Trends in Incidence and Mortality of Tuberculosis in India over past three decades: A Joinpoint and Age-Period- Cohort Analysis

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Abstract

Background

The morbidity and mortality burden of tuberculosis has been a major public health challenge in India. Despite various commitments to end the global TB epidemic, India has the highest burden of TB and MDR-TB. To accelerate progress towards the goal of ending TB by 2025, it is imperative to outline the incidence and trend of tuberculosis in India. This study provides the trends in the burden of TB in India, along with age, period and cohort effect of TB.

Methods

We have extracted the TB incidence and mortality estimates from GBD database over the period 1990 to 2019. Joinpoint regression was used to determine the magnitude of time trends in incidence and mortality rates of Tuberculosis by calculating the average annual percent change (AAPC) and its 95% confidence interval (CI). We have analyzed the tuberculosis incidence and mortality trends in India to distinguish age, period and cohort effects by using age-period-cohort (APC) model.

Results

There has been a decline in age standardized incidence rate in the period 1990-2019. Results from the APC table showed that the incidence and mortality due to tuberculosis in India decreased with the recent cohort. The period RRs of incidence had a downward trend in India in the period 1990-2019. Age standardized incidence and mortality rates of tuberculosis was found higher among males. The period RRs of incidence had a downward trend. Findings show that incidence and mortality were higher in older ages. The cohort effect on the incidence of tuberculosis was found higher among 1990-94 birth cohorts than in the later birth cohorts 2010-14. Wald test results demonstrated that the cohort and period RRs for both sexes and the net drift and local drifts for tuberculosis incidence and mortality were statistically significant.

Conclusion

Higher incidence and mortality in the older age groups is attributed to poor nutrition and socio-economic status. Improvement in India’s public health facility and strategic programs aimed at eliminating tuberculosis might be the reason behind declining RRs in India. The decline in the cohort RRs signifies the effective measures taken to reduce the burden of tuberculosis in the country.

1. Background

Tuberculosis (TB) is a chronic infectious disease and its persistent morbidity and mortality burden remains one of the major public health challenges in India (Pai et al., 2017). It is listed as one of the ten most important causes of death from infectious disease in the world (WHO, 2013). The global TB report published by the World Health Organization (WHO) indicated that in about 10 million people, fell ill with tuberculosis in the year 2019 (WHO 2010). According to WHO estimates, around 2.7 million people developed TB in India and over 400000 people died due to TB

in the year 2017 (WHO, 2018). By WHO estimates, India accounts for 27% of the global estimated 10 million cases and 25% of the estimated 1.6 million deaths. The global burden of disease analysis estimated the number of incident cases to be 3 million people in the year 2016 (Arinaminpathy et al., 2016). A study based on data from the National family Health Survey (NFHS-4) estimates that the self-reported incidence of TB in India is 304/100,000 (Mazumdar, Satyanarayana & Pai; 2019).

United Nation Sustainable Development Goals (SDGs) and WHO's End-TB strategy aims to end the global TB epidemic with targets to reduce TB deaths by 95% and to cut new cases by 90% by 2035 globally (Uplekar et al., 2015). India's National Strategic plan 2017–2025 aims to achieve a TB free India, five years ahead of the global elimination plan (Central TB Division; 2017). India had launched a National Tuberculosis Programme (NTP) in sixties following the epidemiological assessment of the situation during 1955–1958 and has already taken several critical steps to showcase itself as a leader for a TB-free world (ICMR, 1959). Despite these impressive commitments, due to less-than-optimal service delivery and various challenges, it could not make much progress in terms of achieving substantially high cure rates and carries the by-far highest burden of TB and MDR-TB.

The actual prevalence of TB in India is likely to be higher than the available prevalence rates. This may be due to the stigma associated with TB and resulting in underreporting. The other factor may be attributed to undiagnosed TB (Mazumdar, Satyanarayana & Pai; 2019). Studies have found that India's state-wide TB prevalence survey have shown higher prevalence rates than the NFHS-4 estimates (Atre et al., 2004). Likewise, it was higher than the estimates published by WHO in the year 2015 Global TB report (Atre et al., 2004). A major limitation of current estimates of Prevalence and Incidence of TB in India is that India lacks a national TB prevalence survey (Onozaki, et al., 2015). Another limitation is incomplete notification from India's private health sector which uses enormous quantities of anti-TB medications and therefore, disease burden estimates based on TB notifications data may be underestimated (Arinaminpathy et al., 2016). In order to accelerate progress towards the goal of ending TB by 2025, India needs to strengthen the public-private sector response to TB. Thus, India needs to outline the incidence status and trend of TB in India.

To the best of our knowledge none of the researchers studied trends in the burden of TB in India among males and females during past three decades and its relation with age, period and cohort. Therefore, this study was planned to assess trends in the burden of TB in India, along with the effect of age, period and cohort on burden of TB.

2. Materials And Methods

In the 21st century, the continuously changing scenario and the dynamic nature of health-related challenges across the globe can be understood from the estimates, trends and dynamics of several relevant measures and indices as offered by the GBD study facilitated by the Institute for Health Metrics and Evaluation (IHME). The GBD study is considered to be one of the most comprehensive and reliable worldwide observational epidemiological studies to date. Together with the data and relevant tools, the study provides powerful resources and evidences by quantifying and comparing progress in several health-related dimensions both within and between countries and regions, and thus the GBD study results provide important insights to clinicians, researchers, and policy makers that ultimately promote accountability, assessment and improve lives worldwide.

The comprehensive methods and models supplemented by useful and convenient tools, developed and perfected by the IHME over the past 2 decades provide the most precise estimates of the prevailing picture of the burden of different diseases, injuries and risk factors across the globe. These comparable estimates are considered widely as the key indicators of disease burden quantification and assessment, including the incidence prevalence, mortality and DALYs rate of TB. The present study utilized the data extracted from the recent GBD study 2019 database to systematically summarize and analyse the Incidence and mortality of TB and its changes up to 2019 for India.

