Descriptive and Predictive Time Series Analysis of Premature Mortality from Noncommunicable Disease among Filipinos

Paul Adrian V. Pinlac[1] and Ngamphol Soonthornworasiri[2]

[1]*Department of Epidemiology and Biostatistics, College of Public Health, University of the Philippines Manila, Manila, Philippines*
[2]*Department of Tropical Hygiene, Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand*

ABSTRACT

Introduction. The problem of increasing mortality from noncommunicable disease (NCD) in the Philippines warrants an in-depth assessment of premature death rate in the country. This research aims to explore the temporal characteristics of mortality younger than 70 years old from the leading NCD among Filipinos from 2006 to 2012 and forecast premature mortality rates in 2013 to 2016.

Methods. Time series modeling and forecasting using the Box-Jenkins method was performed on secondary ecologic data extracted from the national mortality database maintained by the Philippine Statistics Authority-National Statistics Office.

Results. Premature death rate from cardiovascular diseases has been increasing steadily. Diabetes mellitus, which shows initially rising mortality among the 30-69-year-old age group, has been reversed in 2009. Trends of premature mortality from cancers and chronic lung diseases did not appear to change over time. NCD mortality rates in the 30-69-year-old age group are generally expected to plateau from 2013 onwards.

Conclusion. This novel application of time series analysis on premature NCD mortality data drives both further scientific studies and formal programmatic evaluation by providing a better evidence-based picture of NCD burden in the country.

Key Words: noncommunicable disease, cardiovascular disease, cancer, diabetes mellitus, chronic respiratory disease, ARIMA modeling

Introduction

Noncommunicable disease (NCD) is the leading cause of mortality today, credited for two-thirds of all of the world's deaths. Four-fifths of these deaths are accounted for by the top 4 broad categories of NCD—cardiovascular disease (CVD), cancer (CA), diabetes mellitus (DM) and chronic respiratory disease (CRD)—in low- to middle-income countries (LMIC).[1,2] On the regional level, the increase in NCD deaths are most notable in the Western Pacific Region (WPR) and the Southeast Asia Region (SEAR), where death tolls from NCD were correspondingly augmented by 2.3 million and 1.8 million between the years 2000 and 2012.[1] The NCD picture is not any different in the Philippines. Six out of the top 10 causes of mortality in the country are NCD.[3] A review of local statistical data revealed that the total number of deaths from NCD in 2010 increased by 50% from its 2000 baseline.[4]

The recent steep rise in the burden of NCD has made it to the list of global public health challenges of the WHA. In May 2000, Resolution WHA53.17 was passed, promoting research in key preventive areas—analytical, operational or behavioral—that can enhance program implementation and evaluation as part of the Global Strategy for the Prevention and Control of Noncommunicable Diseases. Eight years later, the endorsement of research as an objective in the Global Strategy Action Plan for the Prevention and Control of Noncommunicable Diseases has been reiterated in the 66th WHA. Indeed, because of its information-generating properties, research became a crucial component of the WHA's response to the problem.[5]

In substantiating this strategy, the WHO NCD Research Agenda has been created. The agenda, which focuses on the 4 main NCD groups and their common risk factors, hopes to provide evidence-based knowledge that can be utilized by decision makers in taking appropriate action.[5] This study seeks to align itself with one of the priority areas for NCD research stipulated in the agenda: "*What research is needed to track the NCD burden and its social determinants?*" Accurately estimating and predicting the local disease burden is anticipated to add to the growing wealth of information about NCDs. The measurement and appraisal of data points evenly sequenced throughout a specified time period, or time series analysis, offers the benefit of both understanding historical occurrences and predicting future events.

Time series analysis as a function provides the investigator an understanding of the past as well as current data in terms of their levels, trends and seasonality. Studies

Presented at the 50th SEAMEO TropMed Philippines Anniversary - Public Health Conference, November 13, 2015, CPH Auditorium, College of Public Health, University of the Philippines Manila.

