## Pattern and Correlates of Multimorbidity in India: Evidence from Demographic and Health Survey


#### Abstract

Objectives: The study aims to identify the socioeconomic, demographic, and lifestyle factors affecting the burden of multimorbidity among both men and women in India.

Methods: The study utilizes a nationally-represented data from the Demographic and Health Surveys, 2015-16. Descriptive statistics were computed to understand the sample distribution under consideration, followed by sex stratified age-standardized prevalence rates. Additionally, two-parts models were fitted to draw inferences from the data.

Results: There is a predominance of multimorbidity among women ( 3.36 per 100 women) as compared to men ( 3.25 per 100 men ). The burden of multimorbidity is greatly influenced by the age of the respondent, i.e., higher the age, more is the burden. Hypertension and diabetes were more prevalent in the country, with an observed difference in the type of chronic conditions by sex. The prevalence of multimorbidity was found to be higher amongst the respondents belonging to urban areas, southern region, and economically well-off classes.


Conclusions: Considering the difference in the type of chronic conditions segregated by sex, it is essential to provide personalized gender-specific healthcare facilities to the patients affected by multimorbidity.

Keywords: Demographic and Health Surveys; Multiple chronic conditions; Multimorbidity; Sex; Social determinants of health

## Introduction

In the avenue to foster a more sustainable future for all, the third objective of Sustainable Development Goals (SDG) aims to ensure healthy lives and promote well-being, for all, at all ages (United Nations- Sustainable development Goals, 2015). However, from the last four decades, the overall health of the population is severely affected by the rising levels of disease burden, with a noticeable alteration in the nature of the diseases burden globally (Marmot and Friel, 2008). In the earlier centuries, the burden of the disease was majorly contributed by the Communicable Diseases (both infectious and parasitic), whereas, in the present era, Non-Communicable Diseases (NCDs), contributes to the significant share of the disease burden. This shift in the disease burden, termed as 'the epidemiological transition' was hypothesized by 'Omran'(Omran, 1971).

Evidence produced by the Global Burden of Diseases (GBD) suggests that a large proportion of the World's population suffers from disease-related morbidity (World Health Organization, 2018). There has been a notion that the problem of morbidity burden persists only in the industrialized and developed countries. On the contrary, the problem is also severe in the Low-and-Middle-Income Countries (LMICs), where, the rising levels of urbanization and industrialization have altered the lifestyle and behavioural patterns of the individuals, which in turn, accelerates the prevalence of disease related morbidity (Yadav and Arokiasamy, 2014). Estimates generated by a recent meta-analysis suggest that the prevalence of multimorbidity for high-income and low-and-middleincome countries are 37.9 percent and 29.7 percent, respectively (Nguyen et al., 2019) .

As an outcome of the demographic and epidemiological transition, a paramount public health concern is multimorbidity (MM), i.e., presence of more than one chronic diseases within an individual without marking any index disease (Skivington et al., 2017). According to the definition of multimorbidity, such chronic diseases could either be communicable or non-communicable (Skivington et al., 2017). Estimates generated for the year 2019, suggest that 54.5 percent of the deaths in India are attributed by chronic health conditions, with cardiovascular and respiratory diseases, being the primary cause of death (Sheth, 2017).

Existing literature establishes the significance to explore multimorbidity as an independent domain, due to its accelerating burden and association with unfavorable health outcomes, like declining functional status, low levels of social interaction, poor quality of life, low satisfaction level, higher mortality risks, increased healthcare utilization and, increased economic burden on the patients' household (Fortin et al., 2004; Gijsen et al., 2001)
(Marengoni et al., 2011). Nevertheless, despite the detection of multimorbidity burden in some studies, the entire literature is flooded by the studies focussing on single-diseases (Lim et al., 2012). Thus, it becomes essential to explore the domain holistically for ensuring community-oriented health-related programs and policies (Boyd and Fortin, 2011).

