 2. Interaction between Economy, Education, and Health.

is also moving always. As far as the whole system is concerned, it exists in a state of equilibrium between both (**Figure 1**).

The underlying deep equality has various external manifestations of inequality. The occurrence of inequality stems from many reasons. It is a multi-factor carrier, which includes both external and internal factors. In most cases, the economy is often

regarded as the most critical cause of inequality (2-4). However, it can only be one of the possible external factors. Even so, the economy is still inextricably linked to various types of inequality, and it will be transmitted between generations due to differences in economic levels (5, 6).

As the basic external manifestation of individuals, health

has obvious characteristics of inequality (7, 8). First of all, in terms of genetic traits, each of us has health differences since birth. Although we cannot accurately distinguish between the conditions of the mother before birth and the impact of investment in childhood after birth, health inequality has existed since the beginning and significantly affects the overall long-term outcome of the individual (9). Moreover, the long-term outcome caused by this kind of health inequality will be combined with its own genetic information to be transmitted between generations (10).

Naturally, genetic inheritance is the biological basis for intergenerational transmission of health inequality. Especially when genetic diseases exist, the resulting intergenerational transmission of health inequality is even more obvious. Regardless of the genetic disease, the result is that the health of the offspring is seriously affected, and a negative vicious positive feedback loop that is closely related to its economic status is generated. Thus, the magnification of this inequality is passed on from generation to generation indefinitely (1). Not merely that, genetically related health inequality can hardly be blocked, and the only way to block it is the generation severance.

In addition to the intergenerational transmission of health inequality caused by genetic factors, external social factors are also one of the important contributors that cause health inequality to occur and achieve intergenerational transmission, such as smoking and alcoholism (11, 12). These social factors themselves (such as smoking) will be transmitted between generations, and the resulting health problems will inevitably lead to more bad habits and poor economic conditions related to the intergenerational transmission of unfavorable health (13). Because families with poorer economic conditions are more likely to be affected by social undesirable factors, the resulting health inequality is more likely to be transmitted between generations through their poor economic conditions (14, 15) (**Figure 2**).

Differences in economic conditions are often regarded as one of the underlying causes of acquired health inequality. It is easy to be understood and apparent. Macroscopically, the regional economy level is closely related to the overall health of local residents (16). A direct manifestation is a direct correlation between the average life expectancy of residents and the economic level (17). At the micro-level, the financial status of a family is closely related to the health of family members (18).

In most cases, the economic level is positively correlated with the family's education level, and high-level education dramatically improves health awareness, which will undoubtedly enable such families to make more investments in the health of their members (19). Therefore, the excellent family economic level is precisely a very pivotal endorsement of the health of its members. On the contrary, low-income family finances will turn the whole situation in the opposite direction (20).

Mechanisms

Genetic Inheritance

Case #2: A 42-year-old Caucasian female, a practicing nurse, has a family history of maternal diabetes mellitus (DM). She was diagnosed with Type 1 DM at the age of five with the primary treatment of insulin injection. At 38 years old, she underwent below-knee amputation due to

DM vascular disease in the left lower extremity. The second toe of the right foot was amputated due to a non-healing wound at 39 years. At the age of 42, the right lower extremity circulatory disorder was diagnosed, and both kidneys were end-stage renal disease stage 4, and she was on the list of kidney transplantation. She was no longer working since the below-knee amputation on the left. Due to her physical disability, her economy and quality of life have declined significantly. She lost hope in life and was subsequently diagnosed with severe depression and attempted two suicides. This is a typical case of intergenerational transmission of health inequality caused by genetic factors.

The transmission of DNA sequence from one generation to the next is the underlying basis of genetic inheritance that works the same for the normal phenotype and the abnormal as well (21). Disease-related genetics is an unavoidable underlying cause that maintains and transmits the pathogenic genes to offspring. Suppose specific disease-causing genes exist in a family. In that case, the health challenges faced by the family under the same external conditions and environment are more significant than those of non-pathogenic gene-carrying families. The transmission of health inequality between generations of the family happened naturally. There is currently nothing to be done about the unequal intergenerational transmission of health with genetic genes as the underlying cause. The so-called gene therapy would leave a vicious cycle without improving a patient's health (22). The only thing we can do is optimize the acquired environment to reduce the adverse effects of genetic diseases or delay the occurrence of genetic disorders (23). Of course, does this genetic-related health inequality mean that future generations are unequal in any other respect? The answer is obviously no. This is a highly complex situation, and various events are interrelated. But what is certain is that this kind of intergenerational transmission of health inequality must impact the offspring (24). Still, it is of different degrees and significantly affected by the external environment. Health inequality from genetic inheritance is not our focus herein of this review.

