



# Clinical Trials and Reductionist Approach Preclude Cures for Chronic Diseases Due to Flawed Presumptions

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## Abstract

Medicine adopted several presumptions when it evolved from ancient experienced-based mind-body medicine to its current art. To understand its failure in finding cures for chronic diseases, we examined the presumptions, and found that statistical population of health properties does not exist for most research purposes, mathematical models are misused to model intensive properties, synthetic drugs are inherently more dangerous than nature-made medicines under their respective application conditions, binary disease classification introduced excessive errors, and reductionist treatments are inferior and inherently dangerous. We found that clinical trials are valid only for research where treatment effect is much stronger than the total effects of all interfering or co-causal factors or where errors introduced by misused mathematical models can be tolerated. In all other situations, clinical trials introduce excessive errors and fail to detect treatment effects, or produce biased, incorrect or wrong results. We further found that chronic diseases are manifestation of small departures in multiple processes attributes in distinctive personal metabolic pathways networks, that medicine lacks required accuracy for accurately characterizing chronic diseases, and that reductionist treatments are good at controlling symptoms and safe only for short-term uses. For all stated reasons, as long as medicine continues relying on the flawed presumptions, it can never find predictable cures for chronic diseases. By implication, predictable cures to chronic diseases are adjustments to lifestyle, dietary, emotional, and environmental factors to slowly correct departures in process attributes responsible for chronic diseases.

**Keywords:** Randomized controlled clinical trials; Mathematical model; Binary scale; Statistical analysis; Epidemiological model; Reductionist treatments; Failure of medicine

## Introduction

The systematic failure of medicine in chronic diseases was extensively discussed as early as 1875 [1], and often the subjects of critique by media [2-4]. As of today, most chronic diseases have no predictable cure in medicine [5]. Population-based treatments have failed in cancer, heart diseases, mental disease, etc. [6-8]. Chronic diseases are the biggest economic burden in the U.S. [7] and are predicted to consume about \$3.5 trillion by 2050 [8]. From medical performance, we see two

distinctively patterns: treatments for acute diseases are successful, but treatments for chronic diseases and cancer consistently fail. Thus, we suspect that the failure in chronic diseases must be of systematic nature that might have precluded cures for chronic diseases.

In our prior study, we found that controlled trials are improper methods for studying weak health factors when many interfering factors (equivalent to covariates in statistics) normally exist in clinical trials [9]. Our findings support the conclusions that all controlled clinical trials are biased [10]. Our prior model

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study shows a common scenario where each weak treatment or factor cannot be resolved or accurately determined if it is interfered with by at least one to thousands of other factors that have similar degrees of effects. If a weak factor is studied in a clinical trial, it is improperly rejected as experimental errors. Most assumptions used in clinical trials and statistical analysis have not been considered [9].

To understand how weak factors affect disease outcomes, we need to examine biological pathways and disease-controlling mechanisms. We have shown that randomized controlled trials do not have the power to overcome sensitivity limits [9]. This insufficient-accuracy problem cannot be seen from the outcomes of clinical trials. When the validity of the research model is challenged, such a challenge cannot be resolved by examining outcomes of research using the model. Moreover, due to complexity of health problems and a massive number of interfering factors that exist in clinical trials, it is impossible to find problems by examining the data of clinical trials. To find research model flaws, we are required to consider all kinds of evidence other than clinical trial outcomes.

Presumptions used in medicine are part of foundation of medicine and are taken as truth so that their validity has never been questioned or examined. When medicine evolved from ancient medicines into modern medicine, it changed natural medicines into synthetic drugs, changed demographic populations into statistical populations, introduced mathematical models as universal tools in medical research, and used the binary scale to model health properties. To find the cause of the systematic failure in chronic diseases, we will examine all presumptions and assumptions. The oldest presumption was that “medicine can cure disease”. While this presumption existed in the early history, “medicine” used in Yellow River Civilization is not the same as medicine we mean today. We will consider what is wrong to use a population to study chronic diseases and what problems mathematical models can create. In addition, we will examine each of the assumptions used in clinical trials and statistical analysis to show additional flaws from biological points of view.

## Materials and Methods

We collect from the medical literature published data and research findings which tend to support or refuse challenged presumptions and assumptions. We rely on data from four sources: one of the sources is research findings that establish the existence of interfering factors and their degrees of effects. Due to an extremely large set of study findings, we will cite only selected references, and treat others as common knowledge. We must use this unique approach because no single set of data or any particular findings can ever resolve this challenge. This is why conducting one or more experiments is meaningless because the data of each study is like a drop of water in a bucket. The second source of data we rely on is online stories, reports from health care providers, personal stories, and our own observations. When the validity of controlled clinical trials is under challenge, we give more weight to those sources of evidence. Based on our prior studies [9], we ignore negative findings from controlled trials directed to weak factors.

Other data considered include biochemical pathways, cellular or structural data, disease mechanisms, host responses to stressors, immune responses, factor-factor interactions, organ-organ interactions, rational explanations based on body structural compartment, rate balance among different biological pathways, and balance between disease process and healing process. Due to the large scope of issues, we do not cite all contributors directly. The third source of data is data from simple mathematical models to refute or support medical concepts and disease mechanisms. Such a method is used only to show that clinical trials with currently accepted data analysis can produce inaccurate, biased, or wrong results, but not used to establish that the use of mathematical method is in fact right. As we show, mathematical models are often misused if research purpose is to assess treatment benefits and find cures. If use of mathematical models in clinical trials is refuted as improper, clinical trials, as a research method, fall for this reason without regarding the details of mathematical models. The fourth source of data is the performance data in treating diseases. However, since most performance studies are based by various degrees, we must read



them to offset potential inaccuracies. In general, the treatment benefits of weak factors are underestimated based on our prior study [9] and obvious logic.

## **FLAWS IN CLINICAL TRIALS AND POPULATION MEDICINE**

To show why clinical trials are invalid for most research purposes, we studied its development history provided in the medical literature [11]. To understand mathematical models, we study biological pathways and their interactions, the multiple interactive disease mechanisms, factor-factor interactions, and the structural effects of tissues and organs, etc. In addition, we will show that treatment unit additivity assumption and an implied random error assumption fail to hold in nearly all clinical trials for studying chronic diseases.

### **A. Clinical Trial Development History**

The development history of clinical trials reveals that clinical trials were developed by adding components piece by piece by different contributors in several centuries [11]. When the clinical trial was first used, there was no need to establish a statistical population because statistical analysis was not part of data analysis for the clinical trial. Population used in the early human history just means a collection of members in a demographic sense, and early medical researchers naturally liked to use a population to study diseases because it always created an impression that a treatment capable of curing more persons must be better than one that does not. This is still a reason for convincing researchers today. In the early days, there was never a need to examine the population of abstract concepts such as biological properties, health condition, and disease outcomes. The controlled trial on scurvy conducted by James Lind in 1747 contained most elements. By 1946, all components of randomized controlled trials have been added. It is fair to infer that the clinical trials have gained general acceptance before the 60's [11] without using statistical analysis. Before about 1980s, medical researchers did not know the massive biological properties concerning diseases initiation, development and reversal, the complex human immune system, and the role of the Central Nervous System. They did not have a vantage to see how personal genomes,

environmental factors, emotional states, etc. affect health and disease properties. It was natural to presume that any health property in different people is similar so that the values of any property for different people can be treated as a statistical population.

Decades after clinical trials gained general acceptance, researchers started looking into the human genome, biochemical pathways, environmental factors, lifestyle factors, emotional problems, etc. The effects of a large number of primitive factors on diseases have been established by tens of thousands of studies mainly after 1980 [See some references in Section E]. Even though, a good portion of studies is conducted by using the population approach, affirmative findings in those studies suffer inaccuracy by various degrees. Nevertheless, those positive findings have firmly established that differences in health and disease properties cannot be treated as random errors, and there is no statistical population as far as health and disease properties are concerned. Unfortunately, the new discoveries have not prompted medical researchers to revisit the presumed statistical populations that had been used in the last a few decades. We have shown that effects of massive interfering factors are responsible for trial outcome uncertainty. When the nature of interfering factors was not understood, it was natural to attribute trial outcome uncertainty and conflicting findings to experimental errors. It is natural to try to solve this problem by using misapplied statistical analysis.

Misuse of statistical analysis in clinical trials is clearly reflected in the development history of statistics. Statistical analysis was added to clinical trials as one of the latest added components. The origins of statistical theory lie in the 18th-century, but improved experimental design, hypothesis testing methods, etc. were developed in the 1910s and 20s by William Sealy Gosset, and Ronald Fisher, and further refinements were made in the 1930s [12]. Hypothesis tests are used to determine whether positive outcomes in clinical trials are really caused by the treatment effect or due to uncontrollable experimental error. Use of hypothesis tests in clinical trials started centuries after the initial use of clinical trials and more than a decade after the



formation of modern clinical trials. Statistical analysis was added as an additional analysis step to clinical trials from the 30s to about 60s. When statistical analysis was added, the traditional concept *population* was silently changed into a *statistical population*. In statistics, a population is a set of *similar* items or events which is of interest for some question or experiment. No published study has seriously discussed whether health properties of human beings can be treated as a statistical population, whether health properties follow any known statistical distributions, how differences in observed health properties between different persons are more than what could cause chronic diseases, and whether the observational values in a population can be added and divided like fungible properties such as weight and volume.

### **B. Flaws in Early Statistical Studies**

Past studies including those done by Altman, Senn, Zhao and Berger [13-18] have made a presumption that any health properties such as survival times, process attributes such as conversion rate and intermediate concentrations, etc. in human bodies can be treated as a statistical population [13-18]. They did so without exploring the effects of all interfering and co-causal factors normally exist in clinical trials. An implied presumption had been accepted for several centuries ago even though no statistic analysis were used. It had been beyond challenges. By using this presumption, even extremely complex health and disease properties such as survival time and emotional health can be studied like statistical populations, where outcome uncertainty can be attributed to random processes like rolling a dice or blowing colored balls out of a lottery machine. After examining disease mechanisms and existing risk-disease data, we found that no disease happens like flipping a coin and blowing colored balls.

Due to historical reasons, early researchers could not pay attention to biological properties and life factors and their effects on health properties. Flaws in early studies can be summarized as follows: first they made a presumption that disease and health properties can be studied like drawing events and that health properties of human beings in a treatment group can be treated as a statistical population. They then made an assumption that

disease or health properties can be mathematically added up and divided to yield a mean for the presumed population. In doing so, they actually made another assumption that health properties are fungible and exchangeable, and all uncontrollable interfering factors do not exist or can be neglected as random errors within a treatment, and failed to examine whether treatments have different effects on different persons, how interfering factors affect health properties, and how their plus and minus effects distort analysis outcomes.

In the early years, they did not have the vantage to see the irrefutable evidence that most so-called errors are not truly random errors that are seen in statistical trials, but a combination effect of hundreds to thousands of interfering or co-causal factors. They did not see abundant evidence that treatments often have different levels of effects and different-sign effects on different persons, that magnitude of measured errors from interfering factors can be larger than treatment effects; the interaction between a treatment and any of potential interference factors is distinctive in each person; that interfering factors can distort treatment effects by their positive and negative effects, with sufficient magnitudes to distort trial outcomes, and that personal biological properties are distinctive. Without considering external evidence, they were not in a position to compare the effects of a treatment with the effects of interfering factors, and naturally attributed all differences among different persons to experimental errors.

Studies by Altman, Senn, Zha and Burger [13-18] share several common errors: They treated health and disease properties of human beings as populations. They assumed that the differences between different persons happen like those in statistical sampling, but never discussed external evidence about health properties such as process attributes [19]. By failing to look into the nature of all interfering factors, they bundled all contributions into experimental errors. They concluded that baseline balance is not a concern. They never proved that health properties of people can be treated as a statistical population. They failed to note that differences between any two persons in a health property is more than enough to cause a chronic disease or



alter disease outcome. If statistical analysis can fix the overwhelming problems, we could reach an absurd conclusion that controlled trials have the power to resolve contributory effects of any weak factors; valid scientific research does not depend on separation method and detection technologies; and research sensitivity limits can be overcome by running bigger clinical trials followed by doing statistical analysis. Each of those conclusions must fail.

What is wrong is that “statistical population” has been taken as granted for any research purpose. This is plainly reflected nearly all medical studies that never even attempt to determine whether a statistical population of a health property exists for intended research purpose. When a clinical trial is used to study a chronic disease, it is required that all persons must be similar in their chances of getting or resisting the same disease. What is important is not physical entity such as size or height, but the health properties to be investigated. Due to the massive interfering factors in clinical trials, clinical trials tend to produce different outcomes. Early researchers could not understand the sources of uncertainty, and naturally assumed that trial uncertainty was caused by experimental errors beyond human control. Naturally, statistical analysis was used to solve this problem. When statistical analysis was added, *population* was silently changed into *statistical population*. Medical researchers have made a presumption that a statistical population exists for any health property and any research purpose. This is evidenced by the widespread abuse of statistical analysis in medical research publications.