According to the Commission on Social Determinants of Health (CSDH); social, economic and political mechanism configures the hierarchical system in the society, which is delineated by sex, ethnicity, income, education and other factors which define the socioeconomic position (World Health Organisation, 2010). These established socioeconomic position alters the individual experiences based on the differences in the exposure and vulnerability to health compromising conditions. Such conditions include there dietary intakes, lifestyle and behavioural factors, and healthcare utilization. Thus, social determinants play a crucial role in the well-being of the individuals in the society (World Health Organisation, 2010). Also, as already established by the studies based on the developed countries, that multimorbidity has severe implication on the well-being on an individual (Fortin et al., 2004; Gijsen et al., 2001; Marengoni et al., 2011). It is therefore, essential to incorporate the concept of social determinants while studying multimorbidity, as it is crucial from the policy point of view. Thus, the present study aims to identify the burden, patterns, and correlates of MM classified by sex of the respondent.

## Methods

## Data

The present study utilizes the data from the fourth round of the National Family Health Survey (NFHS), 2015-16 (https://dhsprogram.com/data/dataset/India Standard-DHS_2015.cfm?flag=1). The primary objective of NFHS is to provide national and sub-national level estimates of the data on population, health, nutrition, and other key demographic indicators. The evidence generated by NFHS abets the policymakers in establishing benchmarks, evaluating the effectiveness of currently running programs, and identifying the need for new programs in the areas specific to family and health. The sampling design adopted by NFHS-4 is a two-stage stratified sampling considering urban and rural areas as the natural strata. The details of the sampling design utilized in the survey are presented in Appendix 1.

For the present analysis, the study utilized a nationally representative sample of 103,291 men and 699,686 women in the age group of 15-49 years from all 36 states/Union Territories (UTs) of the country. For auxiliary information, Census 2011 data been employed (http://www.censusindia.gov.in/2011census/population_enumeration.html).

## Exposures

The study aims to identify the socioeconomic and demographic factors affecting the burden of multimorbidity segregated by sex in India. Existing literature establishes the multidimensional nature of socioeconomic status (SES) (Braveman et al., 2005; Chung et al, 2015), it is, therefore, crucial to incorporate all available and feasible individual-level indicators of SES in the study.

Socio-demographic variables. The variables included under this heading are age, sex, and marital status of the respondent. Age was classified into three categories, namely 15-19 years; 20-34 years; and 35-49 years to distinguish between various stages of life such as 'adolescent', 'adulthood', and 'middle age'. Marital status was included as dichotomous variables with categories never married/ever married.

Socioeconomic variables. The present study includes social group (Scheduled Castes/Tribes; Other Backward Classes (OBC) and Others), Religion (Hindu; Muslim; Others), place of residence (Rural; Urban), region of residence (Northern; Central; Eastern; North-eastern; Western and Southern), years of education (0-9 years; 10 years or more), wealth index (poor; middle; rich), and household size ( $0-4$ members; more than four members). It is worth mentioning that the variables like social group and religion are included in the study as they are building block of Indian society, and thus play a significant role in defining the SES of a respondent (Goli at al, 2016). It is worth mentioning that the information on income or expenditure is not collected in NFHS, and therefore, the wealth Index is utilized to measure the SES of the respondent. Existing literature suggests the advantages of using DHS wealth Index (computed using the information available on assets and amenities) to measure the SES holistically (Filmer and Pritchett, 2011; Rutstein and Johnson, 2004). The information on the classification of the states and UTs into the region is given in Appendix 2.

Lifestyle variables. This included behavioral risk factors like consumption of tobacco (no consumption; only smokes tobacco; only chewing tobacco; both smoking and chewing) and, consumption of alcohol (no alcohol; less than once a week; about once a week; almost every day). Obesity (BMI greater than or equal to $30 \mathrm{~kg} / \mathrm{m}^{2}$ ) was also included as a proxy indicator of physical activity.

## Outcome

For analysis, two outcome variables have been utilized to measure the level of multimorbidity, namely, 1) the presence of two or more chronic health conditions (multimorbidity) and, 2) the number of chronic health conditions present in an individual (severity).

To calculate the number of chronic conditions, present in an individual, information available from both selfreported and clinically diagnosed data is used. The study incorporates all the seven chronic conditions, namely, asthma, cancers, heart disease, diabetes mellitus, tuberculosis, hypertension, and thyroid disorder, available in the NFHS-4 data. Detailed information on the chronic conditions included in the study, along with the nature and tools of data collection are provided in Appendix 3.

## Statistical Analysis

To draw inferences from the data, it is essential to understand it first. Thus, descriptive statistics were utilized to understand the nature of the data, followed by bivariate analyses to examine the unadjusted association between the selected exposure variables with the outcome of interest, which in this case is the presence of multimorbidity. Age-standardized prevalence of multimorbidity was computed for both men and women separately. For the purpose of standardization population enumerated by Census 2011, Registrar General of India was considered as the standard population.