Non-genetic Reasons Epigenetic Signature

Epigenetics is a molecular process that is different from genetics, which does not change the DNA sequence in the organism but only modifies and regulates the genome (25). It includes DNA methylation, acetylation, microRNA interaction, phosphorylation, etc. Epigenetic mechanisms modify individual responses to environmental factors (26). It has been confirmed that epigenetic information can be transmitted between generations (27, 28). Whether in animals or humans, epigenetic changes caused by the environment cannot be ignored in the phenotypic modification of offspring (29). This has become the mainstream mechanism and cause of intergenerational transmission of health inequality (30).

Generally, three possibilities exist for the offspring to be exposed to the environment (31): (i) in utero exposure of developing embryos (F1); (ii) prenatal exposure of the fetus (F2); (iii) the third generation (F3) still has the phenotypic changes come from embryos of the first generation (**Figure 3**).

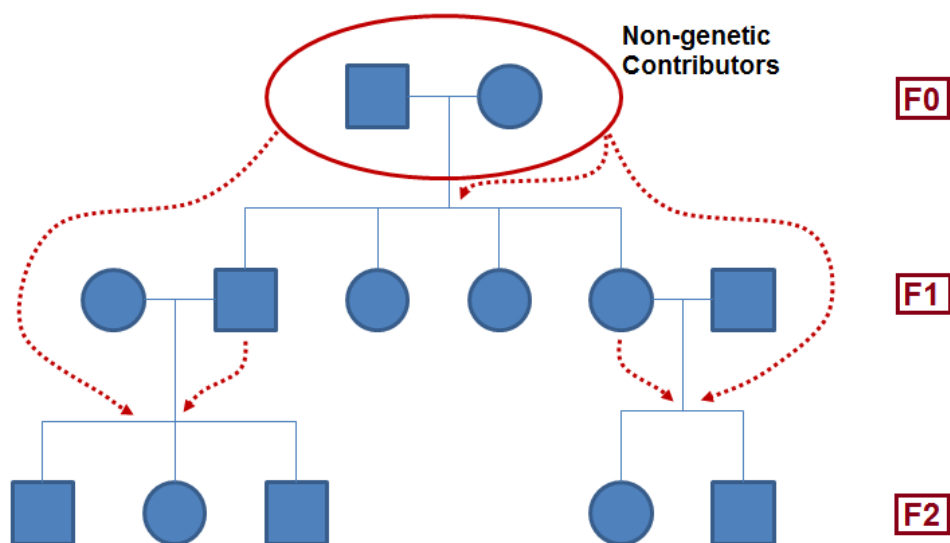


Figure 3. The Role of Non-genetic Contribution to the Intergenerational Transmission of Health Inequality.

No matter what kind of epigenetic modification, its ultimate goal is to realize the regulation of specific gene expression and then affect the biological behavior of the individual. It finally appeared in a different state of health (32). Moreover, this epigenetic change at the molecular level will continue to exist in the affected individuals and will affect the biological behavior of the offspring along with fertilization and the behavior of the parents after the offspring is born.