While hypothesis tests are not wrong for all research purposes, they can address only experimental uncertainties that are truly caused by uncontrollable random errors that happen like flipping a coin, blowing colored balls out of a lottery machine, or rolling a dice. The massive medical research findings have firmly refuted that trial outcome uncertainty is caused by uncontrollable random processes. Rather, the different outcomes are caused by interfering factors that can be controlled. An implied requirement for classical statistical trials is that the coin must have identical weights on two sides to have the unbiased chance to produce each

outcome, all numbered balls in a lottery chamber must have the same weight, same shape, same size, and uniform internal density, and the dice must be a cubic with the same area on all six faces, and has the same density at every inner locality within the dice. If the rim or density near two surfaces of a coin is altered, it will introduce systematic errors that cannot be treated as random errors. A coin with an altered structural feature may produce an outcome ratio other than 1:1. The ball sizes and densities among different balls can be changed to result in different outcome probabilities. Those problems can be easily seen because their normal outcome ratio are known. However, systematic errors in clinical trials cannot be determined by looking at trial results alone, but must be determined by other studies. The systematic biases can be established by external evidence. Systematic biases cannot be corrected without understanding the nature of the biases. All interfering factors in clinical trials can have systematic impacts on trial outcomes, even though they may produce no effects. Inability or difficulty to control interfering factors is not the reason to ignore their existence.

A vast number of the primitive factors such as nutrition, toxins, heavy metals, exercise, emotional issues, etc. are not really uncontrollable. Each of those factors is weak and hidden among the rest of other factors. It is like a situation where the effect of each factor cannot be determined but the collective effects of all factors are responsible for diseases. Even intermediate factors such as glucose or triglycerides levels in the blood can be altered by adjustment to lifestyle. None of those factors work like an uncontrollable driving force that makes a spinning coin to take one particular outcome.

Misuse of statistical analysis could not remove the trial outcome uncertainty. Uncertainty in trial outcomes becomes great room for manipulation of experiments. Instead investigating the inherent flaws, medicine has tried to address this uncertainty problem by controlling selection biases and conflict interests as remedies. Thus, we see massive ethical regulations established after 1946 [11]. While avoidance of selection biases can cure uncertainty caused by identifiable factors such as age, sex, overall health, disease stages, etc, it cannot do away with outcome



uncertainty caused by a large number of other uncontrolled interfering factors such as unknown toxin, deviated nutrients, great emotional state, etc. Conflict-of-interest measures can never do away with outcome uncertainty except that it has become a scapegoat for the flaws of clinical trials. Such measures create massive administrative burden which is rarely seen in other fields such as bridge design, aviation, automobile, etc.

### C. No Statistical Population of Health Properties

While the population concept can be used for various purposes, the population, as used in statistical analysis in clinical trials for diseases, can be refuted by relying on observed health properties and known analytic data. Boys, girls, men, women, healthy persons, and persons with unidentified diseases, etc, are expected to have different baseline health. A valid statistical distribution must comprise the observations that are used to study. For example, a healthy young person may have a baseline survival time of five thousand days while an old patient may have a baseline survival time of fifty days. Here the statistical distribution comprise survival times. Among the persons in a trial, besides the term “person”, they are different in biological age, physical strength, shape and look, size and weight, biological properties, etc. They differ in physical check-up data and laboratory analysis data [20]. Differences in local concentrations of intermediate compounds of some biological pathways in tissue cells between different persons could be more striking even though few studies were done to understand such differences at the cellular level. Even if assuming that diseases were realized in a manner like blowing human physical entities out of a lottery machine, some persons might be “drawn” at much higher probabilities. No population would meet statistical distribution except by approximation in studies concerning non-health issue such as body weight and head count. In most clinical trials, the baseline health property for each person cannot be accurately measured and determined due to all interfering factors. The inability to measure is not a valid basis for treating differences in health properties as random errors.

As a general rule, when a treatment in a clinical trial is sufficiently strong while experimental errors are relatively small, two experiments with two measurements in each would be enough without using statistical analysis. Statistical analysis is never required in most experiments in analytic chemistry. In a drug trial with the endpoint being survival time, real experimental errors are small because survival time, treatment dates, and drug doses can be determined and recorded accurately. If there were no interfering or co-causal factors, repeating the clinical trials to study the drug effect in the same condition would produce consistent results without using statistical analysis. However, interfering factors cannot be characterized in reality. In a trial involving a poorly defined treatment such as a stress-relieving method, part of outcome uncertainty is caused by the uncertainty in treatment definition; and part of the outcome uncertainty is caused by other interfering factors. Statistics is not a suitable method for taking care of interfering factors and definition uncertainty of treatments.

### D. Problems in Health Properties

We will discuss several model problems that make population presumption fail.

**(1) Canceled effects of a treatment:** A first problem is that a factor or treatment can have positive effects or negative effects on different persons. For example, to improve vitamin D supply, its levels in blood of a sample of a population can be represented by a mean and a standard deviation. This mean may be used to determine the total amount of vitamin D supplement required for correcting vitamin D deficiency for the population. Since vitamin levels actually vary among persons, the amounts of supplement intakes cannot be determined on the basis of the population’s mean but on the actual vitamin level in each person. If the same amount of vitamin supplement is indiscriminately used by all persons, the amount is insufficient to those with low vitamin levels but may intoxicate those with high vitamin levels. This treatment will have both positive effects on some persons and negative effects on others. If we assume that 50% persons need to increase vitamin D while the other 50% of persons do not,



vitamin D supplement may happen to show a net zero. This is wrong because it would benefit 50% of the treatment group if vitamin D supplement is not used in those with excessive vitamin D levels. This problem cannot be corrected by using a control. The supplement treatment has zero over its baseline, and the control group also has a baseline. So, the clinical trial shows no benefit. In reality, the effect of vitamin D is more complex than this. Even some persons in the control might have excessive vitamin D. If they reduce their vitamin D intake from their diet, the baseline for the control increases and thus result in a negative result for the treatment. However, if vitamin D is administrated among those who need it, the supplement may benefit 30% the treatment group, and the restrictive measure may “benefit” 25% of the control group. Then, the net responsive rate would be 30% of the treatment group and 25% of the control group, rather than 0%. This implies that clinical trial is terribly wrong.

An overwhelming number of factors can have both positive effects, no effect and negative effects on different persons for any health problem. Each of all nutrients, physical exercises, measures to reduce toxic pollutants, etc. is expected to

have positive effects, no effect, and negative effects. The averaging operation used in clinical trials always produce meaningless results. “Lack of effect” is false because it is an improper average; a negative mean is wrong because at least some persons need the vitamin; and a positive mean may be underestimated because the values have been brought down by those who have toxicity levels. Thus findings based on clinical trials are meaningless and cannot be used as treatment guidelines.

**(2) Distortions by an interfering factor:** Even if the treatment or the treatment factor has a fixed positive effect on a health property on all subjects, this constant number cannot be accurately determined. This constant-effect assumption must be false, but we use it to show that a large number of interfering factors can distort the treatment effect. All interfering factors have positive or negative effects on different persons. Assuming that treatment T has a fixed treatment effect on all persons, the positive and negative effect of an interfering fact can distort its effect so that it may produce a false result. This problem is caused by the inability to resolve the contribution of the treatment and the contribution of the interfering factor on each specific person. This can be shown in the following table:

*Table 1: An interfering factor affects the treatment effects of a treatment of similar strength.*

|   | Person ID                             | 1  | 2  | 3  | 4  | 5  | 6  | 7  | 8  | 9  | 10 | Mean |
|---|---------------------------------------|----|----|----|----|----|----|----|----|----|----|------|
| 1 | Net Treatment Effect                  | 1  | 1  | 1  | 1  | 1  | 1  | 1  | 1  | 1  | 1  | 1    |
| 2 | Interfere Factor Effect (eq. control) | +1 | -1 | +1 | -1 | +1 | -1 | +1 | -1 | +1 | -1 | 0    |
| 3 | Observed “Treatment” Effect           | 2  | 0  | 2  | 0  | 2  | 0  | 2  | 0  | 2  | 0  | 1    |

In Table 1, the treatment has a fixed effect of 1 on all persons. One interfering factor in row 2 has positive or negative effects, and raises the variances of the observed data in row 3. The net interfering factor in row 2 could be viewed as a control. If no interfering factor exists, all values in row 2 would be near zero, all measured values would be 1, and the mean could be

determined without any uncertainty. The interfering factor dramatically raises the variances of the treatment in row 3, and thus raises the threshold of rejecting the null hypothesis. The trial most probably fails to find the true benefit of the treatment. When hundreds of interfering factors exist, the variances seen for the

treatment must be larger even if the interfering factors follow complex or unknown distributions.

**Table 2:** A strong interfering factor distorts the true effect of a weak treatment.

| No | Person ID                        | 1   | 2   | 3   | 4   | 5   | 6   | 7   | 8   | 9   | 10  | Mean |
|----|----------------------------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|------|
| 1  | Treatment Effect                 | 1   | 1   | 1   | 1   | 1   | 1   | 1   | 1   | 1   | 1   | 1    |
| 2  | Interference Effect<br>(Eq. Ctl) | +10 | -10 | +10 | -10 | +10 | -10 | +10 | -10 | +10 | -10 | 0    |
| 3  | Observed<br>Treatment Effect     | 11  | -9  | 11  | -9  | 11  | -9  | 11  | -9  | 11  | -9  | 1    |

In Table 2, a single strong interfering factor dramatically increases the variances of the observed data. The massive variations of the interfering factor find its way into the values of the treatment group relative to a control. Due to the massive variances between different persons within the treatment group, the true treatment effect in row 1 may be completely hidden in the interfering effect. Although the treatment mean is detected as unbiased, the enlarged variances will result in a much higher

threshold for rejecting the null hypothesis. Based on other observational data, we must say that the variances from different persons are very high and result in failure to reject the null hypothesis. We suspect that strong interfering factors are very common in studies intended to study weak and slow-delivery environmental and lifestyle factors. In such situations, clinical trials always produce false negative findings.

**Table 3:** A strong interfering factor overrides a weak treatment.

|   | Person ID                        | 1   | 2   | 3   | 4   | 5   | 6   | 7   | 8   | 9   | 10  | “Mean” |
|---|----------------------------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|--------|
| 1 | Net Treatment<br>Effect          | 1   | 1   | 1   | 1   | 1   | 1   | 1   | 1   | 1   | 1   | 1      |
| 2 | Interference Effect<br>(Eq. Ctl) | +10 | -10 | -10 | +10 | -10 | -10 | +10 | -10 | -10 | -10 | -4.0   |
| 3 | Observed<br>Treatment Effect     | 11  | -9  | -9  | 11  | -9  | -9  | 11  | -9  | -9  | -9  | -3     |

In Table 3, a single strong interfering factor has a biased effect on the measured health property of both treatment and control groups. This kind of interfering factors include fears, development stage, aging, seasonable effects, exposure to bad news, etc. that strike all subjects in both the treatment and control groups. It can dramatically increase the variances of the observed data. In addition, it also moves the measured values as well as the mean to the negative side. Even though the treatment has a net effect of 1 on each person, the observed values are still negative. In addition, aging, development stage, seasonal factor, or exposure to bad news may interact with the treatment. A

treatment may have curative benefits, but negative news may make all subjects so sad that the news might have suppressed the immune system or the whole body health. Due to the large variances and negative interactions, the true treatment effect is most probably rejected as errors.

In clinical trials, there are hundreds to thousands of interfering factors. Their variances can be added like the variances of random variables following well known distributions and their means can be added up [9]. For unknown distributions, the final variances depend on the number of interfering factors and their effects on variances of the treatment group. In clinical

trials, they are automatically treated as the variances of errors. This raises the test statistic for rejecting the null hypothesis and thus results in acceptance of the null hypothesis or failure to recognize weak treatment effects.

**(3) Distortions by interactions:** The impact of interfering factors in clinical trials cannot be corrected by achieving baseline balance between the treatment group and the control group. This can be shown by the interactions between the treatment and interfering factors. Assuming that treatment T is under the influences of uncontrollable interfering factors ( $H_1, H_2, \dots, H_n$ ), the detectable treatment value for a person is  $AT_i = \Sigma(T_i + T_i - H_{j=1} + T_i - H_{j=2} + \dots, T_i - H_{j=n})$ . Each interfering factor  $H_j$  causes plus and minus affects  $(T - H_j)$  over an imagined treatment  $T_i$ . Some interfering factors may raise the treatment effect by various degrees while other interfering factors may depress the treatment effect by various degrees. The net effect of the treatment on a person depends on the treatment and all interaction effects. Thus, the net treatment effect on a particular person must be different from the net treatment effect on another person. In the control, the correspondent treatment term does not exist (it is zero). We ignore each of the interfering factors. All interaction terms  $(T_i - H_{j=1} + T_i - H_{j=2} + \dots, T_i - H_{j=n})$  would depend on the treatment. It is possible that a treatment is predicted to have beneficial effects on a disease, but the interactions with other factors might have brought the predicted effect down to nothing or a negative value. This problem is very serious if many of the  $H_1, H_2, \dots, H_n$  terms are larger than  $T_i$ . Because the number and impact degree of interfering factors are unique in each person, the effect of treatment will be altered by different degrees in different persons. This might be the reason many drugs do not deliver same intended benefits.

