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Review Article

# Chronic Kidney Disease of Multifactorial Origin (CKDmfo/CKDu): Escalating Incidence and Long-term Survival Estimates

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## Abstract

With the implementation of new safety laws, occupational injuries and deaths are decreasing, but the incidence of non-communicable diseases increasing, especially in agricultural communities. Careless use of agrochemicals and agro-equipment pollute the environment and, lack of protective gear continues harming farmers. A chronic kidney disease of multifactorial origin (CKDmfo; also known as CKDu) is affecting mostly male farmers in several equatorial countries, including Sri Lanka, but causative factor is not identified. The current study constructed to assess the impact of this issue on the society. Survival prediction charts were developed using series of assumptions based on the current death rate. The study was designed to assess the rate of CKDmfo and CKD due to other causes; survivals were predicted over the next 35 years. Data support the exposure causing CKDmfo in Sri Lanka began approximately 35 years ago; i.e., in late 1970s. If the current death rate continues, only 15% of males in the region will be alive by 2049 compared with 2012 statistics. Imposing quality control on locally produced and imported agrochemicals, the release of fertilizer to farmers to be regulated by local soil testing data, and gradually reducing the fertilizer subsidy are essential to decrease the agrochemical overuse and associated environmental damage, and the incidence of CKDmfo. While the government is responsible for providing access to clean water, it is accountable for the environment, public health, and disease prevention. Considering the serious impact of this disease in the country, a major preventative effort is warranted, including curbing pollution, educating the public, provision of affordable clean water and sanitation, and alleviating poverty. An effective intervention is likely to reverse the current dangerous trend and save this large farming community from extinction.

**Keywords:** Agrochemicals; Agriculture; Behavior; CKDu; Environment; Fluoride; Heavy metals; Predictions; Premature death; Renal failure

**Abbreviations:**

CKDu :Chronic kidney disease of uncertain etiology;
CKDmfo :Chronic kidney disease of multifactorial origin;
GIS :Geographical Information System;
NCP :North Central Province;
NWS&DB :National Water Resources & Drainage Board;
WHO :World Health Organization

## Introduction

Over the past few decades, water resources have been threatened not only by over-exploitation and greed but also by poor management practices and neglecting ecological degradation. In addition to climatic change, the naturally occurring and man-made contaminations exhibit marked geographical variations [1] that contribute to various health conditions [2, 3].

Despite the existing environmental regulations, there is a gross lack of enforcement of laws, which facilitates environmental pollution. This lack of stringency allows the dumping and discharge of untreated sewage and agricultural and factory effluents into streams, rivers, and lakes, which eventually contaminates drinking water sources; this is a great threat to human health [4-6].

These situations are becoming major issues in economically deprived countries, particularly in those with economies based on agricultural and raw material production. In addition, the over-exploitation of water and overuse of agrochemicals have escalated in recent years [6]. The practice of dumping industrial and domestic wastes and agricultural waste containing herbicides, pesticides, and chemical fertilizer pollutes the environment, including water bodies [7]. This non-point water contamination in agricultural communities in developing countries is a major concern.

The effects of consuming unsafe and contaminated water can be devastating. Enforcing environmental laws and providing clean water and sanitation costs only a fraction of the expenditures required to treat disease. Such proactive efforts save money and save more lives than almost all hospital-based medical technologies put together. Lack of access to safe water and poor sanitary facilities leads to a perpetual cycle of disease, death, loss of productivity, enormous opportunity costs, and poverty, and may even wipe out entire communities.

Chronic kidney disease of multifactorial origin (CKDmfo) is one such environmentally acquired, preventable occupational disease that originates from consuming polluted water in the North Central Province (NCP) of Sri Lanka. This article addresses the issue, using CKDmfo as an example to demonstrate the consequences of water and environmental pollution, which lead to serious outcomes for and poor survival of affected farmers.

## Escalating chronic kidney diseases

There are hundreds of chemicals and toxins routinely used and released to the environment that are hazardous to human health; some cause cancers [8], and others cause harmful genetic mutations [9, 10] or organ damage [8, 11]; still others cause metabolic abnormalities [12, 13] and the disruption of hormones [14-16]. Current evidence suggests one or more contaminants in drinking water and their additive or synergistic effects as the source of CKDmfo in Sri Lanka and CKDu in other countries in dry zonal regions where farming communities are being devastated.

A possible association between CKDmfo and various agents [17], including heavy metals, fluoride, ionicity, eutrophication of reservoirs water with plant nutrients, agrochemicals (such as exposure to organophosphate or organochlorine pesticides, or synthetic fertilizer components) or pollution of drinking water sources has been explored [4, 18, 19]. However, in Sri Lanka, none of the studies conducted to date have been able to identify a single cause for CKDmfo (i.e., single-cause hypotheses), including the World Health Organization (WHO)-affiliated group [20-22]. Meanwhile, the potential interactions or the synergy of causes has not been studied [23].

The incidence of CKDmfo in the NCP has been increasing for the past 15 years, doubling every 4 to 5 years [19] . The disease is now spreading to areas outside the boundaries of the NCP [19, 21, 23]. Broader causes attributable to this disease include water and environmental contamination secondary to the indiscriminate use of agrochemicals, climate change, industrial development and colonization of former forest areas in the NCP region, and the accelerated Mahaweli irrigation project [3, 24-28]. Combinations of these events have led to water sources being contaminated with a variety of substances, including fluoride, plant nutrients, phosphate, nitrate and nitrites, organic matter, heavy metals, toxic chemicals other toxic substances, and bacteria and viruses [19, 23].

This environmentally induced, deadly, occupational disease predominantly affects male farmers in agricultural communities located in dry zones. All affected communities are poor, located in rural agricultural areas, and have little access to modern amenities such as electricity, potable water, education, and Western medical facilities. Moreover, the diagnostic tools used are less sensitive and specific, and therefore able to identify only approximately 40% of those who are affected. Consequently, by the time they receive a diagnosis, many need renal dialysis, of which more than half cannot afford it [4, 19, 29]. In addition, more than 60% affected people do not receive a diagnosis, and many deaths attributable to the disease are not recorded as such [18], so the statistics provided by the health department are grossly underestimated and misleading.

## Geographical distributions and vulnerability to CKDmfo

The CKD-affected areas cover approximately 29,000 km2, and 2.9 million people are currently at high risk of developing this deadly disease [19]. The prevalence of CKDmfo in Sri Lanka is geographically demarcated, but this disease is manifesting outside the NCP, such as in Badulla, Jaffna, Ampara, and Hambantota districts [19, 22, 23]. The distribution of patients with CKD is not uniform, and the disease prevalence is patchy [31].