The results from the primary analysis depict that a significant share of the surveyed population does not suffer from multimorbidity. Therefore, the distribution of the outcome of interest is positively skewed. The description is shown in Appendix 4. In order to solve the issues, as above, a two-stage estimation procedure, like two-parts model, are frequently used. Two-parts model is often used to model strictly positive variables with a large number of zero values. This model consequently formulated as a mixture of a binomial distribution and a strictly positive distribution. Two-parts model is commonly used in health economics studies to model healthcare expenditure data because a large fraction of patients does not spend anything on medical care in a given time (Deb et al, 2006; Matsaganis et al, 2008). Typically, a two-parts model referred to as a hurdle model and is used for count data as well (Kapitula and Valley, 2015)

In the present study, our variable of interest does not satisfy the normality condition (i.e., positively skewed). The first stage defines the outcome as a dichotomous variable, which in this case is multimorbidity (present=1, absent=0). This part can be referred to as the 'prevalence part'. After completion of the first stage it is identified that to which group of the dependent variables the observations belong. The second stage takes into account the number of morbidities (count data) if the selected respondent has the outcome of interest i.e., multimorbidity. This part can be referred to as the 'severity part'. Therefore, to predict the above situation as a two-parts model is to
consider it as a mixture of two distributions, first, one consisting of a point mass at zeros, followed by a truncated count data distribution for the non-zero observations. Thus, for addressing the issue in hand, for the first part logistic link function would be applied (considering multimorbidity as a dichotomous variable; present=1, absent=0), followed by a generalized linear model using a 'Poisson regression' (Braveman et al., 2005; Chung et al., 2015).

The analysis of the present data is done using Stata version 15.0 (Stata Corp Inc. TX, USA) and R Studio version 1.1.463 (R Studio, Inc.) is utilized for the purpose of data visualization. All the estimates provided in this study are derived by applying appropriate sampling weights supplied by National Family Health Survey (NFHS-4), 2015-16.

## Results

Figure 1 provides the prevalence of multimorbidity segregated by the selected age-groups (in years). There is a trend observed in the burden [Prevalence Rate (PR)] of MM, which increases with the age of the respondent. A similar pattern is observed for both men and women. The prevalence of MM was lowest among the respondents in age-group 15-19 years [PR: Men= $0.52 \%$, Women= $0.55 \%$ ] and highest for the age-group, 35-49 years [PR: Men $=6.96 \%$, Women $=7.22 \%$ ].
[Insert Figure 1 here]

Table 1 provides the findings from the descriptive and bivariate analysis for the sample under consideration. Among men, the majority of the men belonged to 20-34 years of age-group ( $45.96 \%$ ). Around 62.0 percent of the men belonged to rural areas, and 81.0 percent belonged to Hindu religion. Around forty-three percent of the men belonged to other backward classes ( OBC ). Fourteen percent of the respondent belonged to Northern region of a country, 3.3 percent belonged to North-eastern region, 22.5 percent belonged to Central region, 18.7 percent belonged to Eastern region, 18.5 percent belonged to Western region and, 23.5 percent belonged to Southern region. Around 60.0 percent of the men had a household size of four or more. Thirty-six percent of the men belonged to rich wealth tertiles. Majority of the men did not consume tobacco ( $55.56 \%$ ) and alcohol ( $70.85 \%$ ). Around three percent of the men were obese.

Similarly, among women, the majority of the belonged to 20-34 years of age-group (47.85\%). Around 65.0 percent of the women belonged to rural areas, and 80.0 percent belonged to Hindu religion. Around forty-three percent of the women belonged to other backward classes (OBC). Thirteen percent of the women belonged to Northern region of a country, 3.5 percent belonged to North-eastern region, 24.5 percent belonged to Central region, 22.1 percent belonged to Eastern region, 14.4 percent belonged to Western region and, 22.8 percent belonged to Southern region. Around 60.0 percent of the women had a household size of four or more. Thirty-three percent of the women belonged to rich wealth tertiles. Majority of the women did not consume tobacco ( $93.20 \%$ ) and alcohol $(98.77 \%)$. Around five percent of the women were obese.