Corresponding author: Paul Adrian V. Pinlac, MD, MPH, MSc
Department of Epidemiology and Biostatistics
College of Public Health
University of the Philippines Manila
625 Pedro Gil St., Ermita, Manila 1000 Philippines
Telephone: +632 5260784
Email: pvpinlac@up.edu.ph

that have looked into the capability of time series analysis evaluated the temporal characteristics of the observations that are mostly derived from routine surveillance, for practical reasons. Meanwhile, the implication of the results of this kind of studies is the improvement of both disease monitoring as well as risk management strategies. Most literature focused on the application of time series analysis on infectious diseases, perhaps because of the short natural history of the disease. Yet, communicable diseases that have significantly long latent periods like tuberculosis can also be plotted using time series models. Time series studies conducted on lifestyle-related diseases likewise have been expanding. Analyses on NCDs have mainly delved on trends in mortality, especially from cancer, and cardiovascular disease morbidity. Time series modeling has also been applied to predict chronic disease burden, either singly or in combination with other mathematical modeling techniques.

Methods

Study Design

The study employed a descriptive ecologic design which focused on demonstrating trends and other temporal characteristics of the variable under study. Aggregate secondary data initially collected for administrative purposes were analyzed and interpreted without reference to attributes specific to each individual in the study population. The study performed Autoregressive Integrated Moving Average (ARIMA) modeling and segmented regression in exploring the temporal characteristics of premature mortality from noncommunicable disease in the Philippines from 2006 to 2012.

Study Population

Data on mortality from one of the four main noncommunicable diseases as reported in the national database from January 2006 to December 2012, particularly among those occurring before the age of 70 years, served as the substrate for the analysis in the study. The study population has been delimited further to deaths from NCDs within the 30-69 year-old age range to adhere to the strictest definition of premature mortality. Deaths were classified under one of the four NCD groups as defined by the WHO based on the 10th revision of the International Classification of Diseases (ICD-10), i.e., CVD, I00-I99; CA, C00-C97; DM, E10-E14; and CRD, J30-J98.

Data Analysis

Following the calculation of the monthly premature mortality rates, the time series was partitioned. The monthly rates from January 2006 to December 2011 comprised the *training set*, while the January to December 2012 monthly rates were the *testing/validation set*. Having a total of 72 time points in the training set, the required number of observations for time series analysis has been satisfied. The data was then subjected to ARIMA modeling using the statistical software package Stata.® The Box-Jenkins method was applied to model for the overall premature NCD mortality and the process repeated for each of the four specific types of NCDs.

Ethical Considerations

The study utilized data gathered for administrative purposes, *i.e.*, data routinely collected by the Philippine Statistics Authority (PSA) for surveillance of vital statistics. Since the research was an investigation of anonymous aggregate secondary data, no major issue regarding patient privacy, confidentiality and information security was anticipated to arise from the study. No group of individuals was to be inequitably burdened nor was anyone exposed to possible harm or social stigma due to the results of the research. The study protocol was submitted to the Ethics Committee of the Faculty of Tropical Medicine, Mahidol University, but was exempted by the latter from ethical review. The PSA granted the permission to use their data for this study.

Results

Temporal Characteristics of Premature NCD Mortality

Visual inspection of the yearly sum of the premature death count for NCDs overall and for each specific type suggested that there was generally a rise in death tolls. Diabetes mellitus, interestingly, showed a slight dip in annual counts of deaths less than 70 years old from 2008 to 2010; the decrease, then again, was not sustained and has reversed since. Meanwhile, results from the calculation of the premature mortality rates (Table 1) provide insight as to the general trend of NCD deaths relative to the concurrent population. Correlation coefficients indicated that the rates have been increasing for most NCDs in the January 2006-December 2012 interval, especially for CVD. Conversely, the fitted values for DM pictured a flat to significantly declining slope during the equivalent time frame.

As a whole, noncommunicable diseases exhibited an ever-increasing trend in premature mortality through the years (Figure 1). Seasonality was quite manifest, peaking annually every December to January and plunging right the next month. Oscillations appeared to be uniform around the fitted line.

Premature mortality from cardiovascular diseases (Figure 2) shared the perpetual incline with the overall NCD rate, together with the crests in between years and the troughs in February every year, albeit the variance around the estimate was more irregular. A consistent secondary dip which may be as prominent as the one in February was seen every midyear in June.