2.1. Data Source

The GBD 2019 precisely estimated and quantified each epidemiological indices of interest for 204 countries and territories that were grouped into 21 regions and seven super-regions (Vos et al., 2020). The estimates are available for incidence, prevalence, mortality, years lived with disability (YLDs), years of life lost (YLLs), and disability-adjusted life-years (DALYs); for 23 age groups; males, females, and both sexes combined. The database utilized a total of 77 different relevant data sources in order to model the cause of death alone and 107 different data sources to model both cause of death and disability estimates for tuberculosis in India. The causes of death studies by verbal autopsy (VA), Medical certification of cause of deaths of the country and its states, vital statistics, other surveys on cause of death and published scientific articles are among the key sources of data to model the cause of death due to Tuberculosis in India (Vos et al., 2020).

The conventional Cause of Death Ensemble model (CODEm) and spatiotemporal Gaussian process regression were utilized to quantify Cause-specific death rates and cause fractions. The detailed description of CODEm was reported in numerous related studies in recent years (Lozano et al., 2012; Murray et al., 2014; Foreman et al., 2012; Murray et al., 2012). The method consists of adjustment of Cause-specific deaths to match the total all-cause deaths calculated as part of the GBD population, fertility, and mortality estimates and subsequent multiplication of Deaths by standard life expectancy at each age to calculate YLLs. Next, in order to ensure consistency between incidence, prevalence, remission, excess mortality, and cause-specific mortality for most causes, a Bayesian meta-regression modelling tool, DisMod-MR 2.1 was used. Multiplication of the Prevalence estimates were done by disability weights for mutually exclusive squeal of diseases and injuries and thus YLDs were calculated. The subsequent Uncertainty intervals (UIs) were reported for every metric using the 25th and 975th ordered 1000 draw values of the posterior distribution (Vos et al., 2020).

We defined the disease of study as all forms of TB that included latent tuberculosis infection, Drug susceptible tuberculosis, extensively drug-resistant tuberculosis and multi drug-resistant tuberculosis without extensive drug-resistant. The ICD-10 codes for TB are A10-A14, A15-A18.89, A19-A19.9, B90-B90.9, K67.3, K93.0, M49.0, N74.0-N74.1, P37.0, U84.3, Z03.0, Z11.1, Z20.1, Z23.2. Data sources for the incidence rate and Death of TB was extracted from the publicly available online GHDx (Global Health Data Exchange) query tool produced by the IHME (http://ghdx.healthdata.org/gbd-results-tool) (GBD Collaboration network; 2019). Finally, the Percentage change and annualized rates of change of the estimates for the above-mentioned indices were reported.

2.2 Join point Regression Analysis:

Joinpoint regression analysis was used to determine the magnitude of time trends in incidence and mortality rates of Tuberculosis by calculating the average annual percent change (AAPC) and its 95% confidence interval (CI) (Kim et al., 2000). AAPC was calculated from the various annual percent change (APC) values obtained from the regression analysis by taking the geometrically weighted average of APC's. (Clegg et al., 2009). The average APC (AAPC) was estimated by using best model considering maximum 5 joinpoint i.e. 6 segments for the full range of our study periods. This analysis was performed using 'Joinpoint' software (Joinpoint Regression Program, version 4.8.0.1, NCI) provided by the US National Cancer Institute.

2.3 Age-Period-Cohort (APC) Analysis

Age Period Cohort analysis is an extensively used statistical technique when individual or population are followed over time to explore age, period and cohort effect from the observed age specific tuberculosis incidence and mortality rates. The age effect represents the rates of disease in terms of different age groups. The period effect indicates the changes in outcome over time that affect all ages simultaneously. The Cohort effect reflects the changes in outcome across group of individuals born in the same year or years. (Robertson, Gandini, and Boyle 1999; Yang, Y. & Land 2013; Wang et al., 2017; Xiaoxue et al., 2020). Holford has proposed that if age, period, and cohort trends are orthogonally decomposed into their linear and nonlinear parts, many useful functions can be estimated (Holford 1983; Yang et al., 2013; Pastor-Barriuso, R. & López- Abente, G, 2014). In the present study we are focusing on the following estimable functions (Rosenberg, Check & Anderson, 2014). The longitudinal Age Curve indicates the fitted longitudinal age-specific rates in reference to cohort adjusted for period deviations (Anderson et al., 2008). The period (or cohort) RR indicates the ratio of the age-specific rate in each period (or cohort) relative to the reference period (or cohort) (Rosenberg, Check & Anderson, 2014). Further local drift and net drift are two other important parameters in the APC model. The local drift (or local net) indicates the (overall) log linear trend by calendar period and birth cohort for each age group and is analogous to the (overall) annual percentage change (Chaturvedi et al., 2013). Wald Chi-Square tests were adopted to test the significance of the estimable parameters and functions, and p-values less than 0.05 were considered for statistical significance (Ding et al., 2017).

We obtained the estimable parameters by the Age-period-cohort Web Tool (Rosenberg, Check & Anderson, 2014) (Biostatistics Branch, National Cancer Institute, Bethesda, MD, USA). Correspondence to the requirement of the APC-Web Tool the incidence (or mortality) and population data of tuberculosis were arranged into consecutive 5-year periods from 1990 to 2019 (1990–94, 1995–99,. . ., 2010–14, 2015-19) and successively incidence and mortality data into 18 five year age groups (5–9, 10–14,..... ., 85–89, 90–94), spanning 23 partially overlapping five-year birth cohorts (1900–04, 1905–09,. . ., 2010–14).

3. Results

3.1 Descriptive Analysis of Incidence and Mortality Trends of Tuberculosis

Trends in the age-standardized incidence rate (ASIR) and age-standardized mortality rate (ASMR) in male, female and both sexes at all ages for tuberculosis from 1990 to 2019 are depicted in Figure 1a and 1b respectively. For all years both age-standardized Incidence and mortality rate of TB was higher among males as compared to females. The age-standardized incidence rates for both sexes of tuberculosis decreased from 1990 to 1996, increased in the period 1997 - 1999 and then again continuously decreased till 2018. Age-standardized mortality rates experienced a slight increase and decrease over the years for male and female. Overall, the mortality rate due to tuberculosis largely decreased in 2019 (36.11 deaths per 100,000) as in for 1990 (121.72 deaths per 100,000).

