

Original Research Article


Epidemiology of Parkinson's disease in South central India - A longitudinal cohort study

Punam Kumari Jha¹, Nalin Chaudhary^{2*}

¹Professor and Head, Department of Community Medicine, Kakatiya Medical College, Warangal, Telangana State, India

²D.M Neurology, Consultant Neurophysician, TNC Medical Foundation, Warangal, Telangana State, India

*Corresponding author email: ncnalin@gmail.com

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Abstract

Background: Parkinson's disease (PD) is the second most common neurodegenerative disorder, commonly found in males above the age of 60. Increased life expectancy due to better health care and aging population will see a proportional rise in case of PD in India during next three decades making it a major health problem.

Objective: There was no published epidemiological study on PD from south-central India. Hence, a longitudinal study was undertaken by a neurocenter from 2004-2015.

Materials and methods: 382 patients with symptoms of PD presented to outpatient department of neurocenter between 2004-2015 were evaluated in relation with various epidemiological parameters.

Results: Out of 382 subjects having clinical PD, it was found to be more common in males and in patients above the age of 60 with rural habitation.

Conclusion: The present study documents the epidemiological data of PD from south-central India called Deccan plateau (Telangana state). It represents varied geographical, social, economic, cultural ethnicity among rural/urban population. There is low literacy rate, predominant rural population and insufficient health infrastructure where PD poses an invisible but major health problem for policy makers.

Key words

Parkinson's disease, Epidemiology, Geographical factors.

Introduction

Parkinson's disease (PD) is one of the most common age related neurodegenerative disease [1]. It is estimated that approximately 6.3 million people suffer from PD worldwide. Among hospital based series of 2,43,021 new patient, 27% had neurological disorders, of which 20% had movement disorders and PD was the third common neurological disorder and the commonest movement disorder (86.5%) [2]. The WHO gives an estimated crude prevalence of 160 per lakh and an estimated incidence of 16-19 per lakh. It affects approximately 1% of individuals older than 60 years and causing progressive disability which can be slowed down but not halted by present mode of therapeutic options. Out of the world's 580 million elderly (over 60 years), 60% live in developing countries and 22% live in India. Caring of this increasing elderly population with increase in age related disease (PD and Alzheimer's) can be very challenging. This is because of the fact that 80% of elderly Indians live in rural areas, 73% are illiterate, 60% are women and 60% live below the poverty line. Moreover in a study it has been projected that 6 out of 10 most populous countries of the world are in Asia (China, India, Indonesia, Pakistan, Bangladesh and Japan). The number of PD patients in these countries is expected to increase from 2.57 million in 2005 to 6.17 million in 2030 [3]. The only solace that PD has a low prevalence in India and Asian countries except in the small ethnic Parsi community of Mumbai [4, 5].

British physician James Parkinson described the *shaking palsy* in his paper two centuries ago (1817), which formed the major symptomatology of PD. It is second only to Alzheimer's disease in terms of frequency when compared to any neurodegenerative disorder [6, 7]. PD is a slowly progressive disorder with no identifiable cause. Due to degeneration of *substantia nigra* neurons, there is depletion of dopamine neurotransmitter which disturbs the transmission of signals between substantia nigra and the next relay station of the brain, the *corpus striatum*, which is

responsible to produce smooth purposeful movement. It is diagnosed clinically by four major symptoms - *tremors* (hands, arms, legs, jaw and head), *rigidity* (stiffness of limbs and trunk), *bradykinesia* (slowness of movement) and *postural instability* (impaired balance). There is always a diagnostic dilemma as a single patient may not have all the symptoms at single point of diagnosis. Hence frequent follow up is necessary over the long period to have complete picture. Neurologists in principle have agreed that presence of two symptoms is enough for clinical diagnosis of PD. There are other conditions which mimic PD with additional neurological symptoms and are called atypical Parkinsonism – e.g. multiple system atrophy (MSA), progressive supranuclear palsy (PSP), striatonigral degeneration etc. The term Parkinsonism is also used where the aetiology of above symptoms are known, such as Parkinsonian signs due to stroke, infection, neuroleptic drugs and sometimes toxic agents.