Unless definitive, region-wide effective action is implemented to prevent it, vulnerability to the disease will continue to increase, with increasing numbers of deaths [23, 31].

The water quality in drinking wells in the NCP varies much within short distances, as does the pattern of distribution and the number of patients and families affected with CKDmfo. In certain places, endemic villages are adjacent to non-endemic villages, yet both are using similar quantities of the same agrochemicals and carry out the same habits and practices. However, they are using different sources of drinking water [6].

The unique and mosaic geographical distribution of CKDmfo in Sri Lanka should not be ignored because it gives clues to the cause(s) of the disease. Overall data suggest that the factors related to geo-water and the environment are major sources for this epidemic in Sri Lanka [19, 23, 32]. Taken together, the demographic distribution of those with renal failure and CKDmfo-associated deaths [30] (with more than 95% of those with a disease diagnosis being older than 20 years), their livelihoods, and their social habits point to an occupational disease, with geo-water contamination—environmental pollution as a key source [19]. This highlights the importance of having a region-wide, real-time, geographical information system (GIS)-based structure that links the disease locations and the sources of clean and contaminated water [19, 23].

Despite clues, research done to date has not looked at the interactions of potential causative factors or the combination of potential synergistic effects. The use of systematic multivariate analysis is limited by inadequate sample sizes and data. Meanwhile, non-standardized protocols, unrelated data sets, the use of variable and unverified data collection methods, and insufficient sample sizes effectively prevent pooling the data and carrying out meta-analysis for meaningful interpretations. The sporadic assessment of agricultural and social practices and groundwater testing, absence of studying local farming and food habits, and without adequately powered sampling method such as cluster sampling [21], and the lack of linking to the GIS, are unlikely to generate meaningful or accurate information that can be generalized [23].

**Potential sources of water contamination**

Among the several potential contaminants responsible for this CKD epidemic in Sri Lanka are agrochemicals, heavy metals (cadmium and arsenic), increased water salinity/ionicity, and fluoride [18, 19, 23, 33]. Agrochemicals include pesticides, herbicides, fungicides, nematocides, and chemical fertilizers [19, 23, 34]. All data accumulated to date point toward consumption of contaminated water as the primary source for the disease. Irrespective of the cause, water, air, and environmental contaminations in general lead to many health problems and premature deaths.

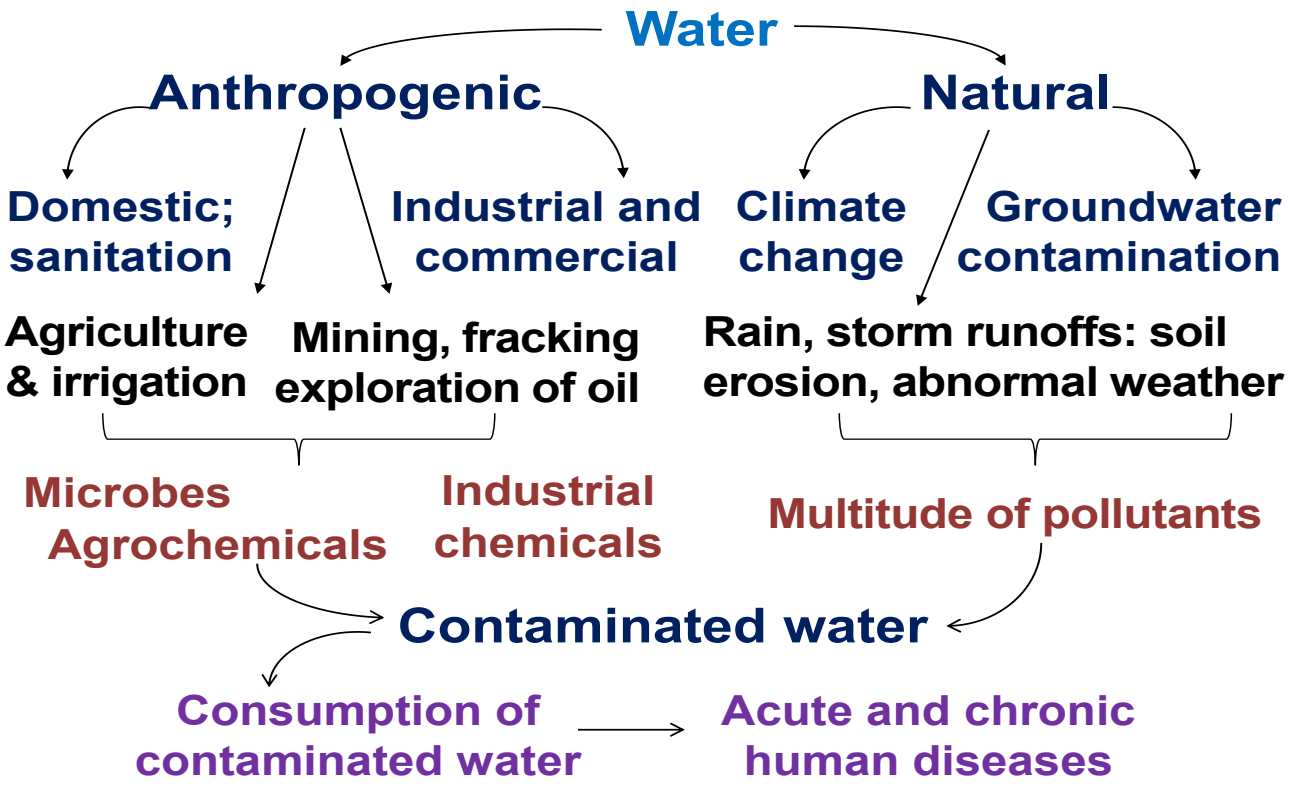

**Figure 1.** Multiple ways in which water is polluted. Anthropogenic contamination is a major source of water contamination in emerging economies. Natural water contamination is caused by rain, flooding, hurricanes and tornadoes, tsunamis, weathering of naturally occurring minerals deposits such as fluoroapatite, and so forth, whereas man-made pollution occurs through mining, fracking, and agricultural and industrial processing. Consumption of water that is contaminated with microbes or chemicals leads to a variety of human diseases and deaths.

The genesis and spread of CKDmfo may be aggravated by other plausible nephrotoxicity factors in the area that have not yet been addressed. These include the use of certain concentrated herbal mixtures [35, 36]; smoking locally grown tobacco that contains higher amounts of heavy metals [21]; regular consumption of illegal alcohol and medications, including excessive use of prescription and non-prescription non-steroidal anti-inflammatory agents (NSAIDs) [19, 23]; and endemic diseases such as leptospirosis [37, 38].