It is worth mentioning, that findings from Figure 1 depict a huge variation in the burden of multimorbidity by age, thus, to nullify the effect of age, the present study utilizes age-standardized prevalence of multimorbidity by background characteristics. Findings from the bivariate analysis suggest that the overall prevalence of MM in among men and women in India is 3.25 and 3.36 percent respectively. This suggests that the prevalence of MM was found to be higher amongst women as compared to men. The prevalence was found to be higher amongst the respondents residing in the urban areas (PR: Men=3.80\% [3.63-3.99]; Women=4.15\% [4.07-4.22]), and those who belong to social groups other than those who are Scheduled castes/tribes or are backward (PR: Men=3.29\% [3.09-3.49], Women $=3.96 \%$ [3.87-4.04]). The prevalence was found to be higher amongst the respondent from Southern region, (PR: Men=4.48\% [4.42-4.73], Women=4.29\% [4.19-4.39]). Age standardized multimorbidity prevalence was found to be higher amongst the respondents who have ten or more years of schooling (PR: Men=3.48\% [3.31-3.66], Women=3.68\% [3.60-3.78]), were married at least once (PR: Men=3.45\% [3.25-3.65], Women $=3.41 \%$ [3.36-3.45], and had less than four members in the household (PR: Men=3.51\% [3.34-3.68], Women $=3.41 \%$ [3.36-3.45]). The prevalence of multimorbidity was found to be higher amongst the respondents belonging to rich wealth quintile [PR: Men=3.87\% [3.69-4.07], Women=4.25\% [4.18-4.33]). The prevalence of multimorbidity was found to be highest for the individual who consumed alcohol almost every day (PR: Men $=5.64 \%$ [4.69-6.76], Women $=5.27 \%$ [4.05-6.82]) [Table 1].

## [Insert Table 1 here]

It is worth mentioning that the present study includes seven chronic conditions. Figure 2 depicts the agestandardized prevalence of individual conditions segregated by sex. The findings from Figure 2 suggest that the most prevalent chronic condition in India is Hypertension [PR: Men=14.39\%, Women=10.87\%], followed by
diabetes [PR: Men $=8.37 \%$, Women $=6.56 \%$ ], and thyroid disorder [PR: Men=0.49\%, Women=2.17\%]. There is preponderance hypertension, diabetes, and cancer amongst the men in India, whereas, chronic health conditions like asthma, thyroid disorder, heart disease and tuberculosis were found to be higher among the women in India.
[Insert Figure 2 here]

There is a variation in the prevalence of multimorbidity by the different regions of the country (as earlier depicted by Table 1]. Therefore, it would be interesting to explore the age-standardized prevalence of multimorbidity by sub-regional level i.e., States and Union Territories. Thus, Figure 3 and Figure 4 depicts the distribution of multimorbidity burden by all 36 States and Union Territories in India. Findings from Figure 3 suggest that the prevalence of Multimorbidity among men was higher for Andaman and Nicobar Island (7.78\%), Tamil Nadu ( $5.62 \%$ ), Sikkim ( $5.22 \%$ ), and Meghalaya ( $5.02 \%$ ). It is worth mentioning that in case of men all the States and Union Territories hailing from the Southern and North-eastern region have a prevalence higher than the national average (PR for India=3.35\%). Findings from Figure 3 suggest that the prevalence of Multimorbidity among men was higher for Andaman and Nicobar Island (7.78\%), Tamil Nadu (5.62\%), Sikkim (5.22\%), and Meghalaya (5.02\%). Similarly, the findings from Figure 4 suggest that the prevalence of Multimorbidity among women was higher for Lakshadweep (6.67\%), Jammu and Kashmir (6.45\%), and Andaman and Nicobar Islands (5.34\%). It is worth mentioning that in case of men all the States and Union Territories hailing from the Southern and Northeastern region have a prevalence higher than the national average ( PR for India $=3.35 \%$ ).
[Insert Figure 3 here]
[Insert Figure 4 here]

Table 2 shows the adjusted effects of independent factors on the probability of suffering from multiple chronic morbidity conditions i.e., multimorbidity using a two-parts model. The predicted probability of having at least two chronic morbidity conditions reveals that the occurrence of MM is affected by different socio-economic characteristics.