Epidemiology of PD is beneficial in two ways for India. It provides highly probable risk factors for developing PD which can guide to achieve a clue of aetiology if further evaluated. Secondly India is a multi-ethnic country with genetic diversity and it needs proper healthcare planning and better investigative infrastructure for research into the aetiology of PD. With increased life expectancy and better healthcare, India is going to have huge disease burden due to PD in future. But so far, there is no prospective study to estimate its incidence and mortality except one [8]. There are two types of epidemiology in PD – descriptive and analytical. Descriptive epidemiologic studies enable us to understand the frequency and the geographical or temporal distribution of PD. These studies help us estimate the burden of the disease and provide etiologic clues. Analytic epidemiologic studies seek to identify specific factors that increase or decrease the risk. Two main study types used in analytical studies are: case –control or cohort studies. Most of the epidemiological factors associated with PD have been obtained from case – control studies. However, in recent years, more

prospective cohort studies have recorded sufficient data on PD to study the risk or protective factors in PD.

Many studies on epidemiology of PD have been published in the last 35 years from all zones of India [5, 8-11]. But there is paucity of literature published from central and south central India. Therefore, a medical foundation based at Warangal (NGO) with a vision of holistic neurocare, undertook a decision to conduct a longitudinal cohort study on PD. Warangal is the largest district (12,846 sq. km) of Telangana State with population density of 273 Males/253 Females per sq. km. The male literacy rate is 67%, whereas the female literacy rate is 50% [1]. It is a part of the Deccan plateau and represents the south-central zone of the country. It has a dry and hot weather through most of the year, except the months of December and January. The population of Warangal is 35 lakh, with 50.5% male and 49.5% females.

Materials and methods

The present study was undertaken between 2004 - 2015. All consecutive patients with possible symptoms of Parkinson's disease presented to outpatient department of neurocenter were registered and evaluated. 372 patients belonging to urban, semi-urban, rural and tribal areas of Warangal district were the source of present study. A structured pre-tested questionnaire was filled up for each patient. The primary data included name, age, sex, address, occupation, addiction to alcohol and tobacco, lifestyle factors (caffeine etc.). Past history of head injuries/stroke/cardiac stroke and family history of similar illness was also noted. Literacy and economic details were also recorded. Thorough clinical examination was done. Routine and special blood examinations were done to exclude other medical illness. Neuroimaging (CT scan /MRI Scan) was done in each case to rule out PD syndromes (e.g. multi-infarct state). Patients are periodically followed up at 3-month intervals for clinical improvement, to titrate the dosage of anti-Parkinson drugs and

counselling of patient and caregivers stressing the importance of regular medication and physiotherapy. Deaths from other causes in PD patients were recorded, which gives an idea about the average survival period on medication from the time of diagnosis and the stage at what it was diagnosed initially.

The data represents hospital-based longitudinal cohort study. The total number of patients of idiopathic PD was obtained after deducting the number of patients having Parkinsonian syndrome from the original documentation. Age and sex distribution of patients were done year wise. Newly diagnosed PD cases were tabled. Predominant clinical features were segregated into the columns. The associated risk factors were enumerated. The crude incidence and prevalence was calculated on the basis of total number of neurological patients attending the out-patient department annually (roughly 6000 patients per year). Chi-square test was performed to find the association between sex and age and PD. Percentage and proportion calculations were also performed on the data with respect to other parameters.