Trends in age standardized incidence and mortality rate for male, female and both sexes

Fig. 2 and Supplementary table 1 shows APC and AAPC of TB incidence and mortality in India from 1990 to 2019 for male, females and both sexes combined. The age standardized TB incidence rate in India between 1990 and 2019 ranged from 390.22 to 223.01 per 100,000 population. The regression model showed a significant decreasing pattern in incidence rate in India between 1990 and 2019 for both male and female; but larger decline is observed in case of females (AAPC: -2.21; 95% CI: -2.29 to -2.12; $p < 0.001$) as compared to males (AAPC: -1.63; 95% CI: -1.71 to -1.54; $p < 0.001$). The overall incidence rate for both sexes combined has decreased significantly over the period (AAPC: - 1.90; 95% CI: -1.97 to -1.83; $p < 0.001$). Similarly, mortality rate due to tuberculosis has largely declined in 2019 (36.11 deaths per 100,000) as compared to 1990 (121.72 deaths per 100,000). The regression analysis also showed decreasing trend in the age standardized mortality rates for period 1990 to 2019 (AAPC: -4.11; 95% CI:-5.03 to -3.18; $p < 0.001$); however the declining trend was sharper for female (AAPC: -4.35; 95% CI: -5.12 to -3.57; $p < 0.001$) as compared to male (AAPC: -3.88; 95% CI: -4.63 to -3.11; $p < 0.001$).

Table 1: Average Annual Percent Change (AAPC) of Tuberculosis incidence and mortality by age and gender from 1990 to 2019 using Joinpoint Regression Analysis

Age-Group (Year)	Incidence (95% CI)		Mortality (95% CI)	
	Male	Female	Male	Female
5-9	-4.16 (-4.28, -4.04)	-4.77 (-4.99, -4.55)	-6.85 (-8.67, -5.01)	-8.34 (-9.52, -7.13)
10-14	-2.56 (-2.87, -2.25)	-3.53 (-3.65, -3.40)	-5.22 (-6.13, -4.31)	-6.11 (-8.91, -3.22)
15-19	-1.37 (-1.59, -1.15)	-2.54 (-2.72, -2.37)	-4.68 (-7.75, -1.51)	-5.61 (-7.13, -4.06)
20-24	-1.57 (-1.69, -1.45)	-2.78 (-2.91, -2.65)	-3.98 (-5.47, -2.46)	-5.45 (-7.01, -3.86)
25-29	-1.13 (-1.30, -0.95)	-2.50 (-2.68, -2.31)	-3.31 (-4.09, -2.53)	-4.82 (-6.23, -3.39)
30-34	-1.02 (-1.17, -0.86)	-2.10 (-2.26, -1.93)	-3.30 (-4.39, -2.20)	-4.47 (-5.56, -3.37)
35-39	-1.03 (-1.19, -0.87)	-1.63 (-1.74, -1.51)	-3.07 (-3.85, -2.28)	-4.08 (-4.78, -3.37)
40-44	-1.13 (-1.23, -1.03)	-1.38 (-1.46, -1.29)	-3.44 (-3.74, -3.13)	-3.92 (-5.16, -2.66)
45-49	-1.41 (-1.55, -1.27)	-1.29 (-1.75, -0.82)	-3.58 (-4.59, -2.56)	-4.13 (-4.85, -3.41)
50-54	-1.55 (-1.73, -1.38)	-1.44 (-1.81, -1.07)	-3.78 (-4.74, -2.81)	-3.61 (-4.56, -2.66)
55-59	-1.53 (-1.63, -1.43)	-1.70 (-1.89, -1.51)	-3.45 (-4.51, -2.38)	-4.03 (-5.06, -2.99)
60-64	-1.80 (-1.89, -1.72)	-1.90 (-2.07, -1.73)	-4.09 (-4.85, -3.33)	-4.31 (-4.95, -3.65)
65-69	-2.37 (-2.49, -2.25)	-2.41 (-2.63, -2.19)	-4.10 (-5.26, -2.93)	-4.40 (-5.82, -2.96)
70-74	-2.49 (-2.57, -2.41)	-2.56 (-2.85, -2.27)	-3.96 (-4.85, -3.05)	-4.38 (-5.53, -3.21)
75-79	-2.35 (-2.55, -2.16)	-2.41 (-2.74, -2.09)	-3.93 (-4.79, -3.05)	-4.53 (-5.91, -3.13)
80-84	-2.29 (-2.47, -2.11)	-2.40 (-2.73, -2.08)	-3.74 (-4.76, -2.71)	-4.26 (-5.73, -2.77)
85-89	-2.34 (-2.66, -2.01)	-2.36 (-2.63, -2.10)	-4.20 (-5.38, -3.00)	-4.74 (-6.54, -2.89)
90-94	-2.34 (-2.63, -2.04)	-2.34 (-2.62, -2.07)	-4.98 (-6.32, -3.62)	-4.65 (-5.65, -3.63)

Note: AAPC, average annual percent change; CI, confidence interval; ASR, age standardised rates

Trends in Age-Specific Incidence and Mortality Rates Using Joinpoint Regression Analysis

Table 1 depicts the average annual percent change (AAPC) in tuberculosis incidence and mortality for both male as well as female in India from 1990 to 2019. For age-specific rates, incidence and mortality rates of TB decreased for both male and female across all ages during the period. Sharper decline was observed in the initial age groups and older age groups for both male and female in the age specific incidence and mortality.