Table 1. Summary of Monthly Premature NCD Mortality Rates,[a] Philippines, 2006-2012

	Mean	**SD**	**CV**	**Lowest**	**Highest**	**R**	**p-value**
Cardiovascular Disease	20.78	1.37	15.18	17.75	23.89	0.67	<0.001
Cancer	7.98	0.34	23.74	7.08	8.79	0.16	0.152
Diabetes Mellitus	3.45	0.26	13.28	2.91	4.06	-0.29	0.007
Chronic Respiratory Disease	2.93	0.22	13.44	2.44	3.49	0.02	0.874
Noncommunicable Disease	35.14	1.76	19.96	30.40	38.62	0.51	<0.001

Source: Principal investigator's calculation of PSA data

a. Age-specific premature mortality rates reported per 100,000 population

CV – coefficient of variation; NCD – noncommunicable disease; R – Pearson coefficient; SD – standard deviation

Table 2. Summary of estimated parameters of the best ARIMA models

Category[a]	Model	Estimated parameters
NCD	ARIMA $(1,0,0)\times(1,0,0)_{12}$	$(1 - 0.714\,B^{12})\,(1 - 0.298\,B)\,Y_t = 34.995 + e_t$
CVD	ARIMA $(0,0,1)\times(1,0,0)_{12}$	$(1 - 0.763\,B^{12})\,Y_t = 3.024 + (1 - 0.490\,B)\,e_t$
CA	ARIMA $(1,1,1)_{12}$	$(1 + 0.485\,B^{12})\,(1-B^{12})\,Y_t = 10.715 + (1 + 0.387\,B^{12})\,e_t$
DM	ARIMA $(1,0,0)\times(1,0,0)_{12}$	$(1 - 0.549\,B^{12})\,(1 - 0.460\,B)\,Y_t = 11.978 + e_t$
CRD	ARIMA $(1,0,1)\times(0,1,1)_{12}$	$(1 + 0.770\,B)\,(1-B^{12})\,Y_t = (1 - 0.943\,B)\,(1 + 0.695\,B^{12})\,e_t$

a-NCD – noncommunicable disease; CVD – cardiovascular disease; CA – cancer; DM – diabetes mellitus; CRD – chronic respiratory disease

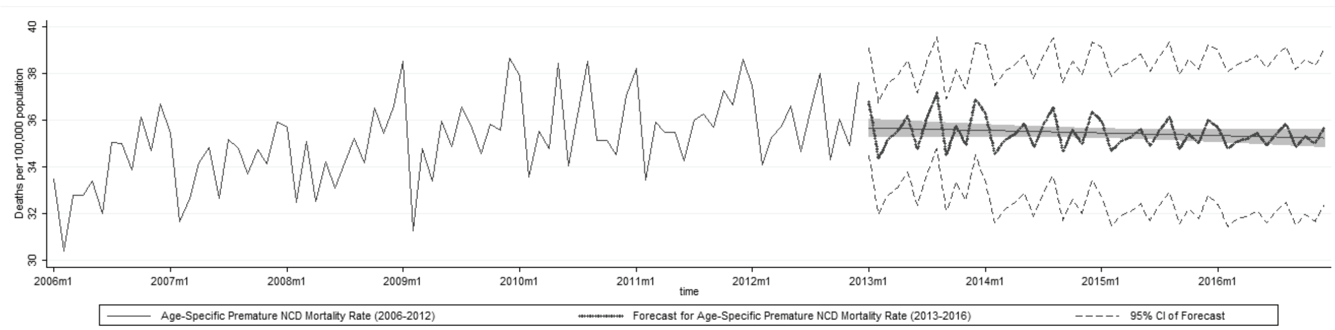

Figure 1. Time series modeling for age-specific premature NCD mortality rate among 30-69 years old, Philippines, January 2013 - December 2016.