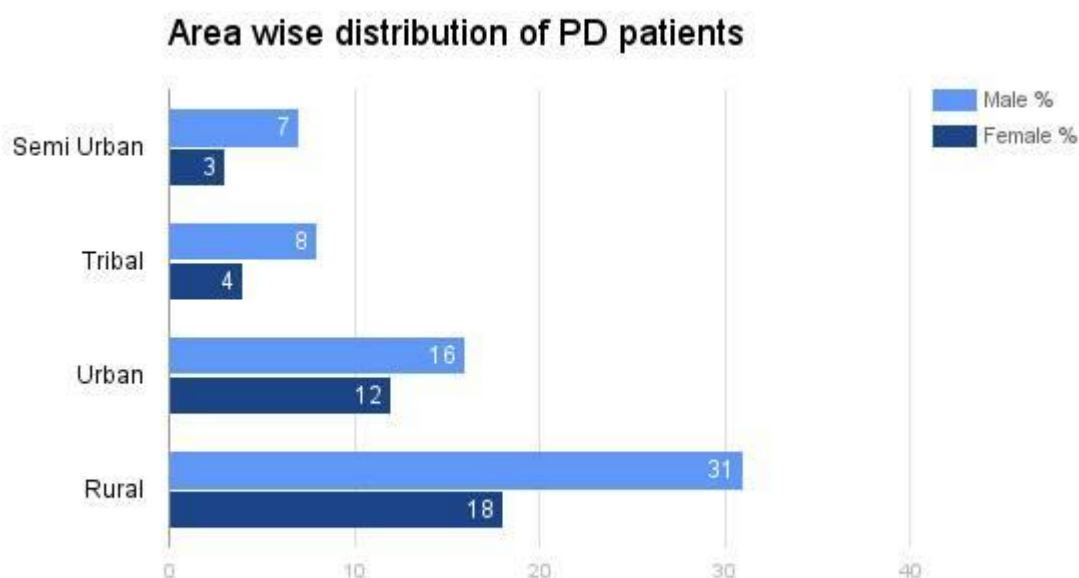
Results

A total of 382 subjects (238 Male, 144 Female) having idiopathic PD are included in the study. The Parkinson's syndrome was excluded by necessary clinical evaluation and radiological assessment. Our results shows that 28% patient came from urban areas, 10% from semi-urban, 50% from rural areas and 12% percent from tribal areas (**Figure - 1**). The neurocenter located in Warangal was the only referral centre for neurology patients in the north Telangana region at the onset of this study. Neighbouring districts of Warangal (Karimnagar, Adilabad, Khammam and Nalgonda) contributed about 20% of PD subjects. Since most of the patients were referred by general practitioners and general physicians, majority of the patients were having at least 2 of the 3 cardinal features of PD (Tremors 90%, Bradykinesia 40% and rigidity 15%). This posed little challenge to diagnose PD clinically. Over

the last decade, the data shows that there is a slight increase in the number of male cases reported whereas there is little to no fluctuation in the case of female PD cases reported per year (**Figure - 2**). The age wise distribution of the patients shows only 30 (8%) below the age of 50 years. The minimum age recorded was 25 years in an office clerk whereas the maximum age recorded was 84 years. So there is significant presence of young onset PD. No family history was found in young onset PD. The maximum number of PD patients was found in the age group of 60-70 years (53.7%) and there was only 6% PD above the age of 80 years (**Figure - 3**). The chi-square test was applied considering

patients of less than 60 and more than 60 years of age which showed $p < 0.005$ (highly significant). Hence, the chances of developing PD is more in elderly aged 60 years or more compared to young and middle age. 44 patients of PD died during the last 11 years of follow up due to advanced age, prolonged bedridden state, cardiac events and cerebrovascular accidents. The literacy rate among the patients was 65% in males and 57% in females. The chi-square test revealed $p < 0.005$ (significant) which means increased awareness about PD, early diagnosis and treatment led to marginal increase in the incidence of PD in males.

Figure - 1: Area wise distribution of 382 PD cases.



Male - 238

Female - 144

Among the factors associated with PD in analytical epidemiology, pesticide exposure was found in 29.5% patients belonging to rural and tribal areas. Exposure to heavy metal was found in 12.09% of the patients who worked in the mines of Warangal and Khammam district (**Table - 1**). Smoking (Beedi and Chutta) and alcohol consumption (Kallu/ Tadi/ Gudamba) is

common social practice and habit among both males and females in this part of Telangana state, which is reflected in (**Table - 2**). Tea consumption is more in rural area (56.18%) compared to coffee consumption. Consumption of coffee was more in urban area (19% of total PD cases). Consumption of milk is limited (44%) due to poverty and non-availability. High uric

acid levels in local population are common in this part of India (Table - 3) due to consumption of meat, tomato, alcohol and leafy vegetable consumption. This was found to be high as well in 54 % of our PD patients.

Figure - 2: Distribution of PD cases detected in males and females from 2004-2015.