The total treatment effect for the treatment group is the sum of all treatment effects on all persons (Ignoring the problem in additivity for the time being). A large number of interfering factors interact with the treatment. If the interference factors interact with the treatment in an unpredictable way, the average of the treatment effects is meaningless. The nature of interactions is determined by the treatment OR interfering factors. For example,

a calcium supplement is predicted to benefit bone health, but a high daily sodium intake promotes calcium loss. The sodium's effect on calcium balance depends on personal sodium intakes. Similarly, exercise can beneficially affect innate immunity, acquired immunity, etc, and people vary in doing exercises. Exercise can dramatically raise the beneficial role of other treatments such as nutrition and detoxification of heavy metals. Upper and down shifts of baseline health properties cannot be determined experimentally for specific persons. Thus, a better strategy for formulating a treatment is use of a theoretical method to predict upper- or down-shifts of health properties which are caused by interfering factors. In the example, a simple mathematical model is used to characterize the treatment effect and its interactions with interfering factors. However, accurate interactions cannot be characterized accurately by using simply mathematical models due to multiple layers of complex healing and disease mechanisms.

**(4) Problems caused by slow speed:** One unique problem in human health is that many lifestyle factors affect health and diseases slowly. This problem is an additional reason for the failure of clinical trials. Even if a treatment is relatively strong, it cannot be detected in a short clinical trial. The treatment may be unable to trump the effects of random and unpredictable interfering factors. Exercise is a very weak factor if it is examined in a short-term trial. No benefit can be detected in a short time trial. Their benefits are seen in long-term studies. If exercise is examined in a long-term trial, its true benefit is interfered with by certain factors that also have systematic impacts. Interfering factors include ages, aging, development stage, menopause stage, hospital isolation, etc. For people at advanced ages, part of the long-term treatment effects is more easily distorted by interference factors.

## A NEW LIFE MODEL AND INTERFERING FACTORS

We will present evidence on some well-known interference or co-causal factors that can affect human health and disease outcome. In the life model, interference factors mean any factor that could affect human health and disease outcome. They



include things like working habit, thinking habit, the way of breathing, air freshness, the order of doing things and things, and a large number of things that might have been found to have no bearing on diseases in clinical trials. Due to the extremely large scope of interference factors, we can present only a small number of them.

### A. Evidence Showing Interfering Factors

Each person is a unique being by personal genome [22]. The typical difference between the genomes of two individuals was estimated to be 20 million base pairs (or 0.6% of the total of 3.2 billion base pairs) [22]. Moreover, even identical twins can become different beings by epigenetic changes that have an effect of turning on or off gene expressions [23-24]. Each disease like cancer is a distinctive product of personal genome, diet, living environment, etc. [25-26]. Since genetics cannot be altered, we focus on diets, personal activities, lifestyle, environment, emotional state, etc. There is no need to distinguish between associated factors and causal factors, which are used in medicine.

All factors that a person may be exposed to can affect the person's health. Emotional shock, chronic stress and social isolation, etc. can affect inflammation degree [26-28], the immune system [29-32], influenza and respiratory infection [34-36], cancer development and metastasis [37-40], heart diseases [41-42] and drug metabolism [43]. Since the brain controls hormonal actions and biological processes, distortions in the brain must affect correspondent tissue ecosystems. The critical role of the CNS was described in 1875 [1]. Nutrition affects immunity to viral infection [44-46], other infection [47-49]?, viral pathogenicity [50], etc. Selenium affects viral mutations [51]; and Zink affects the risk of pneumonia in the elderly [54]. Obesity affects immunity to infection, inflammation, and immune responses [55-62]. Excessive cell phone usage increases the risks of brain tumors [62-65].

Metals, including lead, cadmium, mercury, arsenic, chromium, copper, selenium, nickel, silver, and zinc, and other metallic contaminants including aluminum, cesium, cobalt, manganese, molybdenum, strontium, and uranium are found in

living organisms, plants, contaminated vegetables, industrial materials and polymers, soil and land resources, polluted air, and polluted water [66]. Most heavy metals such as aluminum, arsenic, beryllium, cadmium, lead, mercury, nickel, and radium increase risks of cancers in lungs, kidneys, liver, stomach, intestines, bladder, colon, stomach, nasopharynx, pancreas, breast, gallbladder, esophagus, prostate, testes, gastrointestinal track, skins, and lymphs [67-69]. Exposure to arsenic, lead, cadmium, and copper is associated with increased risks getting cardiovascular diseases and coronary heart disease [70, 71]. Heavy metals can damage cells [74], disturb the Redox balance [72, 74], and suppress the immune system often at very low concentrations [73, 74]. Many heavy metals can damage liver, kidneys, and brain and nerves [74]. Alteration of homeostasis of metals could cause the overproduction of reactive oxygen species, induce DNA damage, lipid peroxidation, and alteration of proteins, and thus increase the risks of developing brain tumors [75]. Heavy metals such as lead, mercury, cadmium, and arsenic may be important contributors to neurodevelopmental disorders and disabilities [76]. The findings in those studies firmly establish that heavy metals can cause specific diseases or cancer, but also cause general adverse health effects because they can interfere with enzymatic reactions that control reaction rates of nearly all biological pathways.

Inorganic and organic substances can have adverse health effects. Sodium, the most common flavor is the number-one silent worldwide killer due to its role in raising blood pressure [77]. Habitual dietary salt intake is positively associated with the risk of gastric cancer [78]. Besides cardiovascular diseases, a high salt intake increases risks of gastric and some other cancers, obesity, Meniere's disease, worsening of renal disease, triggering an asthma attack, osteoporosis, exacerbation of fluid retention, renal calculi, etc. [79]. High sodium intake is associated with obesity [80]. Moderately high salt intakes affect calcium metabolism and bone health [81]. Reduction of sodium intake can reduce both systolic and diastolic pressures [82]. Exposure to common quaternary ammonium disinfectants may decrease fertility based on animal models [83-85]. Hydrogen



peroxide may cause poisoning [86]. Lack of exercise and physical inactivity are found to be the substantial causes of chronic diseases [87-88]. From the benefits of exercises on cancer survival [89-100], it can be inferred that reduced exercise and increased inactivity have adverse impacts on survival among cancer patients. People have different organ reserve capacities [101-103], which are presumed to be the most important factor that affects patients' ability to survive diseases.

Available spaces in the thoracic cages affect personal ability to accommodate tissue swelling in the lungs [104]. Obesity is found to be a high risk factor for COVID-19 disease [105, 154]. Information stored on the CNS neurons is different, and it, like a computer program, affects emotional health and CNS regulatory functions over the body. Lack of medical findings is not a reason to deny its role and importance. Full details of those factors can be presented only in a searchable database. Even environmental factors such as oxygen [148], humidity [149], and temperature [150] affect immunity and pathological responses to infection. The health effects of a massive number of organic compounds, industrial materials, industrial chemicals, pesticides, herbicides, fungicides, etc. can be found elsewhere.

Many factors exhibit non-linear complex health effects and may interact with each other. The CNS interacts with bone, marrow, and the micro-environment [152]. Enteric microbiota, central and enteric nervous systems interact through the gut-brain axis [153]. Sodium also exhibits different effects under different use conditions. High salt (4% NaCl as well as 1% NaCl enriched tap water feed mice for 2 weeks) inhibits tumor growth by enhancing anti-tumor immunity [155] contrary to the long-term adverse effects. Like glucose level that has both good and bad effects, sodium's short-term effect may be realized by influencing blood viscosity and fluid ionic strength while its long-term effects are most probably realized by affecting blood pressure and the vascular system. Any factor affecting viral diseases could also depend on a large number of other factors that affect innate immunity, host responses, acquired immunity, micro-circulation, and structural features of target tissues. The cited findings are irrefutable proof that none of the interfering factors can be

ignored in the mission to find cures. Most beneficial factors can be used to prevent diseases, and most adverse factors can be corrected to mitigate diseases.

### **B. Slow Delivering Effects of Weak Interfering Factors**

To understand the nature of interfering factors, it is important to understand event timing. Some treatments such as consuming glucose to raise blood glucose can show immediate benefits. Other treatments or factors will affect the biological or metabolic pathways networks without immediately causing symptoms. It may take time to distort the biological networks. The distorted network then slowly alters the structures of the body. This is similar to the development of chronic diseases. Altered process attributes in the biological or metabolic network and altered body structures also interact with the Central Nervous system by the mind-body interactions [112-113]. The mind-body interactions may be a mechanism for stabilizing the physical body. Most departures in biological networks in tissue cells cannot be directly determined in clinics because reference ranges of chemical analysis data for normal ranges are very large. Chronic diseases are often diagnosed by examining blood compositions, changes in cellular structures and disease biomarkers. It is difficult to determine the effects of primitive weak factors by using those methods.

### **CLOSE EXAMINATION OF KEY PRESUMPTIONS**

In modern medicine, another presumption is that every health problem can be represented by a mathematical model such as a statistical model. It has become presumption. We refute this presumption as being flawed by examining the assumptions used in statistical model.

#### **A. Nonlinear Effects of A Treatment**

Nearly all statistic models common used in medicine is based on linear model. Whenever statistical analysis is used, it is presumed that health property can be model by using linear models. If linearity does not hold, all statistical analyses are wrong. We will show that this presumption fails in nearly all medical research situations. Most interfering factors influence



health properties in a complex manner. For example, nutritional intake, physical activities, sleep duration, thinking activities, environmental factors such as temperature, atmospheric pressure, and humidity, etc. affect personal health often by quadratic functions (if we do not resolve precise effects at a finer scale). A low nutrient intake has negative effects, its beneficial effect increases with intake amount, and hits an optimal point; after this point, further increased intake causes a reduced beneficial effect, and results in progressively increasing toxic effects. The point of the optimal value for any factor is not static. The shape of the effect vs. concentration curve depends on personal genome, health condition, age, physical activities, lifestyle, diets, and emotional states, etc. This approximate quadratic pattern is true even for physical activities. Too little sleep can hurt due to insufficient rest time and too much sleep time may result in excessive fat accumulation. It is even true for things like usage levels of body parts such as hands, feet or joints. Long inactivity hurts but excessive activities also hurt. The model assumptions used in most statistical models do not reflect the changing and flipping natures.

Mathematical models cannot model complex interactions of health properties and primitive interfering factors. Health properties such as glucose level, triglycerides levels, oxygen saturation, etc. may work like influencing factors for other health and disease properties. They also affect other high-level health properties such as disease risks, death rates, survival time, etc. Due to complex interactions, we found that most health properties must affect health or disease by multiple complex functions of a large number of primitive variables. It cannot be expressed by a simple linear equation. There is no best nutritional profile, no best diet, no best copper intake, no best environment, etc. for the population because the effect of each factor also depends on other factors and personal activities. There are no objective criteria for determining what is the best. There is no best amount of exercise, and nor best kind of exercises for all people in a population. Even for a given person, there is no static best value. An imagined best value may exist only under certain evaluation conditions, and must change with age, health condition, activity levels, emotional

health and other personal, environmental and lifestyle factors. The notion of the best value such as the best sleep duration for a population is flawed. Linear models used in statistics can model only simple properties like crop weights and production yields when research purpose concerns a fungible property (having nothing to do with health).

The unique nature of process attributes implies that health properties are not the types of properties for mathematical operations. Moreover, interactions between disease initiation and multiple layers of disease defense mechanisms also refute the validity of mathematical operations. Disease mechanisms are further influenced by a large number of lifestyle and environmental factors. Clinical trials can produce unpredictable and inconsistent results due to effects of influencing factors at different layers. A factor for diseases may be found to have no effect if a strong defensive mechanism in most human subjects can overcome initiated diseases; and in another trial, the same factor effecting disease initiation may be found to be a strong controlling factor if the defensive mechanism in most subjects has been compromised. In sum, the best health measures must be based on personal health and condition.

The unit treatment additivity assumption is used in regression and variance analysis. Most weak factors are used as treatments, this assumption must fail because they have positive and negative effects on different persons. Besides, human body always has several layers of disease mechanisms including innate, host response, acquired immune responses, resolution of inflammation, and recovery of damage. Whether a treatment shows its effects would depend on the mechanism targeted by a treatment relative to other mechanisms used by other factors. A weak mechanism must be hidden within a strong mechanism is working. Exercise may have negative effects on some people whose blood vessels are severely damaged, but positive effects on others. Even if a treatment has a constant effect, interfering factors can distort their values or they always have different values as a result of their interactions with other influencing factors. A large number of nutrients, physical properties, environmental factors, etc. can distort treatment effects by



interacting with the treatment, making this assumption fail. Thus, a treatment may have positive effect, negative effects in different degree. No statistic model is good enough for model health even for one single person.