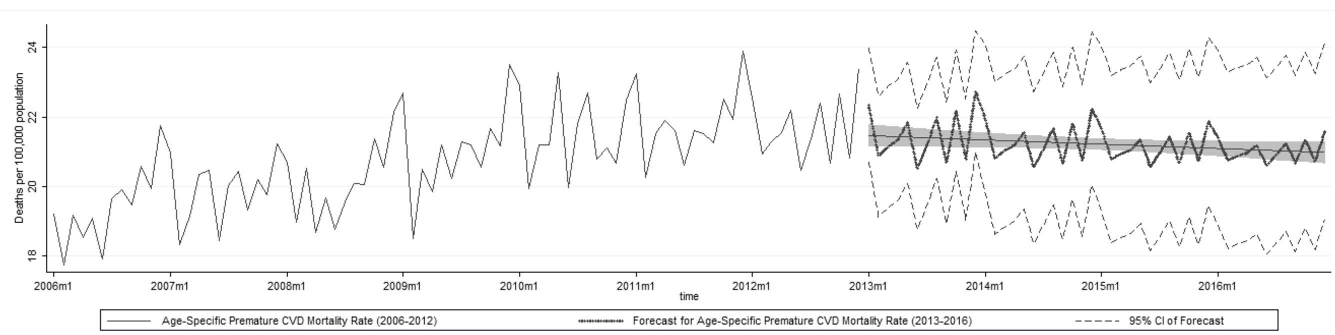

Figure 2. Time series modeling for age-specific premature CVD mortality rate among 30-69 years old, Philippines, January 2013 - December 2016.

Cancer premature death rates (Figure 3) likewise demonstrated a continuous rise, although it was not as steep as that of CVDs. There was also some evidence of yearly cyclical fluctuations, with the lowest point in February and the highest points in July or August. The flux was arguably even about the trend line.

Diabetes mellitus, unlike the other NCDs, had a declining fitted line for premature mortality at a glance (Figure 4). Still, a closer look at the graphs revealed an escalating trend from 2006 to 2008 and a flat estimate from 2009 onwards. Seasonality if present was not really obvious, especially in the last four years.

Chronic respiratory disease had almost a constant trend and no evident cyclical fluctuations in terms of premature death rate (Figure 5). Its oscillation around the baseline was also the most indiscriminate among the five disease entities.

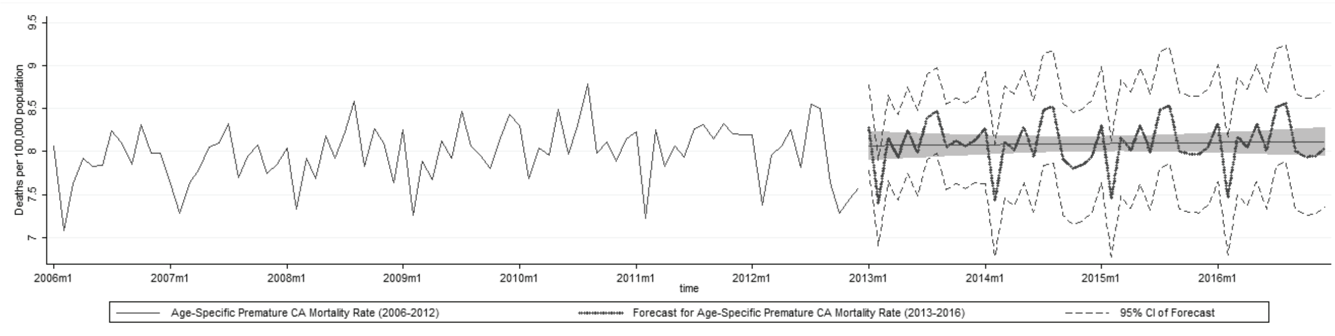

Figure 3. Time series modeling for age-specific premature CA mortality rate among 30-69 years old, Philippines, January 2013 - December 2016.

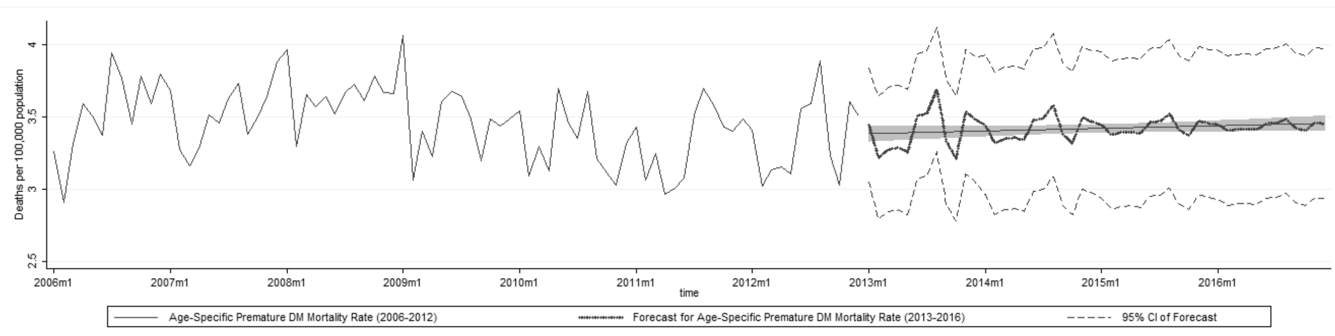

Figure 4. Time series modeling for age-specific premature DM mortality rate among 30-69 years old, Philippines, January 2013 - December 2016.