In addition, the potential synergistic and cumulative nephrotoxic effects from products and ailments have not been studied, but need examination [32]. It is possible that a yet-unidentified nephrotoxins or conditions could be responsible for precipitating the CKDmfo [19, 23, 39]. Figure 1 illustrates various ways that water is polluted, leading to human diseases.

**Agrochemicals, phosphate, and heavy metals**

In addition to natural sources, arsenic and cadmium contamination of soil and water come from various other sources, including poor-quality phosphate (TSP) fertilizers, haphazard disposal of material such as, pesticide containers and batteries [19,39,40,41]. These may contaminate, locally grown tobacco, illegally brewed alcohol, and food and water. However, considering the amounts of heavy metals, such as arsenic and cadmium, in the soil, what is introduced through contaminated triple super phosphate (TSP) fertilizer is negligible.

With reference to agrochemicals in Sri Lanka, only phosphates have been found consistently exceeding the stipulated threshold in water (0.1 mg/L) [6, 23, 42]. The recommended amount of TSP to be applied for potato farming is 70 kg per hectare, but farmers are known to apply between 250 and 800 kg. Consequently, approximately 70% of the farms in the hill country have soil phosphorus levels in excess of the agronomic critical level of 30 ppm [5, 6].

Moreover, half the potato and some vegetable farmlands in this region have more than 60 ppm in soil, and a few have more than 300 ppm. Plants are unable to absorb these excess plant nutrients added to the soil. Thus, crop output does not increase beyond the recommended agronomic level of plant nutrients [6]. Excessive application and runoff not only drain the funds of farmers and the government but also pollute the environment, in particular causing eutrophication of water [23].

Sri Lanka is one of the countries in Asia that uses a great deal of synthetic fertilizers [43]. In fact, per arable land basis, Sri Lanka uses more chemical fertilizers and agrochemicals than any other Southeast Asian nation [4, 31]. For example, in 2013 it used approximately 284 kg of synthetic fertilizer per hectare of arable land [43], but usage has plateaued since 2011. Moreover, fertilizer use in Sri Lanka on a per-hectare basis has increased by three- to four-fold during the past three decades [43]. Consequently, the average reservoir water phosphorus content in the NCP has increased from 0.3 mg/L in 1982 to more than 0.12 mg/L in 2013 (data from Department of Agriculture).

**Other potential causes of CKDmfo merit study**

There are several organic and inorganic environmental contaminants prevalent in the regions that can potentially aid the development of chronic renal failure in vulnerable persons [19, 23]. Some of these relatively unlikely causes include synthetic and volatile organic chemicals, by-products of industrial processes and petroleum production, gasoline stations and vehicle discharges, urban storm water runoff and septic systems, bacterial and viral infestations, and so forth.

A variety of physical, chemical, and biological agents render many water sources less than wholesome [19, 23]. The United States Environmental Protection Agency (US-EPA) has published, maximum allowable levels (MAL) of contaminants in water in different watersheds that can lead to health hazards [40]. Most other countries have developed on their own or adapted the US-EPA guideline to suit to their own requirements. Groundwater contamination with fluoride is endogenous but inconsistent and hydrogenous; thus, water fluoride levels vary greatly within a region [45]. There is no good overlap between geographical disease distribution and the health hazard of any of these postulated agents [19, 23, 30, 39].

With reference to ionicity and phosphorus, no data suggest that consuming phosphate eutrophicated water at the current levels present in the NCP region can lead to chronic renal failure [5, 23, 28, 45]. Nevertheless, it is paramount to establish a long-term plan to develop and protect water bodies and watersheds [6]. If ignored, such conditions can lead to watershed degradation that causes not only water scarcity but also serious health consequences, including the potential for chronic diseases such as CKDmfo [19, 23].

Water pollution, whether it involves sewage, plant nutrients, organic material, pesticides, herbicides, cyanobacterial or mycotoxins, salinity, acidification, or other conditions, has a negative impact on human and animal health [23]. In addition to increasing nutrient loads that unbalance the ecology of rivers and water bodies [34, 46], sewage carries harmful microbial

pathogens that lead to diarrhea and other diseases. On the other hand, excess plant nutrients, such as phosphate and nitrate contamination of surface water, result in major alterations of aquatic habitats and overgrowth of algae and cyanobacteria that may negatively affect the quality of water [46-49] and threaten marine life [50, 51].

**Prevalence of CKDmfo in NCP**

All studies reported to date, except one [22], point to contaminated water as the main source that precipitates CKDmfo. The research information collected over the past decade by a number of scientists suggests that the consumption of contaminated drinking water is perhaps the key cause contributing to the escalating incidence of CKDmfo in Sri Lanka [21].

The disease primarily affects middle-age, male farmers [18, 52]; however, a recent report by the WHO group suggested that CKDmfo mostly affects women [53]. The WHO study provided no explanation for this contradictory finding. Because of a longer duration of expose necessary for the development, children younger than 18 years are rarely affected with CKDmfo [23, 31, 54].

Research carried out by several agencies, including the National Water Resources & Drainage Board (NWS&DB), has revealed marked heterogeneity of water quality in the region, even within adjoining villages. This heterogeneity together with the un-standardized water and soil sampling methodology and inadequate numbers of sampling might have contributed to the inconsistency of water quality data reported in the NCP by various groups [23, 55]. In certain villages in this region, one in 10 adults has renal impairment [56] and as many as 20% of adult males have CKDmfo.

**Methodology and Results**

**Prevalence of CKD attributable to all causes in the NCP:**

The prevalence of CKD attributable to all causes in adults is approximately 12% in the NCP region; the prevalence of CKDmfo is approximately 7.5%. Thus, approximately 4% of adults across the region are affected with the more common type of CKD (i.e., that attributable to diabetes and chronic hypertension) (Figure 2). However, the prevalence of the latter is not grossly different across the country; there is a higher incidence of CKD among city dwellers. Our data suggest that the overall prevalence of CKDmfo among adults is about 7.5%, but in certain villages, more than 15% of the middle-aged men are affected.

In 2012, the final WHO report estimated that CKDmfo prevalence is 16% in the region [53], whereas other researchers reported prevalence between 2% and 23% in the region [21]. Because of the use of small sample sizes, the potential for significant sampling-related bias and errors, the different methodologies used to identify those with the disease (i.e., the diagnostic methods and criteria used), and data collection methods, it is difficult to reconcile the major differences reported in the various studies [19, 23].

**Development of CKDmfo**

The development of CKDmfo is insidious, and by the time the disease clinically manifests, pathological damage to kidneys has occurred (stage III and beyond) [56], and the disease is difficult to reverse. As mentioned, CKD related to diabetes and hypertension is not uncommon in the region these conditions are poorly controlled in most patients [33].