Genetic Polymorphism

Genetic polymorphisms are the simultaneous occurrence of two or more discontinuous genotypes or alleles in a population (33). It determines the diversity of individuals (34). In general, a susceptible gene is strongly associated with an individual's susceptibility to a particular disease (35). Moreover, the internal and external environment will cause significant alterations in the expression of a susceptible gene related to the occurrence of a specific disease (36). Buck and colleagues found that the *CHRNA5* single nucleotide polymorphism rs16969968, which leads to an aspartic acid to asparagine substitution at amino acid position 398 (D398N) in the alpha-5 nicotinic acetylcholine receptor subunit, i.e., N397 variant, may protect against the intergenerational transmission of DNE-induced neurodevelopmental disorder-like behaviors in mice (37). Parent (G1) maternal acceptance was associated with higher offspring (G2) acceptance among those G2 participants with the oxytocinergic (*OXTR*) rs1042778 GG/GT genotype, but not among those with the TT genotype, indicating that oxytocinergic genes may influence sensitivity to the quality of parent-child relationship (38). In addition, women with a high *OXTR* expressing genotype rs237895 are more susceptible to childhood maltreatment-related impairments in maternal behavior that, in turn,

predict attachment security in their children, supporting the role of the oxytocin system in the intergenerational transmission of risk associated with maternal childhood maltreatment (39). Although the evidence of genetic polymorphism in the intergenerational transmission of health inequality is not robust, it still can be seen from the available data regarding its contributing role in health inequality carried on between generations.

Small Non-coding RNAs

Since the discovery of micro RNAs (miRNAs) in 1993 (40), a number of different types of small RNAs with < 40 nts have been discovered that play critical roles in biology. Small RNAs include miRNAs, endogenous silencing RNAs (endo-siRNAs), and the germ-line enriched P-element induced wimpy testis (piwi)-interacting RNAs (piRNAs). They take part in the processes of transcriptional regulation (transcriptional regulation by targeting DNA methylation and repressive chromatin formation), post-transcriptional regulation (degradation or deadenylation of target RNA), and translational repression (41).

The implication of sperm small RNAs in the intergenerational inheritance of paternal environmental conditions was demonstrated by studies using direct microinjections of small RNAs purified from the sperm of exposed males into control zygotes (42). This study provided direct evidence that paternal environmental information could be transmitted through sperm small RNAs. Other studies observed stress-related behavior inheritance from the paternal side by small RNAs mechanism (43, 44). Similarly, tRFs potentially act as epigenetic information carriers of paternal dietary information (45). Overall, these studies suggest that different environmental exposures direct distinct small RNA changes in sperm: diet majorly affects tRFs, whereas psychological stress influences miRNAs. Envi-

ronmental changes function as an essential modulator to the sperm epigenome throughout life, but it would be more vulnerable at early developing stages like embryogenesis and primordial germ cell during which rapid cell division occurs.

Health Characteristics with Inequality Property

The intergenerational transmission of health inequality includes two major aspects: one is positive, and the other is negative. Positive health inequality means that when a person has health traits superior to others (such as Trait EI, Resilience, self-control, and generosity), the advantage is that they can more easily face and deal with difficult problems or psychological events they are facing, preventing them developing into severe consequences. This positive health inequality is showed up after comparison with those with a non-positive trait. It is a dominant feature and is worthy of encouraging and training. This kind of intergenerational transmission of positive inequality is expected to be obtained and has a particular inhibitory effect on negative counterparts. This review will only discuss above mentioned four favorable properties. Of course, when individuals lack these properties, their performance is naturally at a disadvantage. On the contrary, negative health inequality takes adverse life events as the carrier, harming individuals' physical and mental health. Moreover, in reality, most of them fall into this category.

Positive Inequality of Health Characters Trait Emotional Intelligence

Trait emotional intelligence (trait EI), the perceptions of people's emotional world, is a vast, hierarchical, multidimensional construct that could promote positive development in adolescents and predict affect-related outcomes (46). Individuals with high trait EI can efficiently deal with challenging conditions and generally have a good relationship with people around them. The development of emotional intelligence is a significant contributor to greater happiness and emotional well-being (47). It is an encouraging feature an individual should be trained to help get better psychological health that contributes to the overall health status, which could be passed on to successive generations.

Resilience

Resilience is the capacity to recover from difficult life events (48). It is beneficial for health by giving more flexibility in an individual's life. The higher this psychodynamic property an individual has, the easier it is for them to recover from the adversities, the healthier their lives would get. Eventually, they deserve more health bonuses (49). Compared with those with more and strong resilience, those with less and weak resilience would demonstrate low levels of flexibility, adaptability, and perseverance in their lives. Therefore, this is the difference of resilience among individuals when they cope with and work through challenging life experiences. That is inequality. When this kind of inequality of resilience is transmitted from generation to generation, it will inevitably get individuals to be prepared with a more flexible manner to face challenges if they got more resiliency.