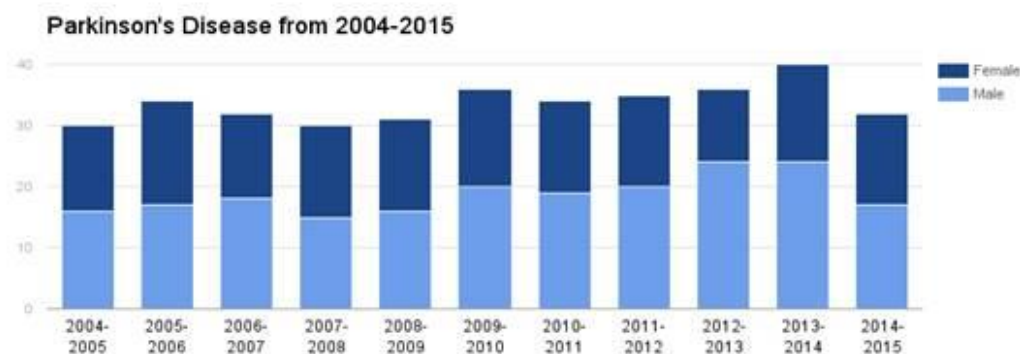


Figure - 3: Age wise distribution of 372 PD cases.

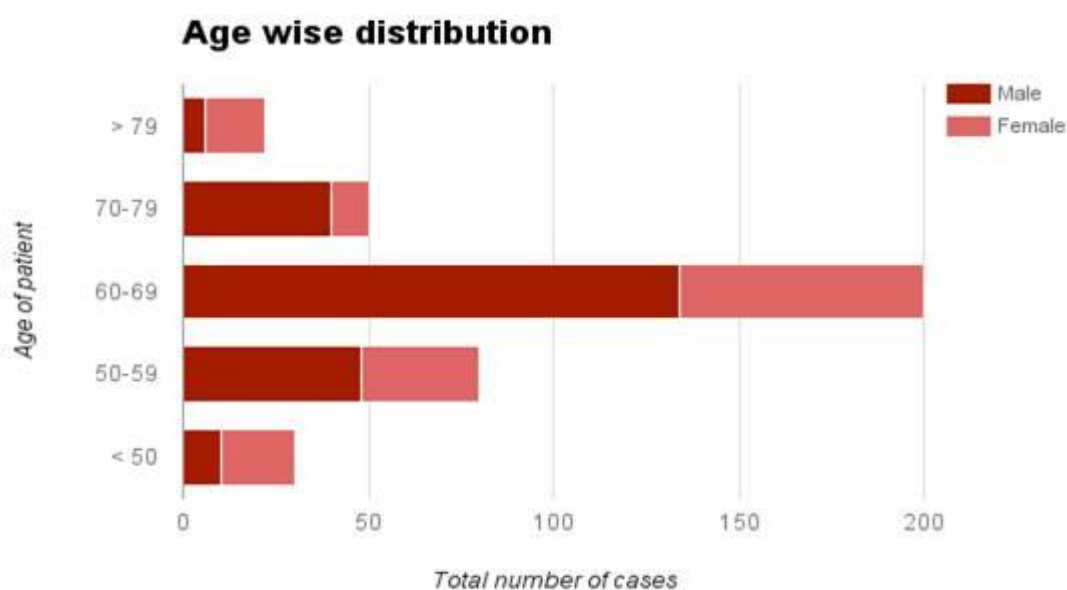


Table – 1: Possible occupational risk factors of PD other than age/gender/ethnicity (N=372).

Factors	Male	Female	Overall
Pesticide exposure	68	42	110 (29.5%)
Heavy metal exposure	33	12	45 (12.09%)
Head injury	15	2	17 (4.56%)

Table – 2: Lifestyle risk factors (N=372).

Factors	Male	Female	Overall
Smoking	96	22	118 (31.72%)
Caffeine	46	25	71 (19.08%)
Alcohol	78	14	92 (24.73%)
Tea	124	85	209 (56.18%)
Obesity	32	26	58 (15.59%)

Table – 3: Dietary risk factors (N=372).

Factors	Male	Female	Overall
Milk	110	54	164 (44.08%)
Uric acid	120	81	201 (54.03%)

Discussion

The present study was done over a period of one decade in a single neurocare centre based at Warangal, the second largest city in Telangana state. This is an on-going, longitudinal cohort study of PD. The geographical significance is evident from the other studies published worldwide. Warangal can be considered as a sample representation of south central India from epidemiological point of view. The meta analysis of 47 studies worldwide has shown a prevalence 1601 in individuals from North America, Europe and Australia compared with 646 in individuals from Asia ($p < 0.05$) [13]. This suggests a difference in the occurrence of PD amongst different ethnic groups. In USA the proneness to PD is highest amongst whites (45 per lakh population) and lowest among African-Americans with an incidence of only (23 per lac population). A similar study in the multi-racial country of Singapore was conducted and published in 2004 [14]. 9000 Chinese, 3000 Malays and 3000 Indians aged 50 years and above living in central Singapore underwent a door to door survey. After the completion of third phase the age adjusted prevalence rate was found to be the same in all three ethnic groups. This is the only study from Asia comparing three ethnic groups for prevalence.