However, the CKD prevalence secondary to these two disorders in the NCP is not significantly different from that in the rest of the country. As illustrated in Figure 2, most of the excess prevalence of CKD in the NCP is attributable to CKDmfo. The remainder, a smaller percentage, is attributable to other causes predominantly affecting agricultural dry zonal regions such as NCP, including snakebites, renal stone disease, acute pesticide poisoning, and so forth.

In the current analysis, median incidences, modeling and calculations, and survival predictions were based on data obtained from various sources and the author's own data collected over the past several years. In addition, some of the facts and assumptions used include the ratio of male-to-female birth remains about one-to-one in the region, and the average birth rate is approximately 2%, so the new addition of males to this community is about 1% per year.

Meanwhile, the average death rate of adult males is currently approximately 6% (approximately, 5% is attributable to CKDmfo). Therefore, the estimated average net decrease in adult male population in the NCP is approximately 5% per year, an assumption that was used in the modeling and analysis. The actual numbers could be slightly higher or lower, but irrespective of the numbers, the trend remains the same.

Figure 2 demonstrates that, compared with the data from the rest of the country, the total prevalence of people with CKD sharply increases in the NCP region starting at approximately 25 years of age and continues to increase until it plateaus around 65 years (Figure 2A). Beyond age 65, no significant difference exists between the prevalence of CKD attributable to hypertension and diabetes in the NCP region compared with the rest of the country. Those who are affected with CKDmfo in their mid-30s are highly unlikely to survive to age 60 [4].

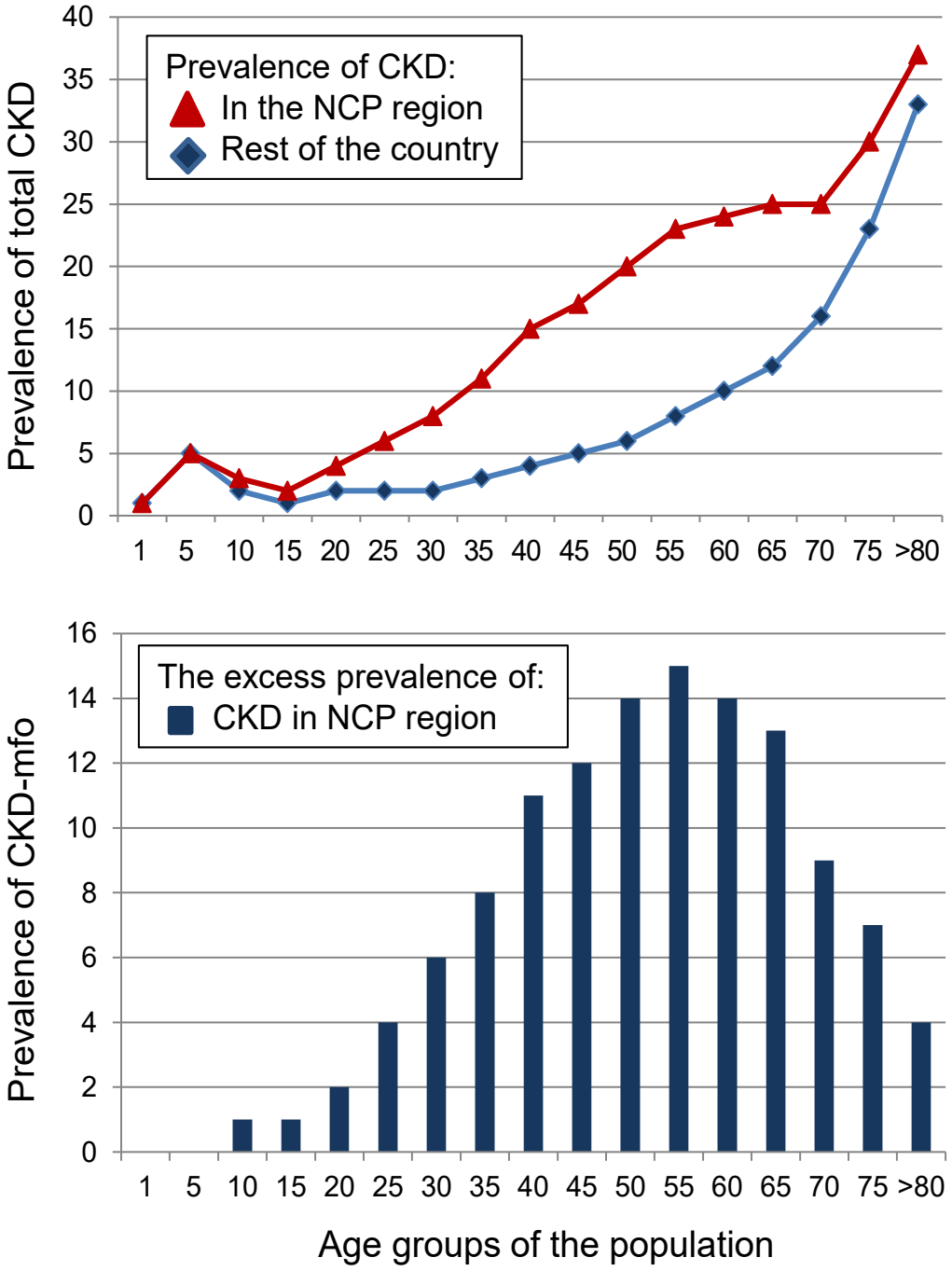


**Figure 2.** (A) The overall prevalence of total chronic kidney disease (CKD) in the NCP (in red) and in the rest of the country (in blue) across ages 1 through 80+ years. The blue line represents the common form of CKD that mostly occur secondary to diabetes and hypertension. A significant divergence of the two curves is observed between the ages of 25 and 65 years. This is primarily due to the increasing incidence of CKDmfo after the age of 25 years. (B) The net differences of the prevalence of CKD is illustrated as percentages (i.e., the difference between the two curves, illustrated in the figure 2A) and demonstrates the age distribution of the prevalence of CKDmfo in adults in the NCP region.

Considering that a long duration of exposure (i.e., more than 15 years) is needed for disease development, one could postulate that the adverse exposure of farmers in this community began in the mid-1980s. Figure 2B illustrates the prevalence of CKDmfo in the NCP. The data are derived by subtracting the CKD prevalence attributable to hypertension and diabetes from the total prevalence of CKD in the region in each age group in the NCP.