### **B. Improper Mathematical Averaging of Health Properties**

The notion of equating average of a population as the best value was formed from a false perception of comparative benefits. By using a comparison, clinical trials always produce a false impression that the positively determined treatment must be good for the population. Thus, treatments developed from clinical trials have been regarded as the best in practice for centuries. The validity of controlled trials has been presumed for centuries with no proof. The purpose of a clinical trial is to determine whether a treatment is better than a control often by using statistical analysis. In conducting a statistical analysis, measurement values from all persons in the treatment group are added up to yield a mean. There is no scientific proof that such health properties can be added and that a computed mean can represent all persons in the treatment population. Statistical mean may be found only if all persons in the population actually have such a mean, and the averaging operation can remove truly random measurement errors.

Most health properties are process attributes such as conversion rate, the concentrations of reactant intermediates, or the matrix of those things. In the treatment group, a mean determined by mathematical averaging can represent none of the members in the treatment group. If a treatment is found to have positive effects over a control group, what is proved is that the treatment has sufficiently positive effects on the members of the treatment group over the control. Such a positive value can be detected if the treatment effect is stronger than the sum of all interfering factors in the treatment group, the treatment produces beneficial effects on more persons than it produces adverse effects of same degrees on others within the treatment group, or the treatment has a net beneficial effect on the treatment group over the control for whatever reasons. It does not prove that the

treatment is effective for the treatment group, is effective for treating the disease, or is the best for all persons with the disease.

The notion that “an average represents a population” is generally wrong unless a statistical population can be established by independent evidence. In politics, number-based representation is a principle imposed by will, but not natural law. In a statistical population, the members must share enough similarities so that the members can be used to investigate a treatment. This requirement is entirely relative to the research purpose. Computed average can represent a population only if a statistical population actually exists. The existence of a statistical population cannot be proved by mathematical operation itself, reasonable data pattern or a computed average value. Mathematical summation may determine average weight of a sesame seed and a fighter carrier or the average heart output of an elephant and a bird. Such averages can represent neither the weight of the sesame or the carrier, and nor the heart output of the elephant, and nor the bird. While the values in those two examples are extreme, similar data values do not provide a basis for finding a statistical population. Similar reaction rates in certain tissue cells in tigers and turtles do not make the rates a statistical population (even if turtle’s mean may be used to estimate the tiger’s mean in practice). It is possible that apple tree data might nicely fit into human data purely by accident.

Existence of a statistical population must be established by examining individual members and the purpose of investigation. If an identical nutrient intake has a beneficial effect on one person but a toxic effect on another person, the average value, which has the same value, does not represent a beneficial effect for both, and nor a toxic effect for both. While a study on nutrition intake is invalid for finding the best treatment, the same study could be valid for estimating demand and supply. Similarly, apple, orange, and plum in a compartment mixture could be treated as a reasonable statistical population if the investigation purpose is to estimate packaging volume. In contrast, the same study cannot be used to improve their quality. Even abstract concepts may become a statistical population if their differences do not defeat the investigation purpose. Even in many marketing



studies involving abstract concepts, statistical analysis may be reasonably good if those abstract concepts are used to study sales in the amounts of cash (the only question is accuracy requirement). Similarly, a deformed coin, irregular balls, and a non-cubic dice with varying inner densities cannot be used in drawing samples in classical statistical trials. All problems come from the need to cure diseases or find treatments. In a vast number of medical research articles, research purposes and accuracy requirements have been ignored. This single error makes many medical study findings meaningless.

The permissible use of mathematical operations for population-based study depends mainly on the purpose of research. Grain weights may be added and divided if research purpose is to study grain supply and demand. In this situation, grain weight is fungible because mathematics does not differentiate sources just like market demand. However, if the research purpose is to increase individual seed weights by using a new treatment, grain weight is not a fungible property. We must consider if the treatment has the same effect on each individual seed. If the same treatment can have different effects on different seeds with different genetic compositions, a mathematical model that the treatment has the same effect must fail. Lifespan is partially controlled by complex biological pathways, and thus is not fungible: extending 20 years for a boy is not the same as extending 20 years for an elderly person. However, survival time could meet statistical population if research purpose is to determine total community life spans for the purpose of getting a financial reward under a lifespan-based reward program. If a mathematical model treats positive and negative effects of influencing factors as experimental errors, the errors must be sufficiently smaller than the treatment effect so that study validity can be justified by approximation. Based on this rational, mathematical operations cannot be used to find the best treatments for persons who have distinctive biological properties.

Mathematical averaging of process attributes is improper also because most process attributes have no standalone meaning. One class of properties is *intensive property that reflects local physical property of a system. Examples of intensive properties*

*include temperature, pressure, refractive index, density. Extensive properties such as the mass and volume are additive. Temperature is not additive because heat absorbed at different temperature would be different, and temperature at different systems such as water and gas means completely different things. Process attributes and health properties are similar to intensive properties.* A Civic uses fuel at the rate of 1 gal/time (where time is a suitable time unit) and an Accord consumes fuel at 2 gal/time. Their average would be 1.5 gal/time. This number may indicate average usage of fuel from fuel supplies. However, this number cannot be used to study the performance of the cars because the performance of each car depends on a large number of other variables such as driving distance and weight of carried goods. The average, 1.5 gal/time, has no meaning if it is viewed out of context. Imposing the average to both cars would cripple both. Fuel injection rate can be evaluated only against criteria such as shipping weight and running distance. We can infer that all process attributes such as fuel injection rate, coolant flow rate, heat dissipating rate, etc. from individual cars or planes cannot be added and averaged across individual models, and then applied to any specific model or unit.

Direct mathematical average is proper only for fungible properties such as crop weight, production volume, count and frequency. For such properties, the significance of each unit of weight or volume does not depend on other associated variables. For example, direct averaging of weight of alcohol of 99% purity and alcohol of 30% purity without using weighting factors is improper. The net weight of two sources of alcohol depends on their purity which is an associated variable. For nearly all health properties, the significance of process attributes always depends on associated variables. For example, use of a drug for raising 50 mm Hg blood pressure is good for correcting low blood pressure, hurt those with elevated blood pressure, and kill those with very high blood pressure. The net benefit depends on overwhelming factors controlling the vascular system in each person. Mathematical operations used in classical probability trials do not have such a problem. In probability trials, events are defined accurately. The appearance of a numbered ball, a dice position, or



## SUNTEXT REVIEWS

a coin face is not subject to additional variables. Each outcome has the same significance as any of other outcomes. That is the basis for adding them up to get a sum. Observing examples in statistical books, we found that an intensive property may be used as a statistical population only for the same system or similar systems. For example, daily production rates of a machine can be added up and averaged for different days because all other variables are fixed and thus the number of product pieces is the only variable. In this example, the associated variables can be dropped out because they are constant. Whether production rates from different machines can be summed and averaged depends on the purpose of mathematical operations and accuracy requirements.

Process attributes are generally not the kind of properties that can be summed up and divided. The specific values of process attributes do not have standalone meanings. Each of the values is incapable of determining system performance such as health or disease states. Glucose level, a process attribute, affects health by interacting with other factors or variables. When the glucose level is low, it is vital to survival. If it increases, its benefit reaches a plateau. Further increase in the glucose level will cause negative effects by damaging the vascular system. Thus, raising 15 mg/liter in the low end and increasing 15 mg/liter in the high end have different effect even for the same person (glucose is dynamic); and 10 mg/liter in diabetes patients and 10 mg/liter in hypoglycemia patients have different significance. Averaging glucose levels for diabetes patients and hypoglycemia patients would result in a “healthy” mean, which is clearly contrary to reality. We can find that all process attributes share this same problem. Other examples include blood pressure, body core temperature, metabolic intermediate concentrations, etc.

Any process attribute as well as unit change to an attribute such as glucose level (mg/liter), red blood cells (no/liter), white blood cells (no/liter), enzyme activity (in any units), etc. have no standalone meaning unless it is considered for a specific person under a set of specific conditions. Thus, a computed mean of any health property has no meaning to each of the persons. If

the reaction rate of a specific biological pathway in one person is  $X$  while that for another person is  $2X$ , the mathematical average can represent neither. Intermediate concentrations also have no meaning. A low glucose concentration would imply low conversion speed only if the rate constant for the biological process is same. It is possible that 110 mg/liter in an obese person may reflect even an lower conversion speed than 70 mg/liter in a young person. Similarly, the rate constant or activity level of an enzyme has no meaning unless it is considered in context. The high level of glucose in an obese person might be caused by excessively slow conversion rate so that more of absorbed glucose is backed up in the blood. Given the complexity, there is no basis to add glucose levels for persons in a population and then say the mean is the best. It is best for none, not even any of those in the population except by accident.

Each process attribute in the biological network [106-108] of a person is distinctive and this nature bars approximations. Given the long development time of chronic disease, departure in any process attribute in the biological network is very small [Sup. A]. Based on above discussion, we find that all process attributes have non-linear, complex effects on personal health, and that their effects on personal health depend on many other associated factors or interactive factors. Personal health values cannot be added up across different persons except in situations where research purposes can tolerate such errors. Computed mean cannot be imposed onto any specific person because the mean must be different from the correspondent value for the person for all reasons stated above. All above examples imply that imposing population means on any persons must be harmful to the persons or even kill them. This can be seen from blood pressure, heart output, metabolic intermediate concentrations, car repairing model or plane repairing model. Treatments from the population approach not just have failed to find cures but most probably have been hurting patients for centuries.

Many large-scale clinical trials such as the TAILORx trial [109] reveal misuse of representation principle. It attempted to get better “representation” from people by running a multiple



national trial. Since findings from clinical trials always had some kind of average of personal numbers, they cannot represent a super majority of the persons other than lucky persons whose numbers luckily fall on the average (which may happen by the chance of winning a lottery). The average is not the optimal value of any person in the trial subjects. Since the mean of a health property derived from a population cannot represent different persons, a treatment on the basis of such health property cannot be valid for any of participant persons except the abstract person that does not exist. There is no basis to find that such a treatment is best for other patients outside the trial. The flawed logic is that the validity of the treatment for persons in the U.S. depends on how good the treatment is to persons in Brazil.

### **C. Inaccuracies Introduced by the Binary Scale And Disease Classifications**

Another problem arises from using the binary scale. Most of health properties are continuous properties except a few things like gender and death. Most health properties actually exhibit 0 and 1 states, with 1 state further comprising values in non-linear continuous profile. One example is exposure to a virus. Exposure can be classified as no and yes. Among exposures, infection risk would depend on the number of viral copies exposed. However, nearly all health properties or process attributes of biological pathways are continuous. They differ in amount or degree. Blood pressure may take any values in the observed range, but is artificially divided into several ranges. The convention of disease or no-disease is imposed by human wills and is foreign to nature. Conversion of such properties into the binary states introduces excessive errors. By common sense, digitizing a sound by two-bit digital scheme can introduce great distortions. Conversion of data into the binary scale can introduce as much as 50% relative error. The 49.9% will become zero while 50.1% will become one, but each of the two numbers could get a different binary value. The binary scale has been widely used to characterize health conditions, disease definitions, blood pressure, selection of control groups, etc. The normal and abnormal system is widely used for chemical analysis data, and thus introduces

excessive errors relative to the required accuracy for correcting chronic diseases. Categories are also used in classifying side effects, cancer stages, etc in an attempt to break continuous properties into categories by human wills. The use of the binary scale has a severe tension with holistic balance necessary for maintaining health. The worst problem is that the convention of research question. The binary scale cannot provide precision required to characterize chronic diseases. In medical studies, nearly all medical research articles ask a question and then provide a yes-or-no answer. Most health properties such as blood pressure, glucose levels, body weight, etc. are classified into two statuses. This convention affects patient selection (patients v. Healthy persons), material selection, background data, and measurement methods (e.g. chronic liver diseases and no liver disease). Part or all experimental data may be acquired as non-binary measurement data, then are processed quantitatively in statistical analysis. Then, the resulted data are converted back to a binary scale in order to support a conclusion. Those processes introduce too many and too bigger errors. Even ignoring all other problems, a final conclusion like that vitamin D is effective for treating COVID-19 is meaningless. Those under vitamin D intoxication should never take vitamin D supplement. The biggest problem is the use of symptom-based diagnosis method. Damages to a vital organ can range from local and sporadic damages to organ cells to widespread damages to all cells and whole organ to depress the organ's function to nearly disability or death level. Since human vital organs normally have massive functional redundancy [101-103], binary disease categorization methods, which are frequently used in clinical trials, consistently fail to detect side effects in early stages.