For men, the predictive probability shows that the variables such as age (in years), place of residence, the region of residence, marital status, wealth index, and consumption of alcohol and obesity are statistically significant
predictors of MM. The findings suggest that an increase in the age-group from 15-19 years to 35-49 years, increases the probability of having multimorbidity by five percent points after controlling for key factors. The findings also suggest that as an individual move from urban to rural, decreases the probability of having MM by 0.43 percent points after controlling for key factors. Whereas, individual moves from Northern to Southern region, there is an increase in the probability of having MM by around two percent points. Similarly, the probability of having MM for the ever-married individuals is higher by one percent point as compared to those who are never married. An increase in wealth index from poor to rich increases the probability of having MM by one percent point. An increase in the frequency of consuming alcohol from never to almost every day increases the probability of having MM by two percent points. The findings suggest that a shift in an individual from non-obese to obese, increases the probability of having multimorbidity by six percent points after controlling for key factors.

Similarly, for women, the predictive probability shows that the variables such as age (in years), place of residence, religion, social group, the region of residence, years of education, marital status, household size, marital status, wealth index, and consumption of alcohol and obesity are statistically significant predictors of MM. The findings suggest that an increase in the age-group from 15-19 years to 35-49 years, increases the probability of having multimorbidity by six percent points after controlling for key factors. The findings also suggest that as an individual move from urban to rural, decreases the probability of having MM by 0.39 percent points after controlling for key factors. Whereas, individual moves from Northern to Southern region, there is an increase in the probability of having MM by 1.25 percent points. As the level of education is increased from 0-9 years to 10 or more years, increases the probability of having MM by 0.67 percent point. Similarly, the probability of having MM for the ever-married individuals is higher by half percent point as compared to those who are never married. A shift for less than four members to more than four family members decreases the probability of having MM by 3.8 percent points. An increase in wealth index from poor to rich increases the probability of having MM by two percent points. An increase in the frequency of consuming alcohol from never to less than once a week increases the probability of having MM by around two percent points. The findings suggest that a shift in an individual from non-obese to obese, increases the probability of having multimorbidity by five percent points after controlling for key factors.

## Discussion

From last four decades, there has been changes in the vital demographic processes, which is an indication of arrival epidemiological transition in the Country (Yadav and Arokiasamy, 2014). In the current era of transition, there has been an observable shift in the nature and burden of disease occurrence. Increasing Industrialization and westernization has altered the lifestyle related factors of the individuals in the country (Singh and Srivastava, 2018). This has resulted in the simultaneous occurrence of more than one chronic conditions in a single individual, a phenomenon commonly known as 'multimorbidity'. This simultaneous occurrence of chronic conditions could be owed to the common risk factors or causation of one condition by another (Hajat and Stein, 2018; Ward et al, 2014). However, there are only few studies exploring multimorbidity in India, where the majority of the literature is based on single diseases without any discussion on other associated long-term conditions (Singh and Srivastava, 2018 ; Singh et al., 2018). To the best of our knowledge, the study is first of its kind to utilize a large nationally representative sample to examine the burden, pattern, and correlates multimorbidity among adult population segregated by sex in India.

A recent systematic review conducted on the studies based on low-and-middle-income countries (LMICs) suggest that the prevalence of multimorbidity ranges between 2 percent to 82 percent for LMICs (Nguyen et al., 2019). Findings from the present study show that the prevalence of multimorbidity among men and women in India is 3.25 and 3.36 percent respectively, which falls in the range of the above research.

Evidence generated shows that the burden of multimorbidity is greatly influenced by the age of the respondent, i.e., higher the age, more is the burden of multimorbidity in India. Evidence generated by the study suggests a preponderance of multimorbidity among women for most of the age-groups. This finding is in concordance with the existing studies (Alaba and Chola, 2013; Gamma and Angst, 2001). This could be attributed to the genderbased inequities in the health sector, which is majorly designed to support the maternal and child health outcomes. Thus, influencing the consultation rates among the women. Studies conducted in past, supports the idea that the health related consultation rates are higher in women as compared to men majorly due to their reproduction related visits (Hajat \& Stein, 2018; Wang et al, 2013; Ward et al., 2014)

It is worth mentioning that, the commonest chronic condition in both men and women are hypertension, diabetes, and thyroid disorder. Findings further show that the prevalence of chronic conditions like hypertension, diabetes and cancer were higher for men, whereas, chronic conditions like asthma, heart disease, tuberculosis and thyroid disorder were higher among women in India. This establishes a potential difference in the type of chronic conditions segregated by sex. On one hand, women are affected by conditions which are related to household
environmental factors, and conditions caused by hormonal imbalance in the body, which is majorly linked to their reproductive capabilities. Whereas, on other hand, the diseases more prone to men are related to the stress (which may be induced by work and economic responsibilities) and behavioral risk factors like consumption of alcohol, both of which are interlinked (Singh et al., 2018).