Approximately 40% of the country's paddy output comes from the NCP region, the area predominantly affected by CKDmfo and which is known as the breadbasket of Sri Lanka. Although approximately 75% of those affected are males, 90% of CKDmfo deaths occur in males. Moreover, 90% of the total deaths caused by CKDmfo occur in the NCP, and 90% of those who died were involved in paddy farming. Considering these data, the current analysis focused on assessing the long-term survival of males (vast majority are farmers) and calculating survival rates and productivity in terms of paddy output in the NCP.

**Long-term survival of males in the NCP region**

Because 90% of CKDmfo-related deaths occur among males, current data analysis was restricted to males. For the analysis of longer-term survival and the predicted paddy output, an interactive statistical model was developed that used the assumptions mentioned regarding the number of deaths and death rates among the male farmers, as well as the cultivable paddy land and the estimated paddy (rice) output [57]. These data were then reanalyzed with hypothetical changes, both increases and decreases in the death rate compared with the current death rate (Figure 3).

The assumptions made include (A) the death rate remains stable at 5% per year or increases by 0.5% every 5 years (i.e., 0.1% increase in death rate, per year) among the CKDmfo-affected male farmers; (B) the population at risk in the region was considered to be approximately 2.0 million, with 50% (i.e., 1 million) being male and 50% of them being younger than 18 years. Therefore, the starting point of the population as of 2012 was considered to be approximately 500,000 living adult males in the NCP. Instead of absolute numbers, we use the rates of declining survival of adult males. Thus, the starting number of male farmers would not have an effect on the final calculated survival rates. However, it made the outcome analysis simpler and easier to understand the gravity of the problem.

The current evidence and data suggest that on average, one in 10 adult males is affected (i.e., 10% prevalence of CKDmfo) with CKDmfo in the NCP, whereas the distribution of prevalence varied from 3% to 18% in different villages. Therefore, of the 1 million adults in this high-risk area, with the conservative estimate that 10% of people are affected, at least 100,000 males are affected in this area alone. However, this is likely to be an underestimation because the current screening methods allow diagnosis of only 40% of those who are affected.

Considering the approximate death rate of 5% among the affected, each year one would expect approximately 5,000 of them to die of this disease, which would represent approximately 13 deaths each day across the region [18]. For the expected overall change in the percentage of males indicated per year, a male birth rate of approximately 1% was subtracted in the calculation.

Other assumptions included in the analysis are a current static death rate of 5% attributable to CKDmfo among the affected males, which is adjusted for increased male population growth of approximately 1% (i.e., male birth rate), decreasing fertility because of illness, and a slight increase in deaths of other causes. The latter includes the rising incidence of suicides, especially among those with CKDmfo, currently accounting for one death each day, making the current daily death total 14.

Figure 3 was constructed based on the above-mentioned series of assumptions. It illustrates four different plausible survival scenarios: (A) the excess death rate is decreased to 1% per year because of interventions; (B) death rates decrease to a steady 2.5%, instead of the current 5%; (C) the death rate remains steady at 5% per year; and (D) the death rate increases by 1% per year (i.e., CKDmfo-related death rate of 6% per year). These data were extrapolated 37 years into the future. To make it easier to understand the graphics, the numbers and variances at each data point are excluded in the figure.

The assumptions used to generate Figure 3 can get worse because of the declining male population and the decrease in overall fertility rates attributable to CKDmfo. Therefore, the current birth rate may decrease by 50% over the next two decades, worsening the statistics. Based on these models and calculations with the assumption of 5.0% static death rate, only 20% of the number of adult men in the NCP will be alive in 2043 (compared with the number of males alive in 2012).

If the death rate increases by 0.1% per year, only 10% of the number of males will be alive in the year 2043. Although these data provide a grim picture, appropriate, timely, and effective actions can reverse this predicted negative trend [19, 23, 55]. Table 1 summarizes the data in numerical terms to make it easier to understand. It provides predicted crude survival rates by 5-year intervals in male farmers.