3.2 The Age, Period, Cohort Effects of incidence and mortality rate from Tuberculosis

The existence of period effect on incidence rate of tuberculosis (A, B) and mortality rate (C, D) for male and female from 1990 to 2019 are depicted in the figure 3. In case of tuberculosis incidence, period effect did not show much variation up to age 14 year for both male and female. Incidence rate (Fig-3: A, B) of TB was higher among male than female in all ages. Lower incidence rate of TB was observed in later period (2015-19) than earlier period (1990-94) for both male and female. Overall, the incidence of TB increased with age group from 10-14 to 65-69 and slightly decreased from ages 65-69 to 75-79 and again increased with high pace after the age group 75-79 for male. However, female incidence also increased but with a slower pace after the age 75-79 year. In case of mortality rate of TB (Fig-3: C, D) period effect did not reflect clear variability up to age 25-29 year for male and 45-49 year for female. Mortality rate were higher among male than female in all ages. It was also evident that within the same period older males and females had higher mortality. In a particular period, mortality rate of TB increased with high pace for male in all ages while with a slower pace among female.

Figure 4 (A, B, C and D) suggested the existence of a cohort effect of incidence and mortality of tuberculosis in India 1990-2019. Earlier birth cohort (1990-94) had high incidence and mortality rate than later birth cohort (2010-14) and within the same age group incidence and mortality decreased from older cohort to newer cohort for male and female both. Within a particular age newer birth cohort had lower incidence and mortality among both male and female. For instance, among males in the age group 90-94 years incidence was found to be higher for the birth cohort (1900-04) with reference to the birth cohort (1925-29). It was also clearly depicted from the figure that males had approximately double incidence and mortality of tuberculosis in the older birth cohorts.

The longitudinal age curves of tuberculosis incidence and mortality by sex are depicted in Figure 5a and 5b respectively. In the same birth cohort, incidence rate of tuberculosis substantially increased in the ages 5-9 to 20-24 and after that it decreased in all remaining age groups for female.

In the context of incidence very uneven pattern was observed among males. In early ages (before 30-34 years) tuberculosis incidence was higher among females within the same birth cohort. Thus, females were at better position in the context of Tuberculosis incidence. In the same birth cohort mortality rate of tuberculosis increased for all ages except in the age 5-9 years and started declining from age 80-84 years for both sexes. Within the same birth cohort males had higher risk of tuberculosis mortality which was approximately similar in all birth cohort except the earlier cohort for instance before age 25-29years. In both the sexes tuberculosis mortality was highest for the age 80- 84years.

Table 2 Period RRs of Tuberculosis incidence & mortality rate adjusted for age and birth cohort effects comparing to the reference period (2000-04) and the corresponding 95% CI

Period	Incidence		Mortality	
	Male	Female	Male	Female
1990-94	1.04 (1.02 - 1.07)	1.16 (1.13 - 1.19)	1.37 (1.33 - 1.41)	1.56 (1.49 - 1.63)
1995-99	1.00 (0.98 - 1.03)	1.06 (1.03 - 1.09)	1.20 (1.16 - 1.24)	1.26 (1.21 - 1.32)
2000-04	1 .0 (1 .0- 1.0)	1 .0 (1 .0- 1.0)	1 .0 (1 .0- 1.0)	1 .0 (1 .0- 1.0)
2005-09	0.90 (0.88 - 0.92)	0.86 (0.84 - 0.88)	0.78 (0.75 - 0.80)	0.72 (0.69 - 0.75)
2010-14	0.77 (0.75 - 0.78)	0.75 (0.73 - 0.77)	0.63 (0.61 - 0.66)	0.56 (0.53 - 0.59)
2015-19	0.67 (0.65 - 0.69)	0.68 (0.66 - 0.70)	0.51 (0.49 - 0.53)	0.47 (0.45 - 0.5)

The period effect RR of tuberculosis incidence and mortality for both sexes are depicted in table 2. Through the years 1990-2019 of observation, the RR of tuberculosis Incidence and mortality decreased for both sexes. With respect to the reference category (2000-04) mortality due to tuberculosis among female decreased by 53 percent which was higher than male (49 percent) in (2015- 19).

Table 3 Cohort RRs of Tuberculosis incidence & mortality rate adjusted for age and period effects comparing to the referent cohort (1955-59) and the corresponding 95% CI.