Warangal is a part of the tribal belt starting from Vidarbha and passing through Telangana, Chattisgarh, western Odisha, Jharkhand and ending in South West Bengal. This population belt provides the ideal platform to study the occurrence of PD in different ethnic tribal population (e.g. Lambada in Warangal). The Indian study by [5] noted that a small sect of Mumbai population called Parsis have an age adjusted prevalence rate of PD, similar to white Caucasians which is two times higher than other Indian studies [2, 5, 10]. Thus the classical

example of variable occurrence of PD among the different ethnic population in India. Though it is important to note that Parsis in India are Zoroastrians who came to India 1200 years ago from Persia who might have a different genetic origin. Ethnically, Parsis are members of the Aryan or Indo Germanic family.

Warangal has a predominant rural population of 72 % as per CENSUS 2011, which includes semi urban, rural and tribal also. In the present study there is more number of patients from rural background than urban (Figure 1). Similar pattern of higher prevalence in rural area have been found from different parts of India [2, 10]. Though PD is more common in rural areas but it differs from country to country (Italy 2.03:1.14). The possible association of PD with deep well water use has been documented in many papers. Pesticide exposure may be an additional extension of the same theory. Rotenone an insecticide is a known possible cause of PD through the action of MPTP [15]. Paraquat is another pesticide which is widely used herbicide in the world has been found to be causing selective nigral neuronal injury. At the same time Warangal and surrounding districts are endemic for fluorosis. This raises a pertinent question of association between fluorine content and PD because the population are drinking deep well/bore well up to 500-1000 feet deep water since many decades.

Though Henri Huchard documented the first case of juvenile PD in a three year old child in 1875 it is very uncommon for people under the age of 30 to develop PD. The PD becomes more common with age. The average age at which PD symptoms begin differ from country to country but the likelihood of PD increases sharply at the age of 60. Similar results are found in our study where the maximum PD patients belong to 60-70 years of age group (Figure - 3). We have the

youngest PD in our series at the age of 25 also, with no family history. It is interesting to note that PD is rare amongst the very old (those people over 100 years). Since PD is a neurodegenerative disorder age is an independent demographic factor for PD which is directly proportional to the advancement of the age [4]. The onset of young PD is low in published studies but is quite significant in our study.

The data shows that PD affects males more than the females (1.58:1). Because of biological and social differences [16]. This is consistent with other studies done in various parts of India [9] with the exception of eastern India where women are more commonly affected than men and this was postulated to longer life expectancy in women [17]. In another study from Japan, Kimura, Kurimura and Wada M have also reported female preponderance of PD [18] Investigations on gender difference is limited because women have historically been underrepresented in study population moreover the other possible factors may be protective roles of sex hormones in females or decreased exposure to causative environmental factors and decreased sex linked genetic disposition [4, 19].

The prevalence of PD in India is low when compared to western countries [3]. Community based surveys have used interview based questionnaire. Depending on the number of questions, the sensitivity and specificity fluctuates in screening PD. Fairly large number of patients belong to rural areas and agricultural background (40%). Literacy and language play an important role in screening the desired population for prevalence for any neurological disorder like PD also. With varying levels of education in varying cultural setup in different geographical settings it is more relevant. In Warangal literacy rate is 75% in males and 56% in females as per census 2011. So the preformed questionnaire for community based survey may be erroneous in the terms of specificity and sensitivity. Moreover literacy is directly linked with increased awareness and early intervention

for therapy. In our study we found the same with positive outcome [3].

Among the predominant clinical features, rest tremors was found in 90% of patients in present data which shows many patients came during the peak of their illness rather than at an early stage. The tremors never occur in 11% of cases of PD [20] but tremor occurs in 100% cases during the lifetime of a PD patient at some stage [11].