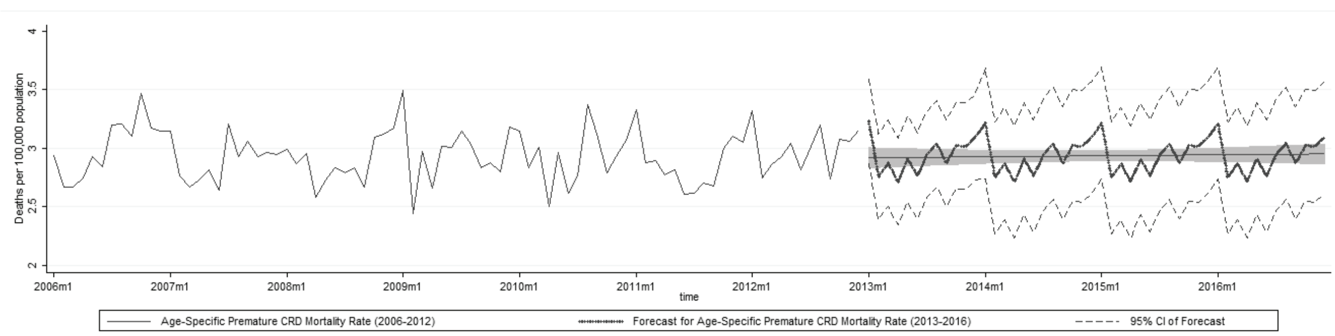

Figure 5. Time series modeling for age-specific premature CRD mortality rate among 30-69 years old, Philippines, January 2013 - December 2016.

Time Series Modeling

Describing and predicting the age-specific premature mortality rates of NCDs in general and of each type was dependent on the time series models identified using the Box-Jenkins process. The final models selected for each disease entity are enlisted in Table 2.

Premature mortality from NCDs (Figure 1) among 30-69-year-old Filipinos was expected to plateau in the years 2013-2016 (R = -0.197, p-value = 0.180), with age-specific rates fluctuating between 34.3 and 37.1 per 100,000 population (mean = 35.4; 95% CI: minimum = 31.4, maximum = 39.5).

There seemed to be some borderline decrease in the age-specific premature mortality rate from CVD (Figure 2) among 30-69-year-old Filipinos in the years 2013-2016 (R = -0.267, p-value = 0.067). Rates would range from 20.5 to 22.7 per 100,000 population (mean = 21.2), but it could be as low as 19.1 or go as high as 24.5 (95% CI).

Death rate from malignancy (Figure 3) among 30-69-year-old Filipinos in the years 2013-2016 was projected to vacillate between 7.4 to 8.6 per 100,000 population (mean = 8.1; 95% CI: minimum = 6.8, maximum = 9.2), but the baseline level technically remained constant through time (R = 0.050, p-value = 0.735).

Fluctuations in the age-specific premature mortality rate from DM (Figure 4) among 30-69-year-old Filipinos in the years 2013-2016 apparently would decrease with time, ranging from 3.2 to 3.7 per 100,000 population. The rate, which averaged 3.4 deaths per 100,000 population (95% CI: minimum 2.8, maximum 4.1), stabilized in the following four years (R = 0.234, p-value = 0.110).

Deaths from CRD (Figure 5) among 30-69-year-old Filipinos were anticipated to have a stable trend in the years 2013-2016, with a premature mortality rate oscillating between 2.7 to 3.2 per 100,000 population (mean = 2.9; 95% CI: minimum = 2.2, maximum = 3.7). The slope of the line was flat at a coefficient R = 0.068 (p-value = 0.648).