### **D. Inherent Dangers of Synthetic Drugs**

“Medicine can cure diseases” is the oldest presumption that everyone takes it for granted. The first synthetic drug, chloral hydrate, was discovered in 1832 by Justus von Liebig in Gießen and introduced as a sedative-hypnotic in 1869 [110]. Before the start of new drug industry, all medicines, referred in the old medical literature, are natural products comprising a mixture of



natural compounds, and most medicines are even formulations of natural products like herbs. After 1869, medicine definition was changed without examining its validity into synthetic components [111]. There are several important changes to the original meaning. Old medicines work like multiple-component diets with much milder effects while synthetic drugs are used at higher concentrations. Second, early medicines are things that once worked as selection pressure in evolution. For example, the compounds from herbs, plants, and natural products might have found their way to human bodies through the food chain. It is reasonable to infer that human body can tolerate them in low concentrations. Fecundity phenotype will not be passed on to the next generation if the person cannot tolerate natural compounds at low concentrations, and die before reaching reproductive age. In comparison, most human beings are not exposed to synthetic drugs, and thus selection will start upon ingesting such compounds. Those two things affect drug side effects, long term safety, and possibility to cure chronic diseases.

### E. Flaws In Reductionist Treatment Model

Most medical treatments are developed according to reductionist thinking. The reductionist idea is that human body is like a machine, and any fault can be fixed by targeting the fault part. This notion has been proved in some aspects such as organ transplant. However, we also see severe limitations. For example, after a person has died for some time, there is no way to revive the dead person like restarting a car. The human ability to intervene brain is very limited. A reductionist treatment always has two components: a treatment is developed from a population and applied to the patient in treatment of a disease.

**(1) Evidence Proving Limitations:** The flaws in clinical trials and failure of reductionist treatments are two different things but share some common elements. We have proved that treatments derived from clinical trials are deemed to be poor or inherently dangerous due to mismatched application [9]. Reductionist treatments have been found poor or unworkable in nutrition [114-115], lower back pain [116], neuroscience and brain research [117-118], diagnostics [119], exercise [120],

patient care [121-132], public health programs [124], and holistic medicine [125-127, 151]. The evidence, taken as whole, has firmly established that reductionist treatments are inferior. Those findings in combination of our simulation study [9] prove that reductionism is a wrong approach to chronic diseases.

**(2) Implications of Automobile Repair:** It is generally believed that a treatment developed from a population must be good for persons A, B, C, etc. While this idea formed in old history, it can be summarily rejected by using a car repairing model. Automobiles made by Honda, Nissan, and Ford cannot be repaired by using a common method or common specification because they are distinctively designed. None of the average process properties such as fuel flow rate, heat dissipation rate can be imposed on all of them. We now know that each human body is also distinctively designed. Second, even for cars, many process attributes cannot be altered without changing the whole car. For example, the cooling system and exhaustion system for each model of car must be matched to the rest of the car. Even the wheels for a given model of car cannot be replaced by average sizes of the wheels used in all cars. The average of the fuel consumption rates for a Civic and a Mercedes-Benz G550 cannot be imposed on either the car. We should easily see that if auto repair and plane repair industries have used a population approach, mechanical problems in automobiles and planes must be incurable. All planes will crash.

A treatment derived by clinical trials must be mismatched to patients. For example, John Doe suffers Vitamin A deficiency but Jack Doe suffers Vitamin A poisoning. Both are sick even though their average is perfect. If a treatment is developed from such a population, the treatment reflects impermissible transfer of process attributes between two different biological networks. The treatment cannot be valid for both of them. This is not an isolated problem but a universal problem in treatments for chronic diseases. Most, if not all, of nutrients, pollutants, activities levels, etc. are expected to have both positive and negative effects. If a treatment can affect one or more of such factors, the treatment must be improper for a considerable portion of persons. Even if a treatment has a constant treatment effect, the



interfering factors can distort the treatment (see Tables 1, 2, and 3). Mathematical models make impermissible averaging and treatments deduced by the wrong methods cannot be good for anyone except by accident.

Treatments derived from population trials always make improper trade harmful to patients. In a mini trial comprising a 90-year old man, a 40-year old man, a 40-year female, and a 10-year old boy, their health and disease properties must vary greatly. We acquire data and find an averaged value in a health property for this population. The data does not form a statistical population. If we impose the averaged value onto all of them by an imagined measure, we should anticipate that the measure most probably will kill all of them in a long run. Obviously, to develop a treatment by the population approach, attempts have been made to balance age effects and sex effects. Treatment of the old man is balanced by the need to offer benefits to the young boy. A treatment for the man is balanced by the need to offer benefits to the female. This mathematical averaging in data process violates our observed principle that health property cannot be altered arbitrarily and cannot be transferred from a person to person. Any treatment based on the representation principle must be detrimental to all persons if the treatment is used for the long term. This flaw cannot be cured by increasing the number of participants in the trial. If a treatment is better for some, it must be worse for others.

Even responsive rate used in medicine is a poor concept. Two treatments with 5% curative rates are considered in mathematics as same. However, they mean completely different things if one treatment cures only females while another cures only males. The population model makes an assumption that all persons are treated in the same way, but in reality, they cannot. In reality, what is really important is who will survive and who will die. Treatments determined by using mathematical model are insensitive to personal differences and cannot be used to formulate the best treatments for all persons. Two treatments respectively with responsive rates of 50% and 40% lack comparative basis and cannot be compared. If they work on entirely different persons, they would benefit 90% of the

population if each of the two treatments are matched to right persons. If their joint responsive rate is 20%, they would benefit 70% persons in the population.

### (3) Constraints of the Metabolic Pathways Networks:

Each person has a unique biological pathway network [106-108], and chronic diseases are manifestation of a large number of departures in process attributes in the network. All attributes in one person's biological pathway network are different from those in another person's network. This distinctiveness is implied by well known variations of chemical analysis data [128]. The distinctiveness of physical check-up profile of a person is well known. If a treatment is used on different persons, changes caused by the treatment in process attributes in one person's network must be different from changes in other personal pathways networks. If the treatment is derived from a population study, the treatment cannot be matched to any person because the personal networks are different in different persons and the driving factors are even more different. Thus, if a treatment is best for one person, it cannot be best for another person.

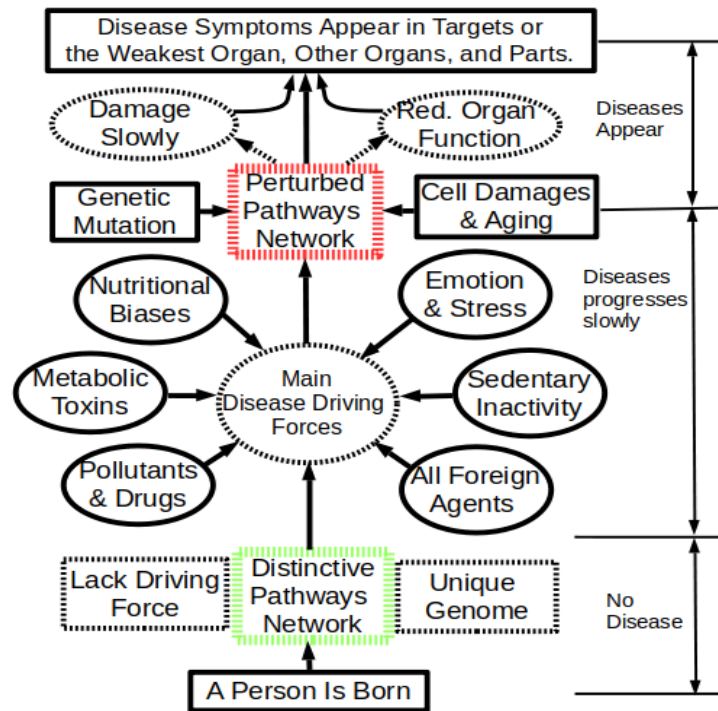
It is obvious that a treatment cannot correct all departures in the biological pathways network. One well known example is the alteration of biochemical and cellular pathways in cancer patients: attributes of six categories of biological properties (growth signaling, cell apoptosis, anti-growth signaling, angiogenesis, tissue invasion and metastasis, and cell replication limits) are changed in cancer patients [108]. Those process attributes may like those shown by P1, P2.... Pn in Figure 2. The top diagram shows a plurality of normal process attributes. Fault environmental, dietary, emotional, and lifestyle factors slowly drive some process attributes to depart from healthy values. It is highly unlikely that the disturbed biological networks can be corrected by using one single synthetic drug. This may be the reason why drugs deliver results that are poorer than what is predicted in theory. It is anticipated that application of a number of influencing factors can have better chances to correct the departures in process attributes responsible for chronic diseases.

**(4) Drugs Cannot Fix CNS Problems:** The role of the CNS was known even in 1875 [1]. Now, more and more evidence

shows the important role of the CNS on personal health and chronic diseases. The mathematical models used in medicine cannot characterize interactions between the Central Nervous System and the body running biological pathways. It is well known that the CNS and body constantly exchange neuronal signals but little about the signals are understood. It is expected that any changes caused by emotional interventions will invite the CNS to respond. We reasonably assume that the CNS-body

interactions are to resist changes in the body. Mind and body interactions are like a gearbox containing two gears. One gear cannot be freely altered without making correspondent adjustment to the other.

**(5) Drugs Disrupt Metabolic Pathways Networks:** All process attributes in personal biological networks are caused by a large number of interfering factors.



**Figure 1:** Environmental, dietary, emotional and lifestyle factors slowly drive the processes attributes of metabolic pathways in the pathways network to slowly depart from their normal values, resulting in chronic diseases.

Correction of problems in personal biological or metabolic networks cannot be made by targeting only one or a few steps in the network. This is shown in Figure 1. For example, the immune system can be suppressed by emotional distress, chronic stress, toxins and heavy metals, nutritional imbalance, poor vascular system attributed to lack of exercise, toxic micro-organic byproducts, etc. The actual causes may comprise a large number of primitive environmental, dietary, and lifestyle factors. Simultaneous correction of hundreds of fault factors is more

powerful than doing one single treatment which may completely miss the target.

A treatment targeted to one attribute such as P2 of one pathway lacks sufficient driving force. Such a treatment cannot correct all departures in process attributes but most probably disturb other process attributes. If a treatment is to alter the rate of one biological pathway, it is impossible to tell how the treatment might alter other pathways. Besides, responses in other pathways might depend on personal variations (associated factors and interactive factors). Thus, one should find that diseases cannot be



cured by correcting one seemingly fault pathway. It is possible some unexpected changes in other process attributes may make personal health or disease worse. This is one reason that synthetic drugs fail to work.

Figure 1 shows how a chronic disease develops, where the disease may be colon cancer. In this case, P1 to Pn could mean, respectively, genetic mutations, foreign agents, microbiota, pollutants and toxins, nutrition, heavy metals, vascular condition, organ functional capacities, inflammation biomarkers, micro-circulation condition, innate immunity, CNS condition, nerve health, glucose level, emotional states, etc. Microbiota affects metabolic byproducts which may damage cells; foreign agents such as infectious agents, fiber grasses and asbestos may affect tissue's local environment. P1 to Pn represent relative values of plural process attributes (e.g., the glucose level) or anything that could directly or indirectly affect the process attributes of metabolic pathways in the metabolic networks. Each of the P1 to Pn factors may mean a combination of a large number of lower level attributes. Foreign agents may be anything that could disturb the metabolic pathways with an effect of promoting cancer. Toxins may mean one or more of potentially thousands of known and unknown compounds. Figure 2 represents process attributes for any person. Due to difference in personal genome, the process attributes for each person are distinctive. The baseline profile of one person must be different from that of another person. During development, the pathways profile is driven by a large number of fault environmental, dietary, emotional and lifestyle factors. Thus, it is expected that two colon cancer patients have completely different process attributes and naturally require different adjustments to their lifestyles. The cancer in one person may be caused by using a large amount of salty, excessive hot, fried snacks while the cancer of the other might be caused by excessive stress, distinctive microbiota, and lack of exercise. While any two persons may share some common things by various degrees, they must be treated differently to achieve best results. It is possible that some lifestyle factors may be used in the opposite way.

**(6) Oversimplified Mathematical Models:** We will consider how mathematical model might perform when it is used

to predict disease outcome of COVID-19 disease for a person. Infection diseases are mainly controlled by (1) exposures to the virus, (2) viral reproduction ability, (3) innate immune responses and host responses, (4) acquired immune response, and (5) the capacity to withstand tissue damages [104, 137-142]. Thus, disease severity such as risk of death could be expressed as multiple functions of a large number of influencing factors under various conditions. If the virus exposure is well controlled, the contribution from (2) to (5) will appear to have no role in the disease outcome. If acquired immune response is fast and powerful in the early stage of infection, all of the defense mechanism from (1) to (3) and (5) may appear to have no role. From those large contributory ranges, we believe that a realistic mathematical model must comprise multiple equations with various conditions. Each of the equations may be a linear equation, a polynomial equation, or other numeric equation, etc, which has tens to thousands primitive lifestyle, personal, dietary, emotional, and environmental factors. Disease severity also depends on aging or development stage, information in neurons, hormonal regulation, epigenetic changes in cells, menopause status, personal activities, etc. Many of the factors are random variables so that some of the component equations are also random variables. For a population, disease severity is just viewed as the sum of all functions for all different persons. No solution could be found to such complex functions, there is no way to combine all personal functions for the population, and there is no way to solve a combined function for the population.