Self-Control

Self-control is the ability an individual has to manage impulses, emotions, and behavior to execute function properly and the suite of skills that the individual can use to plan, monitor, and attain goals (50). Self-control is not self-deprivation, but it often redefines what is pleasurable to you to keep destructive behaviors in check. Through self-control, individuals can always avoid situations where they know they will confront temptation. For instance, if smoking is a big temptation, strong self-control will help stay away from smoking triggers (51). Of course, weak self-control will quickly get individuals trapped by destructive behaviors that negatively affect their overall health state. Self-control can be transmitted intergenerationally through offspring's attachment to parental models (52, 53). Even the level of self-control tends to wax and wane over a day. In contrast, it allows people to direct their attention despite challenging competing stimuli and underlies their achievements.

When people fall into the trap of temptations like drugs and food, their life and health will undoubtedly change as a consequence. These changes will cause significant changes in their cellular epigenetic traits that subsequently pass on to subsequent generations. This is obvious in families where specific family-favored stuff will pose a similar effect on both parents and children as found by Qiu and Hou that family socio-demographic factors are strongly associated with their food preference, eating behavior, and physical activities, which eventually affects the overall health status of the family especially children and adolescents (54). Of course, parental self-control in this situation is crucial to the whole family's health. Therefore, strong self-control capability with the favored positive direction would contribute to developing a healthier lifestyle that will substantially improve the health state and benefit the intergenerational transmission of self-control-related good health, or vice versa.

Generosity

Unlike pure altruism, generosity is a learned character trait that involves both attitude and action from which the moral good is expressed. Still, the vices rejected such as greed, selfishness, and fear. Generosity was not just a virtue of individuals but a corporate responsibility, institutionalized in myriad ways (55). The study from Wilhelm and colleagues showed that generosity could be transmitted down to children from their charitable parents (56). Cumulating evidence indicated that generosity could improve health by lowering blood pressure (57), reducing stress and depression levels (58), reducing inflammatory cytokine levels of interleukin-6 (59), and longer life expectancy (60). Not just the positive contribution of generosity produced to the overall health, but its role in helping givers and their family members' generous property more at the molecular level, and this health-beneficial characteristic could transmit down to upcoming new generations. However, the opposite situation is greedy and mean that work differently. To promote a healthier life, generosity is strongly suggested but not greediness.

Negative Inequality of Health Characters

We have to face many health-related inequalities throughout our lives, and most of them are negative. However, regardless of the level and degree of adverse health inequality, transmission be-

tween generations naturally exists and cannot be avoided. Therefore, we herein in this review will only focus on trauma, violence and abuse, and addiction as an example.

Trauma

Experiencing severe traumatic events, like wars, Holocaust, genocide, catastrophic events, car accidents, etc., would cause responsive changes physically and psychologically that dramatically impact patients' health through underlying molecular mechanisms at the cellular level. The evidence of intergenerational traumatic transmission first appeared in 1966 with the report of behavioral problems in the offspring of Holocaust survivors (61). Almost all the traumatic suffers experience psychological and psychiatric stress that lasts the whole life long for the patient and subsequently transmits down to their upcoming generations.

For traumatic injuries, the victims are often passively suffering. The harm caused by the trauma is the indirect contributor to the intergenerational transmission, but not the trauma itself (62). In most cases, the victims themselves are unwilling to repeat their traumatic experiences, let alone become another producer of similar trauma. Under normal and sensible circumstances, they will use the trauma as educational material to inform and remind latecomers to avoid such a bad experience (63). However, in sporadic cases, trauma victims will also evolve into perpetrators of similar trauma (64). Take China's Cultural Revolution, for example. Due to abnormal historical and environmental factors, many victims of the Cultural Revolution have become perpetrators after a period of time (65, 66). Although many possible factors can trigger its change, the biological traces of its experience on its body and psychology cannot be erased. This is precisely the initiating factor leading to the fundamental difference. Therefore, how to break the cycle of negative health inequality caused by trauma requires a strong sense of justice, responsibility, self-control, and a fair and just social and political environment.