The burden of multimorbidity was found to be higher for respondent residing in the urban areas and belonging to Southern region of the country. This could be attributed to two reasons, one being the changing lifestyle and dietary pattern in urban centres and southern region of the country (Alaba and Chola, 2013; Singh et al., 2018). The second reason could be the issue of unequal access to public health in the country which is better for urban centres and southern region, due to higher level of awareness and relatively easy availability of transportation facilities (Balarajan, 2011; Barik and Thorat, 2015).

The burden of multimorbidity was found to be lower for women who have more than four family members (household size). The variable household size can be served as a proxy indicator for social capital. Many studies conducted in the past state that social capital was found to be significantly associated with the well-being of an individual (Marmot and Friel, 2008). However, the direction of the relationship has been debatable, as the definition of the social capital varies from one study to another (Alaba and Chola, 2013; Lin and Si, 2010; Michael et al, 2002). However, the studies which shows a negative relationship between social capital and multimorbidity, suggest that higher number of family member increases the chances of stronger bonds between the family, which help in managing the chronic conditions (Taylor et al., 2010).

Prevalence of MM was found to be higher for respondent belonging to economically well-off sections of the society. This finding is similar to that of other findings that are conducted in low-and-middle income countries. The major reason behind this finding is the fact that, with economic liberalisation, globalisation and westernisation, the dietary pattern of the population is changing, the consumption of food and beverages rich in saturated sugar are increasing and number of individuals practicing a sedentary lifestyle are also increasing considerably (Alaba \& Chola, 2013; Singh et al., 2018)

Additionally, higher frequency of alcohol consumption and obesity were found to be associated with higher multimorbidity burden among both men and women. This finding is in concordance with existing literature, which establishes consumption of alcohol and obesity as the major correlate of various single chronic conditions (Agur et al, 2016; Batty et al, 2009; Bijl et al, 2002).

## Limitations of the Study

The present study does not include large number of chronic conditions (only seven conditions were included) or varieties of chronic condition, missing out important aspect of mental health, as the data does not provide information on it. Additionally, the results were not generated for all the ages due to unavailability of the data on the same. Also, chronic conditions specific to women are excluded from the study to ensure comparability among the study groups.

## Implications and future research

Findings from the present study establishes a potential difference in the type of chronic conditions segregated by sex of the respondent. Men suffer with multimorbidity majorly because of modifiable lifestyle factors such as consumption of alcohol and tobacco, whereas, women suffer primarily because of biological and environmental factors. Considering the aforementioned points, it becomes essential to provide personalized gender-specific healthcare facilities to the patients affected by multimorbidity (Agur et al., 2016; Plochg et al, 2009). However, this would require an in-depth study considering larger number of chronic conditions, specific to both men and women in the country.

## Conclusions

The present study proposes a preponderance of multimorbidity among women in India. The findings necessitate further exploration of the issue, especially in terms of linkages between various chronic conditions in the country. Inclusion of social marketing approaches at primary level of healthcare would assist the policy makers to educate the population about the importance of leading a healthy lifestyle.

## List of abbreviations

DHS: Demographic and Health Surveys
MM: Multimorbidity
NCD: Non-Communicable Diseases
NFHS: National Family Health Survey

## Declaration

Funding No funds were available for conducting the present study.

Compliance with ethical standards This study utilizes secondary data from a national survey conducted under the stewardship of Ministry of Health \& Family Welfare, Government of India with the help of International Institute for Population Sciences as the nodal agency. The data has been archived in a public repository, therefore, the data is easily accessible and there is no need of ethical approval for conducting this study.

Conflict of interest Authors' declare that the article submitted has not been published previously and is not under consideration for publication elsewhere. Furthermore, the publication is approved by all authors and tacitly or explicitly by the responsible authorities where the work was carried out. Authors' declare no conflict of Interests.

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