A mathematical model developed for a person cannot be used to predict disease severity for other persons unless they are close to the person. The model may tell how to change dependent variables to achieve a better outcome. We also found that current epidemiological models [143-147] are irrelevant to the disease and human being. An articulation like "warm temperature or sufficient oxygen in breathing air can cure the disease" has far more science than a bad mathematical model. Epidemiological models contain almost none of the biological factors. Manipulation of twenties to a hundred factors, most of which are conceived out of imagination with no reality, will not help solve



the pandemic. Medicine needs to pay more attention to human disease biology and personal health, rather than coins, dices, lotteries, equations, forms, article structures, etc. It is a wrong strategy to jump onto the population health while forgetting basic disease biology.

Strong treatment that is not matched to the patient condition must produce drug side effects if the treatment is used for a long time [129-136].

## DISCUSSION

### A. Overwhelming Flaws In Medicine

All presumptions -- treating health property as a statistical population, using synthetic drugs as medicines, using mathematical models, disease classification, and using reductionist treatments -- are refuted as invalid unless they are used for purposes unrelated to treatment of chronic diseases. Other kind of population studies share one of more of those flaws. When medicine evolved from experienced-based ancient medicine to modern medicine, it silently changed from multiple-components slow-working natural medicines into highly concentrated synthetic drugs, changed the holistic mind-body medicine into reductionist treatments, turned abstract health properties of human beings into statistical populations, and later added mathematical models into the research models. Those presumptions have been accepted as the foundation of medicine, without ever being questioned and validated. Our analysis using massive data produced by tens of thousands of medical studies firmly refutes their validity. Nearly all assumptions in medicine we have examined fail to hold, introduced excessive inaccuracies, and are completely wrong. Failure is found at multiple levels: the binary scale, the presumed statistical distribution, mathematical models, synthetic drugs as medicines, the reductionist treatment approach, ignorance of emotion and mind, etc. The flaws in mathematical models include use of a linear number scale, summation of intensive properties, across-person modeling, and failure to consider varying significance. Due to overwhelming flaws, medicine lacks required accuracy for characterizing chronic diseases and will never find predictable cures for chronic

diseases. We must find that failure to find cures is only a small part of problems, and a much bigger problem is that population-derived treatments must endanger patients as long as the treatments are used on a long-term basis and such treatments must have hurt human species for the entire history. However, their adverse effects are hidden due to massive organ functional capacities, a large number of interference factors and insufficient follow-up time in studies. Clinical trials have one-way biases against weak and slow-delivering factors. Each of the potentially thousands of harmful and toxic substances might have been found to be harmless; but in reality they actually work jointly to hurt humans, species and the planet.

### B. Limitations in Clinical Trials

Flaws in clinical trials include (1) misuse of statistical population as presumption without considering research purposes and required accuracy; (2) failure to consider a massive number of interfering factors and co-causal factors; (3) misusing mathematical models in an attempt to change process attributes as if they were fungible and extensive; (4) use of overly simplified mathematical models which cannot model complex defense mechanisms; (5) misuse of the representative principle whereas statistical mean cannot represent each person due to the body's restrictions; (6) failure to determine required accuracy relative to interfering factors; (7) failure to address one-way biases caused by the symptom-based diagnosis method and interfering factors; and (8) failure to note that population means cannot be applied to any person including even those in the clinical trials. Each of those problems can make study findings inaccurate, biased, and even meaningless, and may create treatments that actually endanger patients.

A clinical trial cannot produce a right result in following cases: (1) A treatment is used only for a short time so that its treatment effect is hidden among  $N$  interfering factors  $F_i$  (A brief exercise, brief diet and brief emotional invention will show no detectable benefits); (2) a treatment does not have the same or similar effects on all subjects (e.g., cancellation of positive and negative effects); (3) all interfering factors have different impacts



on different subjects; (4) clinical trials conceal side effects by cross-person averaging of side effects; (5) drug side effects are realized slowly while the measured health properties are interfered with by a large number of interfering factors. Clinical trials or population study may be valid if (1) a strong treatment  $T$  is against  $N$  interfering factors  $F_i$ , where  $T$  is much stronger than the total effect of all interfering factors  $\sum f_i$ ; (2) the accumulated effect of the treatment in a sufficiently long period can stand out the accumulated interfering factors  $\sum f_i$ ; (3) the findings are not used for guiding treatment of chronic diseases and accuracy is sufficient for the research purpose; or (4) all introduced errors can be tolerated for practical reasons. The side effects are concealed due to massive organ reserve capacities, interference effects, and their slow materialization. Additional inaccuracies are introduced by use of the binary scale, disease classification, and use of abstract definitions. The representation principle is wrongly used in medical research, but can have even more adverse impacts on the minority. Genetics are more similar between persons within a race than between persons in different races. Computed average of health property for a population of a majority race is expected to be different from that for a population of a minority race. If a treatment is developed by a clinical trial containing more persons of the majority race, the average will be closer to the average of the majority race. This implies that the treatment is more dangerous to the minority race than it is to the majority race. It is well known that antibiotics doses developed in the U.S. may pose higher risks to patients from Asian nations.

### C. Unworkable Reductionist Treatments

Reductionist treatments cannot cure chronic diseases because they (1) attempt to make impermissible trades in health properties between different persons; (2) are not mismatched to specific persons' biological networks; (3) fails to address the interlocking role of the CNS; (4) lack any conceivable theoretical and practical basis to restore departures of biological pathway attributes in the metabolic pathways networks; (5) cannot work with multiple layers of defense mechanisms; and (6) must distort the intervened pathway and other pathways in the pathway

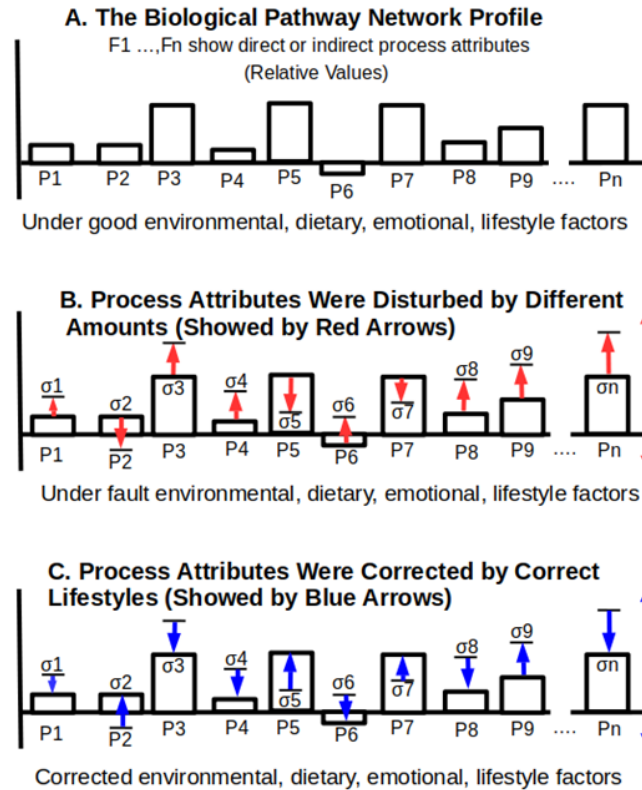
network and thus cause drug side effects. They are the reasons that medicine fails to find cures for chronic diseases for centuries while most side effects are written off. Population-derived treatments should be presumed to be dangerous if they are used in long terms because they can slowly distort the person's pathway network. The process attributes values of any biochemical and metabolic pathway is constrained by upper-stream, coupled and downstream pathways in the pathways network. We predict that medicine will not find cures for chronic diseases but may extend lives for real terminal diseases.

### D. Wrongly Dismissed Benefits of Lifestyle Factors

The magnitude of effects of lifestyle factors on chronic diseases and cancers is much larger than that of synthetic drugs. The beneficial effects of exercise can reduce death by almost 40%, and the impacts of emotional distress are very large as reflected in studies on wound healing, heart diseases, etc. However, clinical trials could not correctly detect their benefits due to (1) cancellation of positive effects and negative effects on different persons, (2) interfering effects of a large number of other factors, (3) the buffering effects of massive organ reserve capacities, and (4) slow delivery of beneficial effects of adjustments to lifestyle factors. Alterations in both organ functional capacities and body structures normally take long times, and disease reversal could take even longer times in some cases. It is agreed that preventive measures may be used to prevent diseases; but we believe that reversing fully developed diseases is not impossible except it requires much more efforts and time. Immediate cures for chronic diseases lie in use of plural weak factors to restore the abnormal process attributes in the personal metabolic pathways network. Use of evolution-compatible life style factors are presumed to be safe. Most biological properties (except genes and ages) can be altered by using lifestyles, foods, exercise, emotional management, and avoidance of toxic substances. The effect size of many influencing factors have been found in studies for different purposes; and effects of other weak factors have not been studied, but will be found to be important. Cancer self-resolution is not

controlled by random odds but triggered by major changes in lifestyle even though patients may not be aware of what have happened. Studies involving weak environmental, dietary, emotional, lifestyle factors, etc. are generally wrong if findings

are negative. However, if their findings were positive, the real treatment effects may be much stronger even though they are not necessarily good.



**Figure 2:** The black squares in (A) represent the normal values of processes attributes of metabolic pathways in the pathways network; the red arrows in (B) indicate how fault lifestyle factors cause attribute values to depart from their normal values; and the blue arrows in (C) indicate how the departed processes attributes are corrected by adjustments to lifestyle factors.

### E. Mathematical Models for Personalized Medicine

Real adverse effects of any weak factor cannot be accurately characterized due to large vital organ reserve capacities, slow delivery of its side effects, interference of a large number of other factors, and inaccuracies introduced by the binary scale and disease classification. Use of statistics must be viewed as junk science in most applications (but they may be used to address true measurement errors; and also same findings in studies can be used for non-medical purposes). The real life model raises several challenges. The health degree and disease outcome of a person depends on the totality of hundreds to

thousands of factors. Any single factor such as a nutrient's status, a toxic substance, a foreign agent, emotional distress, daily activity, even thinking habit, and any of their combinations can control the health and disease outcome. The true effect of any of the potential factors can be masked or distorted by any of thousands of other factors or any of their combinations. We must presume that combined effects of other interference factors are always much larger than the effect of the treatment or the factor under investigation. This implies that treatment benefits rated or estimated by the mean of the treatment group have absolutely no relevance to any specific person. True cures must be based on personal condition. However, we must face several challenges.



First, we immediately see practical difficulties to evaluate all potential factors (e.g., a person might be under chronic poisoning of anything, nutritional imbalance, chronic foreign agent, etc.). The second challenge is the interference of organ buffering effects. Because the vital organs of most people have massive functional capacities, symptom-based measurements nearly always produce false results except when the investigated treatment is a super strong factor and follow-up time is sufficiently long. Those difficulties imply that evaluation of a weak treatment cannot be based on directly on existence of symptoms or lack of symptoms. As we have shown, measured data do not tell reality. Another challenge is practical inability to find and evaluate all potential interference factors by invasive tests and medical diagnosis. Both the current research model and treatment model cannot be used by doctors who practice personalized medicine. A new health model must be based on combination methods with mathematical modeling as the central tool. However, the mathematical model used in future is different from the modeling approach used in the population medicine. It must have large modeling capacities for any person and any health problem.

The real life model even refutes the linear number scale, which is routinely used in pure mathematics. The significance of a given unit change in temperature, blood pressure, vital compound concentration, etc. always change, depending on whether the value is close to a safe region or a death threshold. Moreover, choices of interventions and the level of interventions must be based on the person's vital signs and the totality of all relevant influence factors. If a mathematician wants to prevent a death, he cannot use the equation to make a prediction, but must take different measures by looking at different values. Realistic mathematical models must reflect varying scales and different significance of any health properties. Future health mathematicians cannot assume that number additivity like  $1+2=3$  is valid. Instead, the answer always depends on the body's condition and other relevant factors. The linear number scale may be used for approximation only if introduced errors can be tolerated. Mathematicians must explore constraints imposed by

life phenomenon, life-maintaining processes, host structural constraints, and overwhelming interactions, which can easily decide life or death. We predict that human ability to develop realistic mathematical models for the human body will be a limiting factor in future personalized medicine.