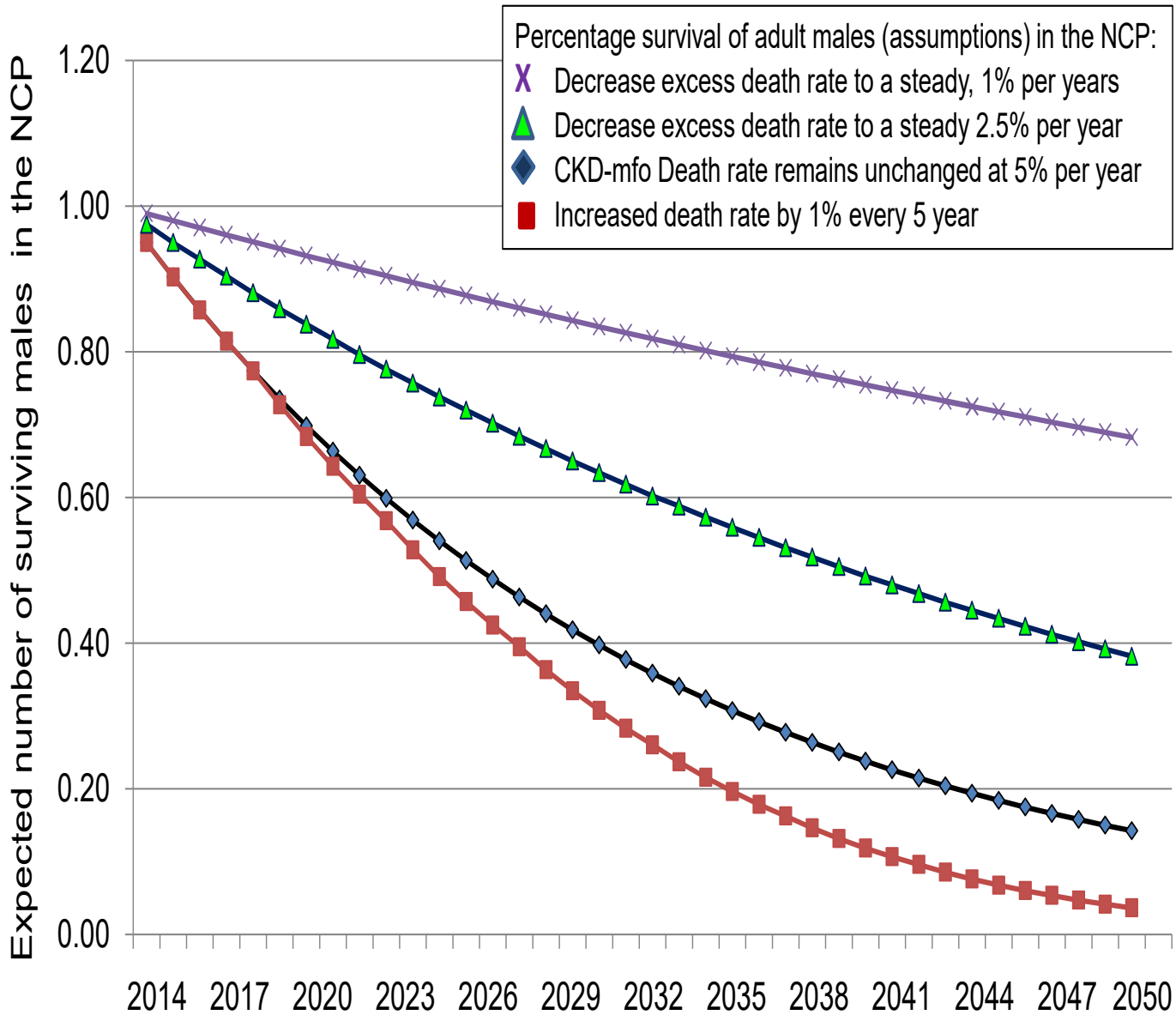


**Figure 3.** The predicted survival curves of adult male farmers using four separate assumptions: (A) Overall excess death rate is static, at 1.0% per year (in purple color) (i.e., 80% less than the current death rate); (B) Overall death rate is static at 2.5% per year (i.e., 50% less than the current death rate) (in green color); (C) Death rate remains static at the current level of 5.0% per year (in blue color), and (D) Increase in death rate by 0.5% every 5 years (i.e., 0.1% increased death rate each year, above the current death rate) (in red color).

**Table 1.**
Predicted crude survival rates among male farmers based on annual death rates of 5.0% and 5.1%, with data provided by 5-year intervals.

| Year | The number of male farmers living (assumption: 5% death rate/year) | Percentage of survival compared with 2012 | | The number of male farmers living (assumption: 5.1% death rate/year) | Percentage of survival compared with 2012 |
|---|---|---|---|---|---|
| 2013 | 475,000 | 95 | | 475,000 | 95 |
| 2018 | 367,546 | 74 | | 363,677 | 73 |
| 2023 | 284,400 | 57 | | 264,065 | 53 |
| 2028 | 220,063 | 44 | | 181,731 | 36 |
| 2033 | 170,281 | 34 | | 118,474 | 24 |
| 2038 | 131,760 | 26 | | 73,119 | 15 |
| 2043 | 101,953 | 20 | | 42,696 | 10 |
| 2048 | 78,890 | 16 | | 23,574 | 5 |

We predict that the combination of preventative efforts, including the provision of affordable access to clean water to the entire region, controlling environmental pollution, and providing region-wide education programs together would lead to an 80% to 90% decrease in the incidence (i.e., occurrence of new CKDmfo patients) and a significant decrease in death rate. This would allow reversal of the downward trend of survival rates in adults in the NCP region. Moreover, these approaches will improve socio-economic status, facilitate re-establishing the sustainability of the region, and bring back the prosperity to this farming community.

## The need for sustainability

Sustainability is a way of working and living that balances the immediate needs for life and business, including healthy living, food, habitation, entertainment, transportation, energy, and the essentials of life. Living in a sustainable way means considering not only today's requirements but also the longer-term needs of generations to come. Thus, preservation of the environment, including protection of natural resources, systems, and livelihoods, for the sake of future generations is important.

Sustainability also addresses human and natural systems, such as social justice, meaningful experiences, social values, biodiversity, harmony and happiness, water-soil-air ecosystems, and healthful lifecycles and the food chain. Moreover, a broader definition of sustainability includes the markets and the micro- and macro-economic systems, globalization effects and resultant effects on the markets, and viability, profits and returns to meet the need, greed, and desires without endangering the vivacity of the future generations. However, these adversary conditions would further deteriorate, including the survival rates, if the environment continues to deteriorate.

Exposure to various toxic agents in unsafe occupational environments is not uncommon, especially for those who are introducing modern agricultural practices, colonization, and haphazardly constructed new settlements. Environmental conditions and agents, such as heavy metals, agrochemicals, petrochemicals, industrial chemicals, harsh and dry weather and high ambient temperatures, and unusual infections, all can interact and have the potential of synergizing the occurrence of chronic non-communicable diseases such as CKDmfo [58].

Chemicals and toxic agents may enter the human body through the oral route, inhalation, or the transdermal route and may exert negative effects on organ systems in the body, including the liver and kidneys. These organ damages are likely to occur through unopposed, oxidative stress [23, 59]. Thus, a balanced diet rich in anti-oxidants (that may decrease intra-cellular oxidative stress) may protect vital organs, including the kidneys, heart, and brain from the harmful effects from chemicals and toxins [23, 60]. In this regards, the use of locally available green leafy vegetables such as moringa (murunga), kathurumurunga, and gotukola, and a number of others vegetables and fruits that containing anti-oxidants, should be explored for their benefits in promoting health, particularly preventing CKDmfo.

## Mismanaged policies prevent taking right actions

The increasing incidence of CKDmfo is more than just a chronic public health emergency and an environmental crisis. It also reflects a failure of governmental policies in domestic matters, including escalating preventable diseases and public policies. The latter includes the failures of setting of priorities; agricultural and irrigation development; design of human settlements; provision of education, healthcare, water, and sanitation; and poverty alleviation and the lack of concern for the poor.

Policy makers have failed to envisage the catastrophe and move beyond their party politics to do the correct things to safeguard the health and safety of the people in the country. This criticism applies to all CKDu-affected courtiers. The lack of national clean air and clean water policies and acting on peer pressure and information provided by lobbyists to please voters or industries, rather than depending on scientific evidence

and advice from scientists has constantly prevented progress in finding the real cause(s) of CKDmfo, practical and effective solutions, and implementing firm preventative actions.

Such misdirected decisions likely to harm the livelihood of farmers, food security and the economy of the country. Policy advocacy in today's world requires problem solving and collaboration, not conspiracy theories, confrontation, or stalling decisions. Considering the inherent conflict of interests within the ministries, government departments, as well as appointed individuals, the only way forward is for the government to establish an independent "CKD-Eradication Authority" to prevent and eradicate CKDmfo. Nevertheless, the latter entity must have full legal authority and complete independence, and should be fully funded by the government enabling it to accomplish the tasks in a timely manner [19, 23].

**Applicability of these data to other countries affected with CKDue**

In addition to Sri Lanka, several other equatorial countries have a similar kind of atypical chronic kidney disease (CKDu), which started to appear in the 1970s; the affected areas include the Balkan regions [61-64] and other countries in Central America [65-71]. However, etiological correlations reported vary from country to country, including arsenic in subterranean water tables in Bangladesh and and certain parts in India [71], aristolochic acid in the Balkan countries [61, 63, 64], possible heavy metal exposure and volatile toxic gases/fumes in Central and South American regions [58, 67, 68], and multiple chemicals in Egypt [70].