Cohort	Incidence		Mortality	
	Male	Female	Male	Female
1900-04	3.57 (1.71 - 7.42)	3.59 (1.23 - 10.5)	11.8 (7.60 - 18.6)	15.6 (7.64 - 32.1)
1905-09	3.17 (2.38 - 4.23)	3.18 (2.13 - 4.74)	8.78 (7.31 - 10.5)	12.0 (9.28 - 15.6)
1910-14	2.81 (2.38 - 3.31)	2.82 (2.28 - 3.50)	6.85 (6.13 - 7.64)	9.18 (7.91 - 10.6)
1915-19	2.48 (2.21 - 2.79)	2.51 (2.16 - 2.91)	5.50 (5.06 - 5.98)	7.24 (6.45 - 8.12)
1920-24	2.19 (2.01 - 2.39)	2.23 (2.01 - 2.48)	4.44 (4.15 - 4.75)	5.60 (5.07 - 6.18)
1925-29	1.92 (1.80 - 2.05)	1.95 (1.80 - 2.12)	3.55 (3.35 - 3.77)	4.21 (3.85 - 4.61)
1930-34	1.67 (1.59 - 1.76)	1.69 (1.58 - 1.81)	2.88 (2.73 - 3.03)	3.18 (2.93 - 3.45)
1935-39	1.46 (1.39 - 1.52)	1.47 (1.39 - 1.56)	2.33 (2.21 - 2.44)	2.47 (2.29 - 2.67)
1940-44	1.28 (1.23 - 1.34)	1.30 (1.23 - 1.38)	1.83 (1.74 - 1.91)	1.95 (1.81 - 2.10)
1945-49	1.15 (1.11 - 1.2)	1.17 (1.11 - 1.23)	1.51 (1.44 - 1.58)	1.59 (1.48 - 1.71)
1950-54	1.06 (1.02 - 1.09)	1.06 (1.01 - 1.11)	1.17 (1.12 - 1.22)	1.23 (1.15 - 1.32)
1955-59	1 .0 (1 .0- 1.0)	1 .0 (1 .0- 1.0)	1 .0 (1 .0- 1.0)	1 .0 (1 .0- 1.0)
1960-64	0.94 (0.91 - 0.97)	0.94 (0.90 - 0.98)	0.86 (0.82 - 0.90)	0.81 (0.75 - 0.87)
1965-69	0.90 (0.87 - 0.93)	0.90 (0.86 - 0.94)	0.74 (0.70 - 0.78)	0.69 (0.64 - 0.74)
1970-74	0.87 (0.84 - 0.90)	0.85 (0.81 - 0.89)	0.64 (0.61 - 0.68)	0.54 (0.50 - 0.59)
1975-79	0.82 (0.79 - 0.85)	0.77 (0.74 - 0.81)	0.54 (0.51 - 0.58)	0.43 (0.39 - 0.47)
1980-84	0.76 (0.73 - 0.79)	0.69 (0.66 - 0.72)	0.43 (0.40 - 0.46)	0.32 (0.29 - 0.35)
1985-89	0.71 (0.68 - 0.74)	0.60 (0.57 - 0.63)	0.36 (0.33 - 0.39)	0.25 (0.22 - 0.28)
1990-94	0.65 (0.62 - 0.68)	0.49 (0.47 - 0.52)	0.28 (0.25 - 0.31)	0.18 (0.16 - 0.21)
1995-99	0.57 (0.54 - 0.60)	0.39 (0.37 - 0.42)	0.21 (0.18 - 0.24)	0.12 (0.10 - 0.14)
2000-04	0.53 (0.50 - 0.57)	0.33 (0.31 - 0.35)	0.15 (0.12 - 0.19)	0.08 (0.07 - 0.10)
2005-09	0.38 (0.34 - 0.43)	0.22 (0.20 - 0.25)	0.10 (0.07 - 0.14)	0.05 (0.04 - 0.07)
2010-14	0.27 (0.22 - 0.33)	0.15 (0.13 - 0.18)	0.06 (0.03 - 0.10)	0.02 (0.01 - 0.04)

The cohort effect RR of tuberculosis incidence and mortality for both sexes are depicted in table 3. Among all 23 cohort's mid cohort 1955-59 was taken as a reference cohort. The incidence and mortality risk continuously decreased from 1900-04 to 2010-14 birth cohort which show the presence of cohort effect. Highest percentage decrement in incidence and mortality was observed among females.

Figures 6a and 6b show the net drifts and local drifts for Tuberculosis incidence and mortality in India among both sexes from 1990 to 2019 respectively. The net drift values are an overall estimated annual percentage change, and local drifts values are an estimated annual percentage change values for each age group. From 1990 through 2019, we found that the net drifts for tuberculosis incidence per year were -1.77% (95% Confidence Interval, -1.87% to -1.66%) for male and -2.16% (95% Confidence Interval, -2.30% to -2.03%) for female. The net drifts for tuberculosis mortality per year were -3.96% (95% Confidence Interval, -4.09% to -3.83%) for male and -4.83% (95% Confidence Interval, -5.00% to -4.67%) for female. The local drift value was found to be below 0 in all age groups in both sexes which was lowest in age 5-9 and highest in age 40-44. The local drift values increased with higher age groups and started declining after 40-44 age.

In addition, the results of Wald test demonstrated that for incidence and mortality, cohort and period RRs and the net drifts and local drifts were statistically significant at $p<0.05$

4. Discussion

This study utilizes the GBD database to analyze the incidence and prevalence of Tuberculosis in the period 1990-2019 in India. The analysis showed that there has been a decline in the age standardized incidence rate in the period 1990-2019 among both sexes. However, mortality rates experienced a zig-zag pattern when standardized for age among males and females. The overall mortality rate declined from 122 deaths per 100,000 to 36 per 100,000 in the period 1990-2019. The long-term trends in incidence of tuberculosis were analyzed using the APC model. The results obtained from the APC table showed that the incidence and mortality due to tuberculosis in India decreased with the recent cohort. Studies have found that the trend of tuberculosis is related to age and period (Vynnycky & Fine, 1997). The regression analysis also showed decreasing trend in the age standardized mortality rates for the period 1990-2014 and the AAPC was found to be -4.1.

Age effect: The rates of disease at different ages are presented by the age effect. It is known that the human age is associated with the disease. Study findings shows that in India incidence and mortality were higher in the older age groups. It is also found that in most of the ages (except some younger ages in case of incidence) females were having lower value of incidence and mortality per 100,000 population. The higher prevalence of tuberculosis among older population is attributed to poor nutrition and socio-economic status (Willis et al., 2012; Strachan et al., 1995). Age standardized incidence and mortality rates of tuberculosis was found to be higher among males as compared to females at all ages. With the increase in the age, the incidence rate increased. This is attributed to the population ageing higher in older age group. With the increase in the age, people are at higher risk of developing disease such as diabetes (Stevenson et al., 2007) and indoor air pollution (Varun et al., 2014). Vulnerable population are more prone to developing tuberculosis. A study by Varun has estimated that the reported annual TB incidence in India will decrease slightly (Varun et al., 2014). Yiran et al. have reported that the age effect of the 35-60 years age group continued to increase and decreased slightly in the 60-70 age group (Yiran et. al., 2020). Further, it was found that the rapid rise of age RRs in India is attributable to alcohol consumption in the age group 35-60. The risk factor for tuberculosis is alcohol consumption, and its related problems (Lönnroth et al., 2008). Alcohol consumption is stated to be a significant risk factor of tuberculosis in various countries. With the upcoming ageing in the country, India will be facing challenges in the prevention and control of tuberculosis. The weak immune system, malnutrition and other physiological changes will increase the risk of tuberculosis in the older population and thus TB burden among the senior citizens will be higher than the other age groups.