## F. Terminal Impacts of Medicine On Human Species

We regard the use of clinical trials and population-based research model as the main reasons for failure to find cures. By relying on flawed research findings, societies fail to explore cures that are immediately available but keep doing futile researches with no chance of success. The flawed medicine and flawed medical knowledge has found their way into all social strands, all federal/state policies, all federal/state laws, all social practices, existing media, etc. Wrong research findings become lame excuses for exposure to avoidable toxic substances such as food additives, synthetic flavors, food texture modifiers, avoidable pollutants, antibiotics, hormones, etc. Now, cancer, infertility, mental diseases, infectious diseases, etc. are striking mankind with unprecedented impacts. For example, the risk of getting cancer in a person's lifetime rises from near nothing, to 0.04, to 0.4 and will soon reach a unit and even multiple units. The first cancer diagnosis ages are shifted to fifties, forties, thirties and even teens and newborns. Incidences like six cancer patients in a family and three cancer deaths in one family have become more and more common. There is no way to control the cancer pandemic, and no magic measure can ever arrest all disease momenta. Other health problems like infertility will become a civilization crisis. The failure of medicine is responsible for tens of million of annual premature deaths from chronic diseases in the world, the waste of a portion of \$41 billion federal research funds administered by NIH, the use of more than a hundred billion dollars private research fund in the U.S., the trillion of medical spending in the U.S., and the wrong knowledge of published medical studies. Failure of medicine is responsible for the incurable notion that works like death spells on all humans. Our findings imply that the total stress of all toxic substances on human life and other species is responsible for the rapidly



degraded ecosystem, environment and climate. Unfortunately, the U.S. medical establishment has built sophisticated protective devices to discriminate against, preclude, and suppress such findings. Refusal to correct the magnitudes of errors is equivalent to keeping death spells for patients and human species, killing other species, and destroying civilization.

### CONFLICTS OF INTEREST

None. The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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### ADDITIONAL INFORMATION

Additional information is provided in a supplemental document and additional factual information will be stored in [igoosa.com](http://igoosa.com) online database.

### References

1. Cole T. Failures of medicine. *British Med J.* 1875; 6: 579-582.
2. Kresser C. Two reasons conventional medicine will never solve chronic disease.
3. Green AR. Why the disease-based model of medicine fails our patients. *West J Med.* 2002; 176: 141-143.
4. Advisory board, precision medicine fails for up to 93% of patients. Are its proponents selling false hope. 2018.
5. List of incurable diseases. In Wikipedia. 2020.
6. Wu JQ, Zha P. Surgery, chemotherapy and radiotherapy promote cancer growth speeds and shorten patient lives. 2019.
7. Tackling the burden of chronic diseases in the USA. *Lancet.* 2009; 373: 185.
8. DeVol R, Bedroussian A. An unhealthy America: The economic burden of chronic disease. 2007; 1-35.
9. Wu JQ, Zha P. Randomized clinical trial is biased and invalid in studying chronic diseases, compared with multiple factors optimization trial. 2019.
10. Krauss A. Why all randomised controlled trials produce biased results. *Ann Med.* 2018; 50: 312-322.
11. Bhatt A. Evolution of clinical research: A history before and beyond James Lind. *Perspect Clin Res.* 2010 1: 6-10.
12. Walker HM. *Studies in the history of statistical method.* Arno Press. 1975.
13. Altman DG. Comparability of randomized groups. *The Statistician.* 1985; 34: 125-136.
14. Senn SJ. Covariate imbalance and random allocation in clinical trials. *Stat Med.* 1989; 8: 467-475.
15. Senn SJ. Testing for baseline balance in clinical trials. *Stat Med.* 1994; 13: 1715-1726.
16. Senn S. Controversies concerning randomization and additivity in clinical trials. *Stat Med.* 2004; 23: 3729-3753.
17. Senn SJ. Seven myths of randomization in clinical trials. *Stat Med.* 2013; 32: 1439-1450.
18. Zhao W, Berger V. Imbalance control in clinical trial subject randomization – from philosophy to strategy. *J Clin Epidemiol.* 2018; 101: 116-118.
19. Althouse AD, Abebe KZ, Collins GS, Harrell FE. Response to why all randomized controlled trials produce biased results. *Annals Med.* 2018; 50: 545-548.
20. Reference ranges for blood tests. In Wikipedia. 2020.
21. Pennisi E. The human genome. *Sci.* 2001; 291: 1177-1180.
22. Auton A, Brooks LD, Durbin RM. A global reference for human genetic variation. *Nature.* 2015; 526: 68-74.
23. Misteli T. Beyond the sequence: cellular organization of genome function. *Cell.* 2007; 128: 787-800.
24. Bernstein BE, Meissner A, Lander ES. The mammalian epigenome. *Cell.* 2007; 128: 669-681.
25. Ogino S, Fuchs CS, Giovannucci E. How many molecular subtypes. Implications of the unique tumor principle in personalized medicine. *Expert Rev Mol Diagn.* 2012; 12: 621-628.
26. Ogino S, Lochhead P, Chan AT. Molecular pathological epidemiology of epigenetics: Emerging integrative science to analyze environment, host, and disease. *Mod Pathol.* 2013; 26: 465-484.
27. Liu YZ, Wang YX, Jiang CL. Inflammation: the common pathway of stress-related diseases front. *Hum. Neurosci.* 2017; 11: 316.



28. Steptoe A, Hamer M, Chida Y. The effects of acute psychological stress on circulating inflammatory factors in humans: a review and meta-analysis. *Brain Behav Immun.* 2007; 21: 901-912.
29. Segerstrom SC, Miller GE. Psychological stress and the human immune system: a meta-analytic study of 30 years of inquiry. *Psychol Bull.* 2004; 130: 601-630.
30. Bae YS, Shin EC, Bae YS, Eden W. Editorial: Stress and Immunity. *Front. Immunol.* 2019; 10.
31. Dhabhar FS. Effects of stress on immune function: the good, the bad, and the beautiful. *Immunol Res.* 2014; 58: 193-210.
32. Marketon WJI, Glaser R. Stress hormones and immune function. *Cell Immunol.* 2008; 252: 16-26.
33. Pedersen AF, Zachariae R, Bovbjerg DH. Psychological stress and antibody response to influenza vaccination: a meta-analysis. *Brain Behav Immun.* 2009; 23: 427-433.
34. Pedersen A, Zachariae R, Bovbjerg DH. Influence of psychological stress on upper respiratory infection-a meta-analysis of prospective studies. *Psychosom Med.* 2010; 72: 823-832.
35. Walburn J, Vedhara K, Hankins M, Rixon L, Weinman J. Psychological stress and wound healing in humans: a systematic review and meta-analysis. *J Psychosom Res.* 2009; 67: 253-271.
36. Hawryluck L, Gold WL, Robinson S. SARS Control and Psychological Effects of Quarantine, Toronto, Canada. *Emerg Infect Disv.* 2004; 10: 1206-1212.
37. Lutgendorf SK, Sood AK, Anderson B. Social support, psychological distress, and natural killer cell activity in ovarian cancer. *J Clinical Oncol.* 2005; 23: 7105-7113.
38. Lutgendorf SK, DeGeest K, Dahmouh L. Social isolation is associated with elevated tumor norepinephrine in ovarian carcinoma patients. *Brain, Behavior, Immunity.* 2011; 25: 250-255.
39. Smith M, Lutgendorf SK, Sood AK. Impact of stress on cancer metastasis. *Future Oncol.* 2010; 6: 1863-1881.
40. Sloan EK, Priceman SJ, Cox BF. The sympathetic nervous system induces a metastatic switch in primary breast cancer. *Cancer Res.* 2010; 70: 7042-7052.
41. Sundquist J, Li X, Johansson SE, Sundquist K. Depression as a predictor of hospitalization due to coronary heart disease. *Am J Prev Med.* 2005; 29: 428-433.
42. Brydon L, Magid K, Steptoe A. Platelets, coronary heart disease, and stress. *Brain Behav Immun.* 2006; 20: 113-119.
43. Wojcikowski J, Daniel WA. The role of the nervous system in the regulation of liver cytochrome. *Curr Drug Metab.* 2011; 12: 124-138.
44. Chandra RK. Nutrition and the immune system: an introduction. *Am J Clin Nutrition.* 1997; 66: 460-463.
45. Keusch GT. The History of Nutrition: malnutrition, infection and immunity. *J Nutrition.* 2003; 133: 336-340.
46. Ritz BW, Gardner EM. Malnutrition and energy restriction differentially affect viral immunity. *J Nutrition.* 2006; 136: 1141-1144.
47. Levander OA. Nutrition and newly emerging viral diseases: An Overview. *J Nutrition.* 1997; 127: 948-950.
48. Schaible UE, Kaufmann SH. Malnutrition and Infection: complex mechanisms and global impacts. *PLoS Med.* 2007; 4: 115.
49. Alice M, Tang ES, Semba RD. Nutrition and Infection. In: Kenrad E., Nelson CMW, editors. *Infectious Disease Epidemiology: Theory and Practice*, Burlington, MA: Jones and Bartlett Learning.
50. Beck MA. Selenium, Vitamin E. status: impact on viral pathogenicity. *J Nutrition.* 2007; 137: 1338-1340.
51. Beck MA, Handy J, Levander OA. Host Nutritional Status: the neglected virulence factor. *Trends Microbiol.* 2004; 12: 417-423.
52. Nelson HK, Shi Q, Dael P. Host Nutritional Selenium Status as a driving force for influenza virus mutations. *FASEB J.* 2001; 15: 18468.
53. Beck MA, Toone DW, Levander OA. Cocksackievirus B3-Resistant mice become susceptible in se/vitamin e deficiency. *Free Radical Bio Med.* 2003; 34: 1263-1270.
54. Barnett JB, Hamer DH, Meydani SN. Zinc: a new risk factor for pneumonia in the elderly. *Nutr Rev.* 2010; 68: 30-37.
55. Kanneganti TD, Dixit VD. Immunological complications of obesity. *Nature Immunol.* 2012; 13: 707-712.
56. Karlsson EA, Beck MA. Diet-induced obesity impairs the T cell memory response to influenza virus infection. *FASEB J.* 2009; 23: 110-113.
57. Karlsson EA, Sheridan PA, Beck MA. Diet-Induced Obesity Impairs the T cell Memory Response to Influenza Virus Infection. *J Immunol.* 2010; 184: 3127-3133.
58. Monteiro R, Azevedo I. Chronic inflammation in obesity and the metabolic syndrome. *Mediators Inflammation.* 2010; 289645.
59. Nieman DC, Henson DA, Cannarella SLN. Influence of obesity on immune function. *J Am Dietetic Assoc.* 1999; 99: 294-299.



60. Kanneganti TD, Dixit VD. Immunological complications of obesity. *Nat Immunol.* 2012; 13: 707-712.
61. Smith AG, Sheridan PA, Harp JB. Diet-induced obese mice have increased mortality and altered immune responses when infected with influenza virus. *J Nutrition.* 2007; 37: 1236-1243.
62. Aroor AR, DeMarco VG. Oxidative stress and obesity: The Chicken or the Egg. *Diabetes.* 2014; 63: 2216-2218.
63. Hardell L, Carlberg M, Soderqvist F, Mild KH. Case-control study of the association between malignant brain tumors diagnosed between 2007 and 2009 and mobile and cordless phone use. *Int J Oncol.* 2013.
64. Frei P, Poulsen AH, Johansen C. Use of mobile phones and risk of brain tumours: update of Danish cohort study. *BMJ.* 2011; 343: 6387.
65. Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR). Opinion on Potential health effects of exposure to electromagnetic fields. 2015.
66. Singh R, Gautam N, Mishra A, and Gupta R. Heavy metals and living systems: An overview. *Indian J Pharmacol.* 2011; 43: 246-253.
67. Carver A, Gallicchio VS. Heavy metals and cancer. *Intech Open.* 2018.
68. Yuan W, Yang N, Li X. Advances in understanding how heavy metal pollution triggers gastric cancer. Hindawi Publishing Corporation. *BioMed Res Int.* 2016; 7825432: 10.
69. Romaniuk A, Lyndin M, Sikora V. Heavy metals effect on breast cancer progression. *J Occupational Med Toxicol.* 2017; 12: 32.
70. Chowdhury R, Ramond A, Keeffe LM. Environmental toxic metal contaminants and risk of cardiovascular outcomes: systematic review and meta-analysis. *BMJ.* 2018; 362: 3310.
71. Lamas GA, Acien AN, Mark DB, Lee KL. Heavy metals, cardiovascular disease, and the unexpected benefits of edetate disodium chelation therapy. *Am Coll Cardiol.* 2016; 67: 2411-2418.
72. Sharma B, Singh S, Siddiqi NJ. Biomedical implications of heavy metals induced imbalances in redox systems. Hindawi Publishing Corporation. *BioMed Res Int.* 2014; 640754.
73. Marth E, Jelovcan S, Kleinhappl B. The effect of heavy metals on the immune system at low concentrations. *Int J Occup Med Environ Health.* 2001; 14: 375-386.
74. Anyanwu BO, Ezejiofor AN, Igweze ZN, Orisakwe OE. Heavy metal mixture exposure and effects in developing nations: an update. *Toxics.* 2018; 6: 1- 32.
75. Caffo M, Caruso G, Fata GL. Heavy metals and epigenetic alterations in brain tumors. *Current Genomics.* 2014; 15: 457-463.
76. Gorini F, Muratori F, Morales MA. The role of heavy metal pollution in neurobehavioral disorders: a focus on autism. *Rev J Autism Dev Disord.* 2014; 1: 354-372.
77. American Heart Association. Get the scoop on sodium and salt. 2018.
78. Ge S, Feng X, Shen L. Association between habitual dietary salt intake and risk of gastric cancer: A systematic review of observational studies. Hindawi Publishing Corporation. *Gastroenterology Res Practice.* 2012.
79. Strnad M. Salt and cancer. *Acta Med Croatica.* 2010; 64: 159-161.
80. Lee SK, Kim MK. Relationship of sodium intake with obesity among Korean children and adolescents: Korea National Health and Nutrition Examination Survey. *British J Nutrition.* 2016; 115: 834-841.
81. Teucher B, Dainty JR, Spinks CA. Sodium and Bone Health: impact of moderately high and low salt intakes on calcium metabolism in postmenopausal women. *J Bone Mineral Res.* 2008; 23: 9.
82. He FJ, Li J. Effect of longer term modest salt reduction on blood pressure: Cochrane systematic review and meta-analysis of randomized trials. *BMJ.* 2013; 346: 1325.
83. Melin VE, Potinini H, Hunt P. Exposure to common quaternary ammonium disinfectants decreases fertility in mice. *Reprod Toxicol.* 2014; 50:163-170.
84. Hrubec TC, Melin VE, Shea CS. Ambient and dosed exposure to quaternary ammonium disinfectants causes neural tube defects in rodents. *Birth Defects Res.* 2017; 109: 1166-1178.
85. Mahmood A, Eqan M, Pervez S. COVID-19 and frequent use of hand sanitizers, human health and environmental hazards by exposure pathways. *Sci Total Environ.* 2020; 742: 140561.
86. Watt BE, Proudfoot AT, Vale JA. Hydrogen peroxide poisoning. *Toxicol Rev.* 2004; 23: 51-57.
87. Tipton CM. The history of Exercise Is Medicine in ancient civilizations. *Adv Physiol Educ.* 2014; 38: 109-117.
88. Booth FW, Roberts CK, Laye MJ. Lack of exercise is a major cause of chronic diseases. *Compr Physiol.* 2012; 2: 1143-1211.