Furthermore, resilience capability will significantly help if traumatic individuals possess this flexible psychological well-being. If all these are not the case, catastrophic trauma will undoubtedly harm the health of the individual and will lead to the intergenerational transmission of health inequality. As for how many generations of health inequality caused by this impact can be passed between generations or the suppression lasts, there is currently no available evidence to rely on.

Violence and Abuse

Whether it is violence or abuse, both will have a tremendous negative impact on the victim's body and mind and even lead to PTSD (67). Although it is controversial whether this external, violent, or abusive behavior is transmitted between generations (68), the transmission tendency of this behavior is evident. From a statistical point of view, it may be "none", but as far as the individual is concerned, many realistic examples and empirical studies provide a solid foundation for it, that is, "yes". Of course, we can't conclude as "no" just because of a meta-analysis. Because the potential physiological and psychological effects of violent or abusive behavior are significant, and its epigenetic changes at the cellular and molecular levels are more powerful

(69). Here we cannot deny the possible transmission of the harm caused by this behavior between generations based on a meta-analysis alone.

Violence or abuse is intense negative stress (70). Moreover, cumulating evidence showed that abused parents are at increased risk for perpetuating maladaptive parenting practices, which would be transmitted to generations to come through not just intimate (71, 72), but also the underlying uncontrollable epigenetic mechanisms (73).

No matter what age this kind of violence or abuse occurs, its direct or indirect impact cannot be fully explained simply by one type of research methodology. Most of the time, it is not the victim who repeats the violence or abuse they have experienced deliberately but does it involuntarily. The most important thing is that the trauma it suffered is like a time bomb; some tiny events will inadvertently trigger to repeat the violent or abusive behavior (74). But this time, the perpetrator and the victim have changed. Therefore, this transition from "being abused" to "abusing" is precisely an example of intergenerational transmission.

This kind of intense stress causes great harm to individual health, and it will inevitably be passed on between generations. Therefore, how to curtail the cycle of violence is critical. This will not only improve the physical and psychological health of the victims themselves but also be essential protection for the health of their offspring.

Addiction

Case #3: A 52-year-old single Hispanic male, a construction worker, had right kidney clear cell carcinoma and right leg superficial femoral artery (SFA) occlusion. He underwent a right kidney nephrectomy and right SFA femoropopliteal bypass graft. The patient smokes over 35 years with 1.5 packs per day. He tried twice to quit but fell off the wagon. Currently, he smokes 0.5 packs per day post surgeries. The patient's family members, including parents and older brothers, are smokers or tobacco product users. His father died from lung cancer at age 56 years of age. Mother had two times of deep vein thrombosis and right below-knee amputation due to Burger's disease diagnosed at her 50 years old. One of his older brothers has had the chronic obstructive pulmonary disease for ten years since his 40 years of age. No family history of genetic diseases. This is a typical case of intergenerational transmission of healthy inequality caused by unhealthy living habits.

Studies have shown that regardless of timing, offspring exposure to maternal smoking is associated with increased risk of smoking during adolescence (75). And this type of transmission strongly correlated with parental smoking habits if they had an early onset, steep acceleration, high levels of smoking, and persistence over time, which pose the highest risk for transmitting the smoking behavior to their adolescent children (76). Besides smoking, other types of addictive behaviors, including drinking (77), drugs (78), sex (79), gambling (80), and foods (81), all possess dramatic effects on their transfer to successive generations.

No matter what kind of addiction an individual has, it will dramatically change their living habits and behavior that signif-

icantly affect their health and socioeconomic status. Addiction itself causes substantial changes in the brain, not just at the molecular level but also at the brain's structure. For addicted individuals, activating the rewarding neuronal system is the most recognized underlying mechanism of addiction (82-85). However, it is merely the tip of the iceberg. The worst thing is its transmissible property between generations. As the case indicated above, addicted objects like tobacco products can get the addicting behavior passed on from parental generation to children, which unavoidably threatens sound health (86-88). We herein do not talk about the potential underlying mechanisms of addiction but the debilitating effect of addiction on health that transmits intergenerationally.