As in a number of other CKDu-affected countries (the disease also is referred to as CKDue, CKDuo), the etiology of CKDmfo in Sri Lanka remains unknown. Although the etiological factors and cultivated crops are different, the histopathologic findings of interstitial renal tubular fibrosis and the progression and course of the disease across these nations are similar. Table 2 illustrates the similarities and differences between the CKDue in other countries and CKDmfo in Sri Lanka.

There are many similarities in the two affected groups, especially the geographical location (close to the equator), harsh climatic conditions, prolonged drought conditions each year, and poor economic conditions, leading to lower social standards, poor hygiene, and lack of access to safe sanitary facilities [19, 23]. Distinctly different in Sri Lanka (CKDmfo) is the lack of arsenic, heavy metal, and pesticides in drinking water above the upper limits (MAL) stipulated by WHO and US-EPA (or in clinically meaningful amounts) [4, 23, 39].

Anatomical renal damage in CKDmfo and CKDue is different to that of the common CKD caused by hypertension and type 2 diabetes. All CKDmfo/CKDuo affected countries still rely on the measurements of urine-based proteins and MCR for screening, and MCR, and blood urea and serum creatinine levels for establishing the diagnosis. These tools are insensitive and non-specific, thus increasing both false-positive and false-negative results and diagnostic difficulties [19]. For example, albuminuria or microalbumin/creatinine ratio (MCR) is still the only routinely used methods in all CKDu-affected countries for screening persons suspected of having CKDmfo/CKDue [23, 59, 72].

In CKD related to hypertension and type 2 diabetes, glomeruli are affected early in the disease, so proteinuria is an early phenomenon and a sensitive marker for renal involvement. However, in CKDmfo/CKDu, which is a tubulointerstitial disease [45], glomeruli are relatively preserved, so proteinuria (and reduction of the glomerular filtration rate) is a late manifestation. Therefore, when using methods such as MCR, fewer than 40% of those who are affected with CKDmfo are diagnosed. Consequently, the disease is diagnosed too late for the affected patients, and the incidence and prevalence reported by the respective health departments are grossly underestimated.

In addition, when diagnoses are made (usually at or beyond CKD stage IIIB), most patients requiring renal dialysis, and have poor prognosis [59]. This adds to the socioeconomic burden of affected families and strains the budgets of respective health departments. Because CKDmfo/CKDue is a tubulointerstitial renal disease, all affected countries must consider replacing the use of urinary MCR method or use it in combination with a precise, urine based tubular-specific (marker detection ) assay/method as a screening tool, as soon as possible [59, 72]. This not only would allow early detection of those with renal impairment but also would enable the reversal of renal damage and thus avoid the need of dialysis.

**Discussion**

The incidence of CKDmfo continues to surge, increasing over the past two decades [73] in Sri Lanka. Despite this, few preventative steps have been implemented to date, so not only the incidence but also deaths caused by CKDmfo continue to increase. The reported clustering of the disease within families, as reported [73], does not necessarily indicate a genetic association but more likely is attributable to exposure to local causative factors in higher concentrations.

Such factors include consumption of poor-quality water (drinking from the same source, and possibly contaminated food), improper agricultural practices, and unusual and unhealthy habits, including frequent consumption of illegally brewed alcohol in the presence of chronic dehydration, storing dangerous chemicals with food, and so forth.

**Table 2.** Commonalities and dissimilarities of the environmentally acquired occupational diseases, CKDmfo and CKDue across the globe.

| Factor or condition | CKDmfo in Sri Lanka | CKDue in other countries |
|---|---|---|
| Disease first manifests | In mid-1990s | In mid-1970s |
| Duration of exposure required | More than 15 years | More than 10 years |
| Potential source | Contaminated water | Contaminated water ± food |
| Potential causes/factors | Multiple factors | Single or multiple factors |
| Affected age groups | Children rarely affected | Children are affected |
| Most affected gender | Male (~75%) | Male (~90%) |
| Economy | Emerging economy | Developing or emerging |
| Access to modern healthcare | Poor | Very poor |
| Access to nutritious food | Low | Very low |
| Nutrition status | Approximately 60% malnourished | More than 70% malnourished |
| Agricultural economic base | Rice and vegetable | Cotton and sugarcane |
| Predominant agriculture base in affected regions | Paddy and vegetable | Cotton, sugarcane, rice, or vegetable |
| Agrochemical overuse | Mostly fertilizer | Mostly pesticides |
| Group most affected | Individual farm workers | Industrial farm workers |
| Landscape | Flat land with poor drainage | Flat with poor drainage |
| Location | Just north of the equator | South or north of the equator |
| Incidence in relation to farming activities | Local as well as distant (hill country) farming | Predominately local farming |
| Climatic condition | Prolonged dry spells | Dry spells alternating with flooding |
| Eutrophication of water | With phosphate | None; occasionally nitrates |
| Heavy metal in drinking water | None | Present in few locations |
| Presence of fluoride in water | Yes | None in most countries |
| Detection of pesticide in drinking water | Virtually none | common |
| Evidence of genetic origin/link | None | None |
| Bio-accumulation | Likely | Possible |

Whether there is a particular susceptibility or a polygenetic trait associated with those who contract this disease is unknown but seems unlikely [73].

Recent statistics indicate the doubling of CKDmfo incidence in 4 to 5 years in the NCP, and the disease is now manifesting in regions outside the NCP in Sri Lanka [23, 56]. Although there is no causality established, agrochemicals are one of the potential causes of the disease [34]. Therefore, it is essential to reduce the overuse of agrochemicals; use these chemicals responsibly, properly, and safely; use protective gear when spraying pesticides; and ensure quality control of all locally manufactured and imported fertilizer consignments [18].

This necessitates increasing the number of trained inspectors and giving them access to imported and local fertilizers and agrochemicals to examine and make determinations about their quality. Similar systematic safety inspections and certification programs should be adopted for all food items—agricultural, dairy, and fisheries products—before they are allowed to market. Countries such as Sri Lanka should adopt a stringent safety, inspection, and approval program such as the one used by the U.S. Department of Agricultural and the Food and Drug Administration.

Because no agrochemical products have been linked to the genesis of CKDmfo (i.e., no proof of causality), banning the importation of these products is counterproductive to the sustainability of agricultural output and the economy of the country. In addition, such a ban in the absence of valid scientific data would have no effect at all in reducing the incidence of this deadly disease. With time, such a ban would destroy the livelihood of small-scale farmers, increase soil erosion because of the necessity for manual weeding, decrease crop output, and lead to increased costs of agricultural products.