89. Cormie P, Zopf EM, Zhang X, Schmitz KH. The impact of exercise on cancer mortality. Recurrence, and treatment-related adverse effects. *Epidemiologic Reviews*. 2017; 39: 71-92.
90. Holmes MD, Chen WY, Feskanich D. Physical activity and survival after breast cancer diagnosis. *JAMA*. 2005; 293: 2479-2486.
91. Meyerhardt JA, Heseltine D, Niedzwiecki D. Impact of physical activity on cancer recurrence and survival in patients with stage III colon cancer: findings from CALGB 89803. *J Clin Oncol*. 2006; 24: 3535-3541.
92. Guetz GD, Uzzan B, Bouillet T. Impact of physical activity on cancer-specific and overall survival of patients with colorectal cancer. *Gastroenterol Res Pract*. 2013.
93. Ibrahim EM, Homaidh A. Physical activity and survival after breast cancer diagnosis: meta-analysis of published studies. *Med Oncol*. 2011; 28: 753-765.
94. Lahart IM, Metsios GS, Nevill AM. Physical activity, risk of death and recurrence in breast cancer survivors: a systematic review and meta-analysis of epidemiological studies. *Acta Oncol*. 2015; 54: 635-654.
95. Friedenreich CM, Neilson HK, Farris MS. Physical activity and cancer outcomes: a precision medicine approach. *Clin Cancer Res*. 2016; 22: 4766-4775.
96. Li T, Wei S, Shi Y. The dose-response effect of physical activity on cancer mortality: findings from 71 prospective cohort studies. *Br J Sports Med*. 2016; 50: 339-345.
97. Otto SJ, Korfage II, Polinder S. Association of change in physical activity and body weight with quality of life and mortality in colorectal cancer: a systematic review and meta-analysis. *Support Care Cancer*. 2015; 23: 1237-1250.
98. Schmid D, Leitzmann MF. Association between physical activity and mortality among breast cancer and colorectal cancer survivors: a systematic review and meta-analysis. *Ann Oncol*. 2014; 25: 1293-1311.
99. Wu W, Guo F, Ye J. Pre- and post-diagnosis physical activity is associated with survival benefits of colorectal cancer patients: a systematic review and meta-analysis. *Oncotarget*. 2016; 7: 52095-52103.
100. Zhong S, Jiang T, Ma T. Association between physical activity and mortality in breast cancer: a meta-analysis of cohort studies. *Eur J Epidemiol*. 2014; 29: 391-404.
101. Bortz WMT, Bortz WM 2nd. How fast do we age. Exercise performance over time as a biomarker. *J Gerontol A Biol Sci Med Sci*. 1996; 51: 223-225.
102. Goldspink DF. Ageing and activity: Their effects on the functional reserve capacities of the heart and vascular smooth and skeletal muscles. *Ergonomics*. 2005; 48: 1334-1351.
103. Sehl ME, Yates FE. Kinetics of human aging: I. Rates of senescence between ages 30 and 70 years in healthy people. *J Gerontol A Biol Sci Med Sci*. 2001; 56: 198-208.
104. Wu J, Zha P. Lung Damage mechanisms for COVID-19 and other lung infections, and driving force in leukocyte recruitment and migration. Preprints. 2020.
105. Christopher MP, Simon AJ, Jie Yang. Factors associated with hospitalization and critical illness among 4,103 patients with COVID-19 disease in New York City.
106. Biological pathway.
107. Metabolic pathway. In Wikipedia.
108. Weinberg H. The Hallmarks of Cancer. *Cell*. 2000; 100: 57-70.
109. Sparano JA, Gray RJ, Makower DF. Adjuvant chemotherapy guided by a 21-Gene expression assay in breast cancer. *Engl J Med*. 2018; 379: 111-121.
110. Jones AW. Early drug discovery and the rise of pharmaceutical chemistry. *Drug Test Anal*. 2011; 3: 337-344.
111. List of drugs by year of discovery. In Wikidiedia.
112. EMBO. Mind-body research moves towards the mainstream. Mounting evidence for the role of the mind in disease and healing is leading to a greater acceptance of mind-body medicine. *EMBO reports*. 2006; 7: 358-361.
113. Massey J. Mind-Body medicine its history and evolution. 2015.
114. Fardet A, Rock E. Toward a new philosophy of preventive nutrition: from a reductionist to a holistic paradigm to improve nutritional recommendations. *Adv Nutr*. 2014; 5: 430-446.
115. Fardet A, Rock E. Perspective: reductionist nutrition research has meaning only within the framework of holistic and ethical thinking. *Adv Nutr*. 2018; 9: 655-670.
116. Cholewicki J, Pathak PK, Reeves NP, Popovich JM Jr. Model simulations challenge reductionist research approaches to studying chronic low back pain. *J Orthop Sports Phys Ther*. 2019; 49: 477-481.
117. Krakauer JW, Ghazanfar AA, Marin AG. Neuroscience needs behavior: Correcting a reductionist bias. *Neuron*. 2017; 93: 480-490.

118. Hyland ME. Functional disorders can also be explained through a non- reductionist application of network theory. *Behav Brain Sci.* 2019; 42: 12.
119. Maguire G. Using a systems-based approach to overcome reductionist strategies in the development of diagnostics. *Expert Rev Mol Diagn.* 2013; 13: 895-905.
120. Bouchard C. Adaptation to acute and regular exercise: from reductionist approaches to integrative biology. *Prog Mol Biol Transl Sci.* 2015; 135: 1-15.
121. Gutierrez CE, Kehoe K. Integrative cardiac care at Queen's Medical Center. *Beginnings.* 2009; 29: 8-9.
122. Fortney L, Rakel D, Rindfleisch JA, Mallory J. Introduction to integrative primary care: the health-oriented clinic. *Prim Care.* 2010; 37: 1-12.
123. Hansen KA, McKernan LC, Carter SD. A replicable and sustainable whole person care model for chronic pain. 2019; 25: 86-94.
124. Dooris M, Farrier A, Froggett L. Wellbeing: the challenge of operationalising a holistic concept within a reductionist public health programme. *Perspect Public Health.* 2018; 138: 93-99.
125. Hayward E. Life and Time Swimming upstream: practising whole-person medicine in a reductionist medical culture. *Br J Gen Practv.* 2019; 69.
126. Manahan B. The whole systems medicine of tomorrow: a half-century perspective. *Explore.* 2011; 7: 212-214.
127. Miles A. On the interface between science, medicine, faith and values in the individualization of clinical practice: a review and analysis of *Medicine of the Person Cox.* *J Eval Clin Pract.* 2009; 15: 1000-1024.
128. Reference ranges for blood tests. In Wikipedia. 2020.
129. Drugwatch. FDA Recalls. 2020.
130. List of withdrawn drugs. In Wikipedia.
131. FDA-Approved prescription drugs later pulled from the market. 2020.
132. Pearce A, Haas M, Viney R. Incidence and severity of self-reported chemotherapy side effects in routine care: A prospective cohort study. *PLoS ONE.* 2017; 12: 0184360.
133. Link MC, Kirkland JL, Ness KK. Biology of premature ageing in survivors of cancer. *ESMO Open.* 2017.
134. Otin C, Blasco MA, Partridge L. The hallmarks of aging. *Cell.* 2013; 153: 1194-1217.
135. Golder S, Loke Y, McIntosh HM. Room for improvement. A survey of the methods used in systematic reviews of adverse effects. *BMC Med Res Methodol.* 2006; 6: 3.
136. Cornelius VR, Perrio MJ, Shakir SA, Smith LA. Systematic reviews of adverse effects of drug interventions: a survey of their conduct and reporting quality. *Pharmacoepidemiol Drug Saf.* 2009; 18: 1223-1231.
137. Yoo JK, Kim TS, Hufford MM, Braciale TJ. Viral infection of the lung: Host response and sequelae. *J Allergy Clin Immunol.* 2013; 132: 1-28.
138. Shi Y, Wang Y, Shao C. COVID-19 infection: the perspectives on immune responses. *Cell Death Differentiation.* 2020; 27: 1451-1454.
139. Handfield C, Kwock J, MacLeod AS. Innate antiviral immunity in the skin. *Trends Immunol.* 2018; 39: 328-340.
140. Tay MZ, Poh CM, Renia L. The trinity of COVID-19: immunity, inflammation and intervention. *Nature Reviews Immunol.* 2020; 20: 363-374.
141. Nutt SL, Hodgkin PD, Tarlinton DM, Corcoran LM. The generation of antibody-secreting plasma cells. *Nature Reviews Immunol.* 2015; 15: 160-171.
142. Tseng CT, Perrone LA, Zhu H. Severe acute respiratory syndrome and the innate immune responses: modulation of effector cell function without productive infection. *J. Immunol.* 2005; 174: 7977-7985.
143. Guerra FM, Bolotin S, Lim G. The basic reproduction number (R0) of measles: a systematic review. *Lancet Infect Dis.* 2017; 17: 420-428.
144. Ridenhour B, Kowalik JM, Shay DK. Unraveling R0: considerations for public health applications. *Am J Public Health.* 2014; 104: 32-41.
145. Heesterbeek JAP. A brief history of R0 and a recipe for its calculation. *Acta Biotheor.* 2002; 50: 189-204.
146. Li J, Blakeley D, Smith RJ. The failure of R0. *Comput Math Methods Med.* 2011; 527610.
147. Wu J, Zha P. Public health intervention framework for reviving economy amid the COVID-19 Pandemis: use of personalized mitigation measures beyond the epidemiological model limits.
148. Michiels C. Physiological and Pathological Responses to Hypoxia. *Am J Pathol.* 2004; 164: 1875-1882.



## SUNTEXT REVIEWS

149. Lowen AC, Steel J. Roles of humidity and temperature in shaping influenza seasonality. *J Virol.* 2014; 88: 7692-7695.
150. Evans SS, Repasky EA, and Fisher DT. Fever and the thermal regulation of immunity: the immune system feels the heat. *Nat Rev Immunol.* 2015; 15: 335-349.
151. Lawrence HA. Perspectives on complementary/alternative and integrative medicine.
152. Canaani J, Kollet O, Lapidot T. Neural regulation of bone, marrow, and the microenvironment. *Front Biosci.* 2011; 3: 1021-1031.
153. Carabotti M, Scirocco A, Maselli MA, Severi C. The gut-brain axis: Interactions between enteric microbiota, central and enteric nervous systems. *Ann. Gastroenterol.* 2015; 28: 203-209.
154. Verity R, Okell LC, Dorigatti I. Estimates of the severity of coronavirus disease 2019: a model-based analysis. *Lancet Infect Dis.* 2020.
155. Willebrand R, Hamad I, Zeebroeck LV. High salt inhibits tumor growth by enhancing anti-tumor immunity. *Front Immunol.* 2019; 10: 1141.