Discussion

Mortality from NCD, specifically among the 30-69-year-old segment of the population, had steadily increased with time, with rates reaching annual zeniths during the holiday season (December-January). These trend and seasonality were mirrored by cardiovascular diseases, practically since they comprised the bulk of lifestyle-related disease deaths. The upward trend in premature CVD mortality rate conformed to the increasing absolute death counts from heart disease and stroke, and as it seemed, contrasted to that of more developed nations. As shown by the Pan-American study on CVDs,[6] standardized premature death rates had been decreasing for all PAHO regions from 2000 to 2009, albeit rates were lower in North America than in Latin America and the Caribbean. A review by the Australian Institute of Health and Welfare of their health statistics from the National Centre for Monitoring Cardiovascular Disease revealed that age-adjusted mortality rates among those younger than age 55 from coronary heart disease and from cerebrovascular events had been declining since 1987, with concomitant rises in the supplies of antihypertensives, antithrombotics and statins from 1995 onwards.[7] Indeed, CVDs remain to be an issue in LMICs because of inequities in health care service delivery. Furthermore, some factors that are known to strongly predispose to myocardial infarction and stroke, namely, hypertension and tobacco use, are prevalent in the Philippines: 1 of every 5 Filipino adults has elevated blood pressure, while 1 out of 4 currently smokes.[8]

The seasonal pattern of CVD mortality was consistent with the findings of several regression studies on cardiac mortality by separate research groups. Kloner et al, partly in response to earlier proponents suggesting a possible link between cold temperatures and coronary events, described in 1999 an increase in cardiac death rate during December and January by a third relative to the period of June to September in Los Angeles, California from 1985 to 1996, but concluded that climate alone could not account for the fluctuation.[9] Phillips and his team five years later concurred that cardiac mortality did spike during the winter months, even identifying twin spikes in the daily number of deaths from heart disease in the U.S. from 1973 to 2001 on Christmas and New Year's Day, but added that the same is true for deaths that are not cardiac in nature, making the holidays a "risk factor for death." The research team also proposed that delayed health-seeking behavior of people during this time of the year might be a more reasonable explanation for the variability.[10] In the same year, Kloner summarized the mechanisms put forward by both scientific groups for what he called as the "Merry Christmas Coronary" and the "Happy New Year Heart Attack" phenomenon: (a) cold climate, (b) respiratory ailments that could aggravate cardiac conditions, (c) deferred medical consultations by patients, (d) reduced hospital staff during the winter break, as well as holiday stress and poor diets, among others.[11]

The yearly nadir of premature CVD death rate coincides with the celebration of Heart Month in the DOH calendar when Filipinos are reminded to take care of their physical hearts by living a healthy lifestyle. A better rationale for the February drop, however, was offered by Phillips in the "precipitation of death" hypothesis wherein a drastic decline is expected to follow the peak in rates, given the premise that the deaths would have come to pass only a little later had not the holidays ushered them in sooner.[10] Following this argument, the apparent secondary dip in June might be artificially produced by a secondary wave of CVD deaths during the summer, which, to some extent, might be ascribed to elevated temperature. The ill effects of extreme heat on existing cardiac conditions had been recognized mostly in the occupational setting.[12,13]

The mounting premature mortality from cancer, though a bit more gradual than that from CVD, had confirmed the conjecture of 1996 evaluation of the Philippine Cancer Control Program—that deaths secondary to malignancy would continue to increase over time, given the pitfalls of the said health program. It is highly probable that these statistics were still underestimated, given that the two national cancer registries where tumor records to which death certificates are matched are concentrated within and near the country's capitol. Laudico and Esteban admitted that mortality certificates signed by physicians other than the attending oncologist (which is a typical picture for patients dying in the more peripheral regions of the Philippines) have the tendency to be inaccurate since it would have to be based on information supplied by relatives.[14]