The mortality rate differs in various studies due to different causes in different parts of the world, but it is more common in advanced stage due to pneumonia in Asian countries and cardiac and brain stroke in other countries. The survival reflects the general pattern of mortality in individual countries depending on life expectancy.

Since there is no biological marker to diagnose PD, the study of risk factors plays an important role to quantify the extent of this health problem in India. There are only 3 studies from India; two are hospital based in Delhi and Eastern India and one is population based study in Kolkata. The families with history of PD were associated with increased risk in Delhi and Eastern India. The additional risk factors were male gender and well water drinking. All three studies showed tobacco (smoking or chewing) to have protective effect. Various occupational factors (**Table - 1**) have been associated with PD but the most extensively studied is pesticide (herbicide and insecticide only but not fungicide). Meta-analysis of 39 case control studies, four cohort studies and three cross sectional studies showed a summary related risk of 1.62 for pesticide exposure [21].

Other occupational factor which has been hypothesised to increase the risk of PD through accumulation of metals in substantia nigra and increased oxidative stress are exposure to heavy metals such as manganese, iron, copper, lead, amalgam, aluminium or zinc. Few case reports and few case control studies have been published so far and there is limited epidemiological evidence for such association. Warangal and

adjoining Khammam district of Telangana shares borders with Vidarbha region of Maharashtra, Chhattisgarh and Southern Odisha. This region is rich in heavy metals and the persons residing in these industries are exposed to them as we can see in our study in varied proportions. The large population of this region can provide for analysis of scientific research to find correlation between heavy metal exposure and PD [7].

Many case control studies have found increased risk of PD in association with mild to moderate head injury, but there are studies which have found that overall head injuries are not associated with PD. Between these two conflicting results, there is one gene called SNCA Rep1 whose presence accelerates the neuro degeneration after the head injury. So the significance of head injury in present study which is only 4% needs further probing by genotyping [22].

Among the lifestyle factors, smoking, caffeine, alcohol and tea are protective in developing PD. In present study, most of the patients have been using these and having PD raises a question about its inverse relationship. A meta-analysis of 44 case control and 4 cohort studies revealed that the relative risk of developing PD was 0.39 (95 % CI: 0.32-0.47) in current smokers compared to never smokers [23]. There is dose dependent relationship (length of time smoked plus number of cigarettes smoked per day). Smoking effect is similar irrespective of use of cigars, pipes, chewing tobacco and snuff. The various possible mechanism have been postulated from direct neuroprotective effect to selection bias i.e. smokers with PD die younger than smokers without PD. Meta-analysis of 26 studies have showed convincing evidence that caffeine intake is independent associated factor for lower risk of PD through its active metabolite adenosine antagonist [24]. Association between alcohol consumption and protection for PD is not convincing as many studies have revealed conflicting results [7]. Analysis of 11 case control study and 1 cohort study found odds ratio of 0.83 (95% CI: 0.74-0.92) [25]. It is interesting to note that intake of black tea and not green tea

is associated with reduced risk of PD [26]. There are conflicting results from 4 cohort studies regarding obesity and developing PD [27]. In the current study the socio cultural value in Telangana state in general shows significant tea, coffee and alcohol consumption (**Table - 2**). However the independent risk factor in relation to PD needs extensive evaluation and long term follow up.

Meta-analysis of three large cohort studies in USA revealed a relative risk of 1.6 for developing PD in persons consuming more dairy products [28]. It is postulated that dairy products are contaminated with toxic chemicals such as pesticide and reduces uric acid levels which increases the risk of PD. In present study milk is consumed by limited number of PD patients. Dairy products are scarcely used in urban area only while its usage is nil in rural population. Similar is the case of uric acid which is supposed to be neuro protective for PD, but 54% of the patients having high level of uric acid with PD needs further scientific evaluation in this era of evidence based medicine [29].

Conclusion

Though the occurrence of PD is low in Asia and India, the rapid increase in the size of the population will create more number of PDs in future. Since the cause of PD is not conclusively known till date, all possible preventive steps should be undertaken to protect from undesirable effect of various epidemiological factors. This needs many more case control and cohort studies across India in many cities because of presence of genetic and ethnic diverse population and different socio economic picture in different parts of our country. Robust health infrastructure and health-care is the need of the hour and future also. The contribution of such study gives an insight into various epidemiological factors from different geographical area of India which will ultimately decide the general and specific health policy of each state and geographical division of India.

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