The key reason middle-age people are affected most with CKDmfo is the "duration" and the "total" exposure to an as-yet-unknown causative factors(s) that precipitate kidney failure. Several significant changes occurred in social practices and habits between 1965 and 1985 in the NCP, including changes in dietetic patterns, drinking water sources (drinking from the paddy field instead of taking water from home, large expansion of tube wells, etc.), poverty, malnutrition, climate change (persisting annual droughts and intermittent floods), and the introduction of agrochemicals.

In Sri Lanka, the disease first manifested in the mid-1990s, approximately 20 years after the introduction of chemical fertilizer and the green revolution. Considering exposure of longer duration seems required to contract the disease, those who are younger than 18 are unlikely to have the cumulative exposure needed to harm their kidneys [23]. Even if they have early signs of renal impairment, if a diagnosis is made early, renal impairment is reversible. However, unless the Department of Health opts to introduce a tubular-specific, urine-based, sensitive and specific, cost-effective assay (not using expensive, imported assay kits) as a screening tool, these adolescents are going to experience irreversible renal failure.

When people receive a late diagnosis of renal impairment, the disease is too advanced (beyond stage IIIa, with the kidneys fibrosed beyond recovery), and it is too late to rescue their kidneys [19, 23]. If disease is diagnosed at an earlier stage (i.e., stage I and II), the need for dialysis can be prevented and lives can be salvaged by providing such patients with clean water and renal-protective basic oral medications.

Similarly, those who are older than 65 years may not have been exposed long enough to the causative agents that lead to renal failure (smaller less amount of the toxin) and may not experience CKDmfo [23]. Those who acquired the disease in their mid-30s are most likely to succumb before the age of 65, so the prevalence of CKDmfo is decreased in older people.

To prevent CKDmfo, the overall goal is to minimize water and environmental pollution at the source—the root cause. The quality of water should be mandated before people are allowed to use water from dug wells and tube wells. The proper management of agricultural waste and petroleum spills and proper and safe disposal of pesticide containers and used petrochemicals would decrease water contamination.

A broader program, including education and provision of safe disposal and recycling opportunities, would prevent pollution of water bodies. These actions are essential to prevent degradation of water sources and decrease the incidence of CKDmfo in the long run [5]. In addition, it is mandatory to implement awareness and education campaigns for farmers and agrochemical sellers regarding the proper use of agrochemicals and management of water, without which it will be impossible to achieve a meaningful decrease in the incidence of this disease.

The provision of domestic water filtration systems has failed for a number of reasons, including fewer than 10% of people actually use such systems in this region, even when the units were provided free of charge. Moreover, our laboratory testing confirmed little effect of domestic water filtration systems in removing the postulated pollutants. Instead, proven and efficient methods, such as reverse osmosis or ozonization of water [18, 74], must be implemented to provide safe, potable water to all affected villages. We estimate that providing easy and affordable access to clean water that is free from all potential chemicals and toxins will reduce the incidence of newly acquired CKDmfo by approximately 45%.

Available data suggest that the environmental contamination

and unique hydro-geo chemistry of the affected dry zonal regions play a role in the genesis of CKDmfo [21]. The ongoing climatic changes and man-made modifications, including the modern irrigation systems, have contributed to soil erosion and water pollution that adversely affect the water cycle and indirectly aggravate CKDmfo.

Because this is an occupationally acquired disease, there is no medical solution to prevent it. Thus, most of the efforts must focus on prevention. Research funds should be directed to a multi-functional, multi-disciplinary, region-wide approach. Meanwhile, the Department of Health should focus on early diagnosis and cost-effective ways of treating affected people.

## Conclusions

The incidence of CKDmfo is escalating because of the lack of preventative actions. It is a chronic emergency, with major socioeconomic consequences. Consequently, this geo-water environmental-related disease is spreading to adjacent and distant regions in the country. Because the geo-chemical parameters vary markedly from village to village, conclusions based on water quality from sporadic water analyses of random samples would be misleading. Therefore, one cannot make generalized conclusions to the region or the disease status by extrapolating analytical data from a few sets of inconsistent water samples.

Little effort and scant resources have been spent on improving and preserving the environment and preventing diseases, including CKDmfo. Residents of remote villages should be given access to clean water that is free from chemicals and toxins, just as is the water available to citizens who live in cities and towns. In this new millennium, it is unconscionable to neglect these vital communities that provide a major supply of food to the rest of the country and in fact are the lifeline of food supply in the country.

As described, coordinated efforts will have a profound impact on limiting the spread of water-borne communicable and non-communicable diseases, minimizing health hazards and deaths. Such effective and intensive approaches could reverse the current dangerous trends in CKDmfo in the NCP in Sri Lanka, as illustrated in Figure 3. The failure to adopt proper soil and water conservation measures and the lack of a nationwide plan contribute not only to water scarcity but also to ill distribution of fresh water, water pollution [3, 75], and soaring increases in disease. In fact, the deaths from CKDmfo already outnumber the losses attributed to the 2004 tsunami in Sri Lanka [76], the largest natural disaster to hit the country for centuries.

To decrease such morbidity, it is essential to make politicians and state officials accountable for taking proper actions to reduce occupational hazards and enact meaningful environmental regulations and strictly enforce environmental protection laws. In addition, it is necessary, to (A) create a public awareness plan for the environmental issues, (B) prevent occupational hazards while encouraging the increased use of forest cover, (C) prevent soil erosion and the hyper-eutrophication of reservoirs, (D) prevent excessive use of agrochemicals, (E) regularly monitor water and soil quality, and (F) implement legislations to protect the environment.

Predictions used in the analysis based on the number of adult males (as of 2012), incidence and death rate of CKDmfo [24, 40], and the arable paddy land in the region. If the current death rate continues, the predicted and extrapolated data indicate that by 2049, the number of male farmers alive in the region will be 15% of that number in 2012.

If one assumes the death rate would increase by a mere 0.1% per year, surviving adult male farmers would decrease from 20% to 10% by year 2043. Taken into consideration the marked reduction of the fertility rates, this would virtually wipe out the people and communities in the region, and destroy the county's economy. Since a third of the food needs in the country is growing in the NCP, devastating the food supply of the country. The latter would force the government to import qualities of food for daily consumption of its 21 million people making it bankrupt. The current preventative efforts are grossly inadequate for reversing this trend; thus, allocation of adequate funds for right projects (not giving handouts) and a major broader initiative carried by the new CKD-Eradication Authority is essential to reverse the trend and save the population in the NCP.

## Conflicts of Interest

The authors have no conflicts of interest.

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