The apparently cyclical component of cancer death rate with its July-August crest might be explained by what several studies have looked into: the effect of sunlight in cancer survival. Using survival analysis techniques, investigators from the U.S. and the U.K. focused on producing epidemiological evidence to the seasonality of mortality from malignancy by proving that cholecalciferol or Vitamin D3, 90% of which are photosynthesized in the skin, improves prognosis of breast, colorectal, prostate and lung cancers, although biochemical mechanisms are not fully understood.[15,16] July and August are rainy months in the Philippines, which generally precludes people from receiving as much sunlight as they do in the summer, which may have an effect similar to that experienced by temperate countries during the winter. On the other hand, the February through might be related to the observance of the National Cancer Consciousness Week every third week of January. The awareness campaigns made during this time might have prompted unknowing cancer patients to come for screening, early detection and treatment, components which are crucial to cure for at least a third of cases. Fifty percent of newly-diagnosed Filipino patients die within the year of diagnosis,[17] and this is because majority of them are detected late in natural history of the malignancy. Esteban and colleagues believed that the results of their study on cancer survival in Rizal province (where one of the two registries is) pointed to the need for more patient education for behavioral change and advocate for more researches that would delve on generating better prognosticating variables to modify current management of tumors.[18]

The seemingly overall declining trend for age-specific premature DM rate was not supported by the earlier discussion on the annual diabetes death tolls, given the discernible shift in trend between the years 2008 and 2009. Up until 2008, DM seemed to be progressively rising, but from 2009 onwards, the slope became relatively flat. Alternatively, the trend might be interpreted as polynomial of the 3rd order, which was convex before 2009 and concave thereafter.

The ostensible absence of seasonal variation in mortality from diabetes was consistent with the rarity of studies demonstrating such temporal characteristic, save a few which has shown annual fluctuations in hemoglobin A1c (HbA1c) and hypoglycemic crisis. HbA1c, or glycosylated hemoglobin, is a measure of average glucose levels in the last 3 months and is often used as a marker of glycemic control among diabetics. High HbA1c levels are purported to be associated with the complications of diabetes, and therefore, with risks of death. In one 2-year study among U.S. veterans, mean monthly HbA1c maxed out during March and plunged in September, concluding a seasonal effect that may be secondary to temperature variations more than dietary indiscretion during the holidays.[19] Another study in Japan retrospectively reviewed cases of hypoglycemia among DM type 1, DM type 2 and non-DM patients. Hypoglycemic events among diabetics are as potentially fatal as the more popular hyperglycemic crises. In the study, occurrence rates of severe hypoglycemia differed between the summer and the winter, with the latter having significantly higher rates among type 1 diabetics, whose sole dependence on insulin (in contrast to type 2 diabetics who are on oral hypoglycemic agents [OHAs] which may be more easily dose-adjusted) makes them more prone to sudden drops in blood sugar levels.[20]

This constancy of the mortality trend for chronic respiratory disease among 30-69 year-olds might sound like good news for Filipinos, since the worldwide trend, particularly of chronic obstructive pulmonary disease (COPD) mortality, had been increasing from 2001, and even a high-income country as the U.S. has the same stagnant feature.[21] Nonetheless, the Philippines can never be too complacent about this, since most other first-world regions of the world have dwindling mortality rates from COPD through time, more so in males. In Hong Kong, age-specific COPD mortality rates continue to fall for both males and females among those below 70 years old.[22] In addition, mortality rates from COPD is highest in the Western Pacific Region, where moderate to severe COPD cases are also most prevalent; 6.3% of Filipinos have moderate/severe COPD, ranking third after Vietnam (6.7%) and China (6.5%) in 2000.[23]

Seasonal variation in CRD mortality, initially anticipated to be the most prominent of the four due to pathophysiology of hypersensitivity behind these diseases (thereby logically causing exacerbation patterns that follow those of its triggers), had not been observed. This non-seasonality, however, could be backed up by existing literature on the exacerbation of chronic obstructive pulmonary disease. In a cohort study of COPD admissions in New Delhi tertiary hospital, Chandra and Guleria did not find any statistical difference in the frequency and/or outcome of admissions for acute exacerbations between the summer and winter seasons in India.[24] Meanwhile, seasonality of exacerbations and hospitalizations was appreciated by Jenkins et al in their 3-year multicenter study on determinants of moderate to severe COPD exacerbations, with the exception of tropical countries like Hong Kong, Malaysia, Mexico, Philippines, Singapore, Taiwan and Thailand, where temperatures are relatively constant throughout the year.[25]

Scope and Limitations

As with any study dealing with aggregate mortality data, the lack of data quality in terms on comprehensiveness, accuracy and coverage still was a significant constraint to generating perfectly valid results.