Period effect: Period effect was not found of much significance up to the age of 14 years for both sexes in case of incidence of tuberculosis. From the available information, it was evident that the period RRs of incidence had a downward trend in India in the period 1990-2019. The factors associated with the decline in the RRs might be due to improved living conditions, increased accessibility and availability of good health facility and increasing awareness towards sanitation and hygiene practices. Coupled with the improvement in India's public health facility and strategic programs aimed at eliminating tuberculosis is the reason behind declining RRs in India. Earlier period (1990-94) had higher incidence rates of tuberculosis than in the later period 2015-19. This was same for both male and females. Yiran in his study reports that the period RRs in India has declined from 1992 to 2017 (Yiran et. al., 2020). At some period, the incidence of TB showed an increasing pattern with a substantially faster pace after the 75-79years for males. However, for females the increase in incidence was not much pronounced after the age 75-79. As far as mortality is concerned, period effect was not much visible upto the age 25-29 for males and 45-49 for females. Mortality rates were higher for males than females for all ages. The introduction of 1993 policy to control the TB in India has been proved successful in the improved treatment of TB which is estimated to avoid 200,000 deaths (Khatri & Frieden, 2002). The TB control program has been quite effective in reducing the incidence of tuberculosis and further preventing its speed.

Cohort effect: Study highlights the existence of a cohort effect in the incidence and mortality due to tuberculosis in India in the period 1990-2019. Differences in the cohort RRs in the birth cohort usually apply to the balance between new infections and compromised immune responses to previous infections (Winston & Navin, 2010). The cohort effect on the incidence of tuberculosis was found to be higher among 1990-94 birth cohorts than in the later birth cohorts 2010-14. Similarly, the cohort effect on the mortality due to tuberculosis in the period 1994-2014 showed a declining trend in India. In the same age group, the tuberculosis incidence and mortality decreased from older cohorts to newer birth cohorts for both males and females. Analysis from a long-term trend study in incidence of tuberculosis has also found a declining trend in the incidence from 1908 to 1962 and from 1987-1997 (Yiran et. al., 2020). TB in India is mainly considered to be originated from poverty. Unavailability and inaccessibility to food will lead to malnutrition in majority of Indians (Padmapriyadarsini et al., 2016). Increasing population and rapid urbanization would result in TB risk factors in the country (Marimuthu, P., 2016). The most prevalent risk factors for tuberculosis in India are AIDS, smoking and drinking and diabetes (Prasad et al., 2009). Study outlines that male have approximately double the incidence and mortality of tuberculosis in the older birth cohorts. The decline in the cohort RRs signifies the effective measures taken to reduce the burden of tuberculosis in the country.

The longitudinal age curve of tuberculosis showed that incidence rate of tuberculosis among females had a substantial increase in the age 5 to 24 years and then decreased thereafter in all ages in the same birth cohorts. Mortality due to tuberculosis was found to be highest among population aged 80-84 years. While considering the period effect, the relative risk of tuberculosis incidence and mortality decreased for both sexes in the period 1990-2019. Considering period 2000- 04 as referent, mortality due to tuberculosis decreased by 53 percent and 49 percent among females and males respectively in the period 2015-19. Cohort RRs showed that the incidence and mortality of tuberculosis decreased from 1900-2004 to 2010-14 for males and females. This decrement was higher for females. Overall, the annual net drift for tuberculosis incidence was -1.77 for male and -2.16 for females. Similarly, for mortality due to tuberculosis the net drift values were -3.96 for males and -4.83 for females. The local drift values initially increased with higher age groups and then followed a decreasing pattern after 40-44 age group.

5. Conclusions

This study shows that overall incidence and mortality of tuberculosis in all ages has decreased in last three decades in India. The incidence as well as mortality was higher among males as compared to females during study period. In India age standardized incidence and mortality rates of tuberculosis significantly decreased from 1990 to 2019. The incidence and mortality rates of tuberculosis increased with advancing age whereas it decreased with advancing period and earlier to later birth cohort for both male and female.

Though the incidence and mortality of tuberculosis significantly decreased from 1990 to 2019 but the annual rate of reduction is not sufficient enough to achieve aim of India's National Strategic plan 2017-2025. Approximately six decades since launch of National Tuberculosis Control Programme, TB still remained a major public health problem in India. Government needs to strengthen four strategic pillars "Detect – Treat – Prevent – Build" (DTPB) to achieve TB free India.

Our study has several limitations. First, Although GBD study has incorporates methods to adjust for incomplete or missing data and quality of the data, still there may be possibility of some inaccuracy in the mortality data. Second, we have performed APC analysis in periods of multiples of five years as GBD provides data in five-year intervals that may leads to the smoothening of certain subtle variations in age, period and cohort effects. Third, being an ecological study, the interpretations derived here are true at population levels but do not necessarily hold for individuals.

Abbreviations

AAPC: Average Annual Percent change; APC model: Age-period-cohort; ASIR: Age Standardized Incidence Rate; ASMR: Age Standardized Mortality Rate; CODEm: Cause of Death Ensemble modelling tool; DALY: disability-adjusted life year; GBD: Global Burden of Disease (study); GHDx: Global Health Data exchange; ICD: International Classification of Disease; MDR-TB: Multi Drug Resistant Tuberculosis; NFHS: National Family Health Survey; NTP: National Tuberculosis Programme; RR: Relative Risk; SDG: Sustainable

Development Goals; TB: Tuberculosis; UI: uncertainty interval; WHO: World Health Organization; YLDs: years lived with disability; YLLs: years of life lost.

Declarations

Ethics approval and consent to participate This is a database study that reuses data from GBD study to solve a research problem. It is observational and does not require ethical approval and consent.

Consent for publication: Not Applicable

Availability of data and materials

The datasets analyzed during the current study are available in the (Global Health Data Exchange) query tool produced by the IHME repository, [(http://ghdx.healthdata.org/gbd-results-tool]

Competing interests: The authors declare that they have no competing interests.