Pandemic Stress

Like the Coronavirus Disease 2019 (COVID-19), when the world is overwhelmed by a pandemic, everyone in it is a victim who cannot escape (89). When faced with the reality of vast numbers of deaths, when experiencing panic and fear while suffering from unemployment, and when various social interactions are restricted indefinitely, the individual's physical and mental health is on the verge of extreme danger (90, 91). For those with low psychological quality, low resilience, and insufficient social support, tragedies occur after suffering mental health, and extreme behaviors such as suicide occur (92-94).

At present, no one can predict the negative impact of the COVID-19 pandemic on the overall health of humans (95), nor is it clear how its impact will be transmitted between generations after it disappears in the future. But one sure thing is that we all hope that COVID-19 can end as soon as possible and return to everyday life (96, 97).

No matter how many unknown secrets there are in the occurrence of the COVID-19 pandemic (98), as an individual, the changes in his health after suffering from external environmental stress cannot be ignored. Although the impact of COVID-19 on the overall future health itself is not the focus of this review, the transmission of its potential health effects between generations may be more critical. The health inequality caused is directly related to the individual's physical and mental health. This effect will most likely exist in the future generations of offspring and adversely affect their health. Unfortunately, because the pandemic is still ongoing, so we still cannot get to know precisely the potential long-term health effects it will have.

Conclusion and Perspective

No matter what kind of environmental stress, and no matter what underlying mechanisms, its impact on an individual's health is not only on the suffers themselves, but more importantly, its impact on the health of offspring. This intergenerational transmission of poor health is the culprit of the intergenerational cycle of health inequality mediated by non-genetic factors. From the basic concept of health, i.e., the comprehensive performance of social, psychological, and biological (99), we know that social and psychological are essential components of biological health. They are precisely the external contributors

to the occurrence of health inequality. Meanwhile, it is also crucial for transmitting this inequality between generations (100). Biological health inequality is the main result mediated by genetics, and it is health in a narrow sense. It is closely related to social and psychological health. In mind, an socially, psychologically, and biologically healthy individual has a relatively low proportion of health inequality, so the probability of transmission of health inequality between generations is considerably reduced (101). Therefore, we present the following prospective suggestion to effectively alleviate the health differences caused by inequality to reduce intergenerational transmission.

First, good social relationships and positive psychological responses are essential factors for maintaining health. Although the biological health of an individual may be problematic, effective social relationship adjustment and powerful psychological intervention will have a positive impact on the overall health. At the same time, it will also be an effective tool to block the intergenerational transmission of health inequality. Of course, the intervention of biological health problems with effective medical methods will also significantly improve the health of individuals and delay the intergenerational transmission of unfavorable health.

Second, although the economy has a direct and vital impact on health, the help of society, including the community, may play a positive role in the overall health of individuals under the premise of working hard to improve their economic conditions. Among them, Medicaid is a good example. It can be said with certainty that timely financial assistance is beneficial for the individual's physical and mental health. In this regard, we suggest that government decision-making departments should fully consider the overall economic situation; and give individuals appropriate compensation. Of course, the premise is that a person can develop laziness by offering it for free, which is counterproductive. Regardless of the various economic compensation measures, the administrator should consider the desired effect thoroughly.

Third, parents should try their best to consciously experience positive life and social events so that the epigenetic characteristics caused by the environment can be passed on to their offspring in a more positive way. Thus, reducing the probability of intergenerational transmission of healthy inequality, that is, to achieve optimal and healthy intergenerational transmission to achieve the gradual reduction of inequality as the generations pass down.

Fourth, health results from a combination of genetic and non-genetic factors. The change depends on the integration of both contributors. No matter which factors, the final result is the embodiment of a sub-representative. When humans cannot control genetic factors, non-genetic factors have become the key to acquired attention. It is also the hope of breaking the intergenerational reaction chain of health inequality. The possible intervention of non-genetic factors will be particularly effective for the intergenerational transmission of non-genetic health inequality. ■

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Received: July 16, 2021 | Revised: November 21, 2021 | Accepted: November 27, 2021