Also, while the study looked into the premature deaths arising from the four leading causes that make up three-fourths of all NCD mortality below 70 years of age, the addition of the remaining quarter of deaths from other non-infectious, lifestyle-related diseases (like kidney disease and mental illness; excluding injuries) in the analysis of the overall NCD premature mortality rates may present significantly different results, and thus, engender different recommendations. This paper did not delve on disparities in the mortality rates between sexes, age groups or urban-rural settings which can be expected of some of the NCDs.

Recommendations

As it is, diabetes mellitus is the chronic disease that has the potential to become the core NCD problem of Filipinos in terms of mortality in the near future, and it is prudent that present services must be dedicated and resources channeled to stop this omen from happening. Primordial and primary prevention strategies may include the latest recommendations from WHO about limitations on sugar intake. As the suggestions to reduce consumption of free sugars are based on a person's total energy intake, collaborations by the DOH with the National Nutrition Council (NNC) and the Department of Science and Technology - Food and Nutrition Research Institute (DOST-FNRI) are necessary to come up with concrete implementable guidelines. Meanwhile, the health sector can also look into the affordability and availability, accessibility and affordability of DM medications in partnership with the Philippines' Food and Drug Administration (FDA) and the Department of Trade and Industry (DTI), among others, to augment secondary and tertiary methods of prevention.

On the other hand, diseases like cancer and chronic respiratory disease, whose premature death rates have been foreseen to remain stagnant in the next few years, may be addressed, similar to diabetes, by first examining and ensuring the public's access to pain medications and airway dilators, in cooperation with appropriate national and local agencies. Furthermore, more studies into discovering cost-effective public health ways of preventing these two NCD groups that are mostly diagnosed late into the disease course or whose approaches to management are mainly clinical are warranted. To date, the best communities at the grassroots level can do is strengthen their information dissemination campaigns on the minimalization of risk factors and prevention of disease onset, as well as screening and early detection of cases.

While the trend following 2010 in premature mortality for cardiovascular disease is most favorable of the four NCDs, complacency has no room in the realm of public health, given the flattening of the slope in the near future. There appears a need to fortify current efforts which have shown great potential in precluding premature death in the first few years following the dissemination of the guidelines. On top of this, it is sensible to ask which particular aspects not only of cardiovascular disease but of the disease subtypes to target, which links to the subsequent proposed action.

Conclusion

Plotting the rates instead of absolute counts of the leading NCD causes of death showed generally rising slopes among Filipinos less than 70 years old from the years 2006-2012. This is particularly true of the overall NCD picture and the rates of CVD deaths; mortality from cancers and chronic lung diseases depicted more gradual inclines. Premature deaths from diabetes, on the other hand, revealed a nonlinear trend.

Forecasts tell us that CVD death rate in the 30-69-year-old segment of the population continued to decrease in time, albeit that it is of borderline significance. Predicted premature cancer and CRD mortality rates were stable. The rate of diabetes deaths in the 30-69 age group, whilst with increasing trends until 2012, would stabilize soon after. In general, NCDs, in terms of age-specific premature mortality rate, would have a flat trend, at least until the end of 2016. Even though this was an improvement from the soaring trend demonstrated from almost a decade ago, the stagnation could eventually thwart the country from meeting the global target of 25% relative reduction in the risk of premature mortality from the leading chronic diseases by 2025, unless a more appropriate (a more aggressive) action is taken.

As an initial investigation into the temporal characteristics of premature mortality rates from chronic lifestyle-related diseases, this study is subject to several improvements and is bound to spawn future researches that shall complement or challenge these preliminary results. The timely focus of the international community on noncommunicable disease and the fairly novel application of time series analysis in a field other than infectious diseases spur ideas for advancement of scientific health knowledge.

Acknowledgments

The authors express their sincerest gratitude to **Dr. Tassanee Silawan** of Mahidol University - Faculty of Public Health, **Dr. Ma. Sandra B. Tempongko** of the SEAMEO TROPMED Network, and **Dr. Ma. Carmen C. Tolabing** of the University of the Philippines - College of Public Health, for their invaluable inputs in the conduct of this research; to the **Rockefeller Foundation**, for the financial support; and to **Dr. Lisa Grace S. Bersales**, National Statistician and Civil Registrar-General of the Philippine Statistics Authority, and the PSA workforce, who facilitated the extraction of secondary data necessary for the study.

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