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Figures

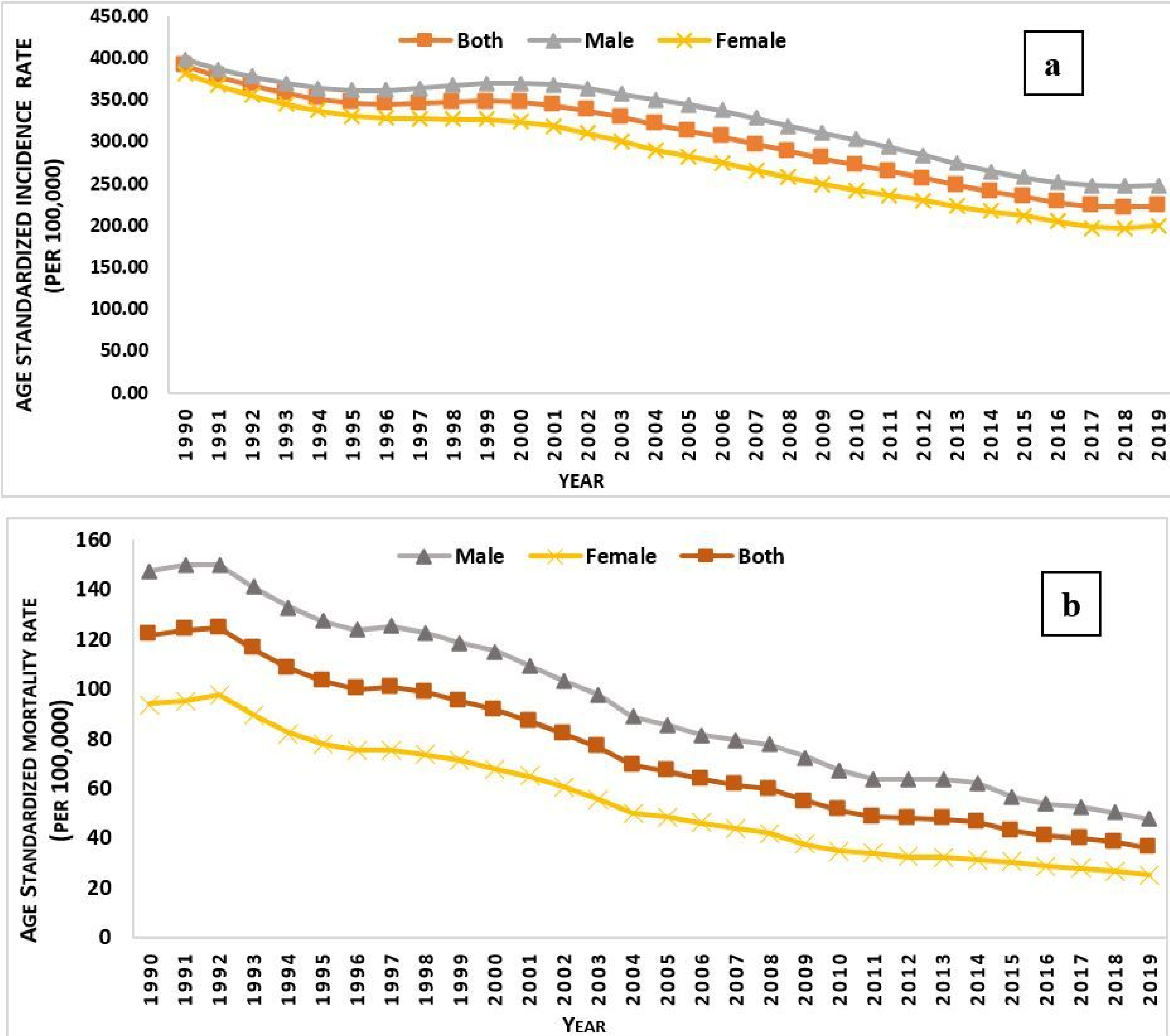

Figure 1

Trends in the age-standardized rates for Tuberculosis in male, female and both sexes from 1990-2019; a) incidence b) mortality

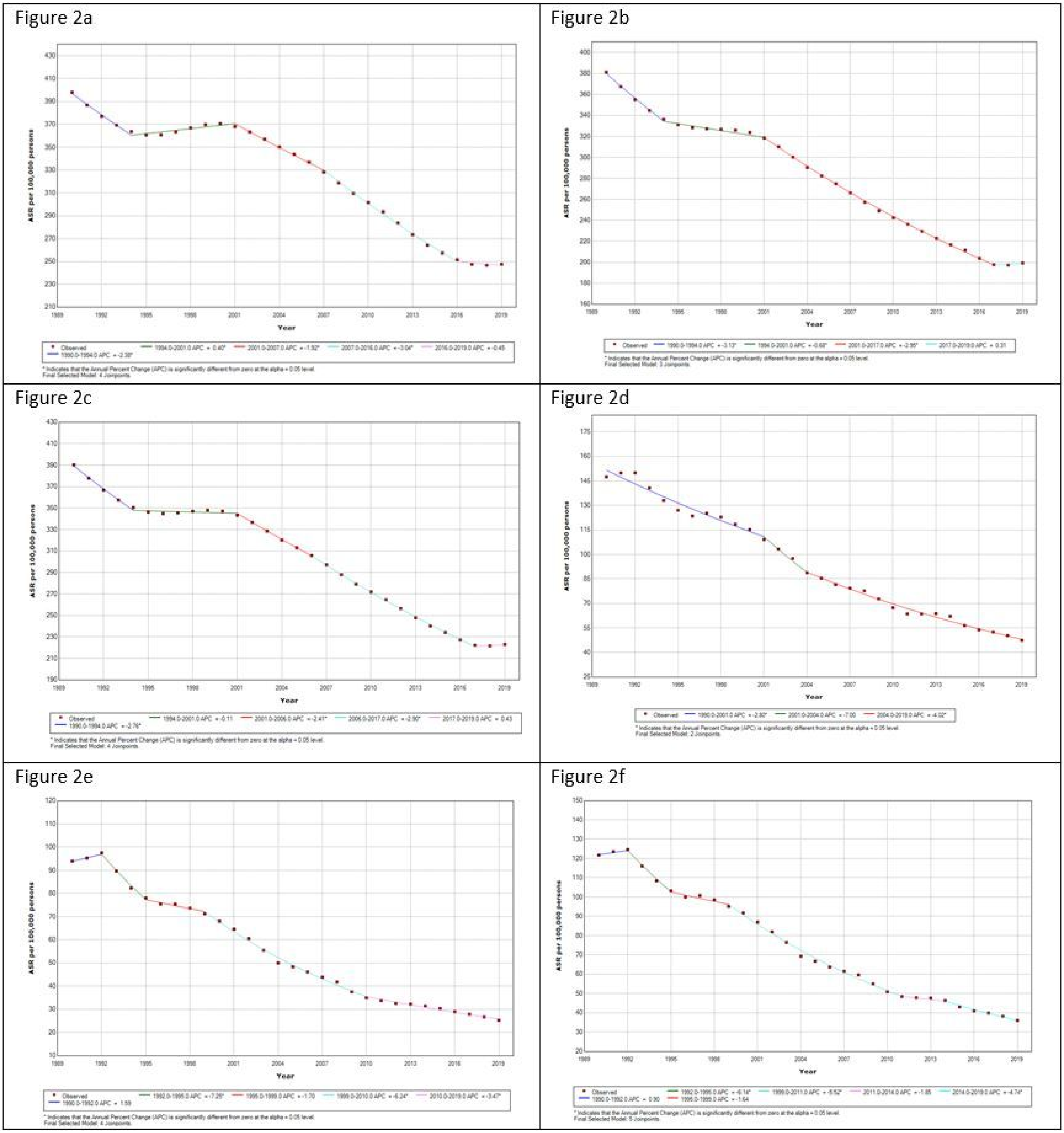

Figure 2

Sex-specific temporal trends in age standardised incidence and mortality of tuberculosis in India based on the joinpoint regression analysis (1990-2019).

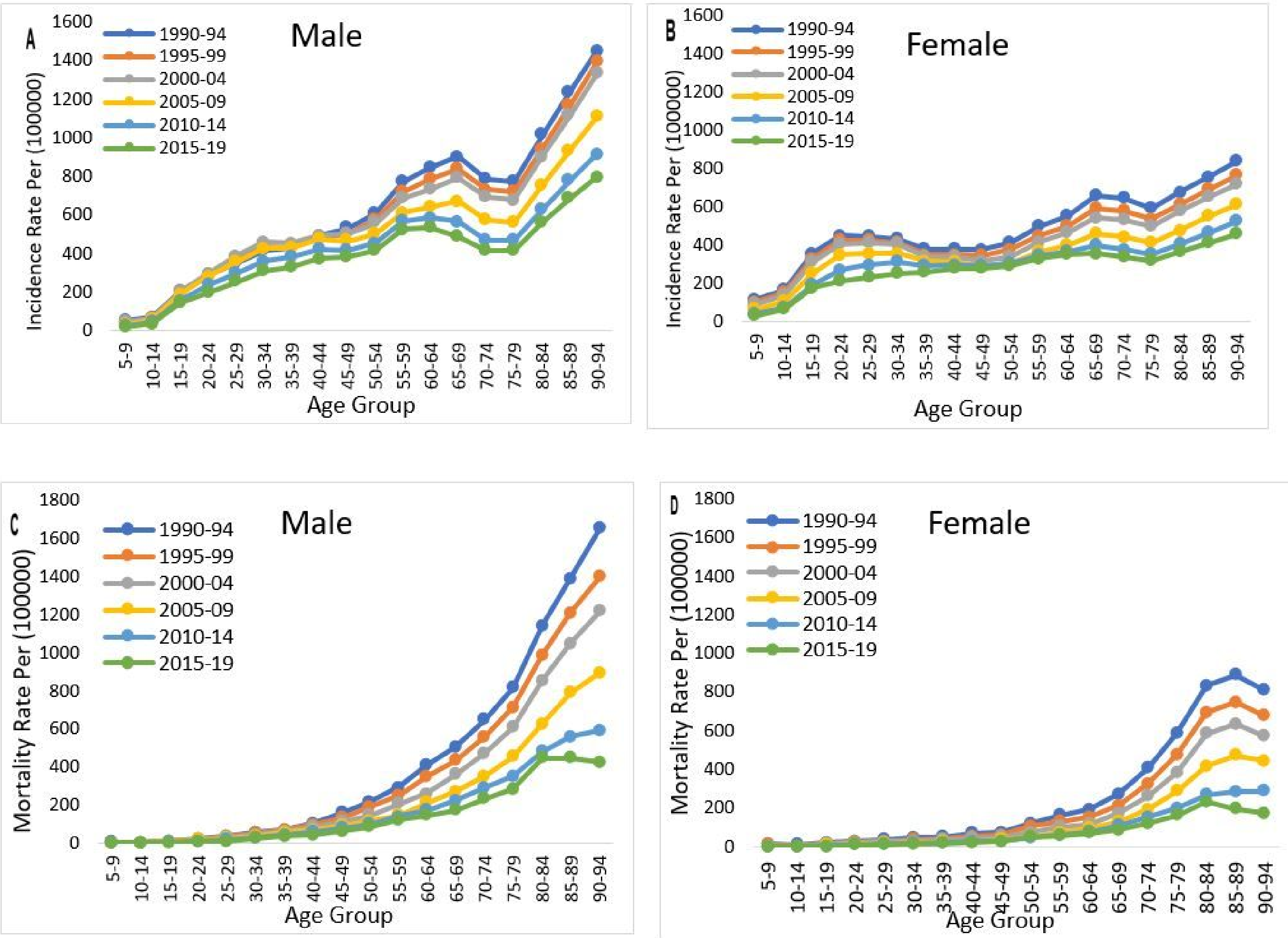

Figure 3

Age-specific Tuberculosis incidence and mortality for India in 1990-2019

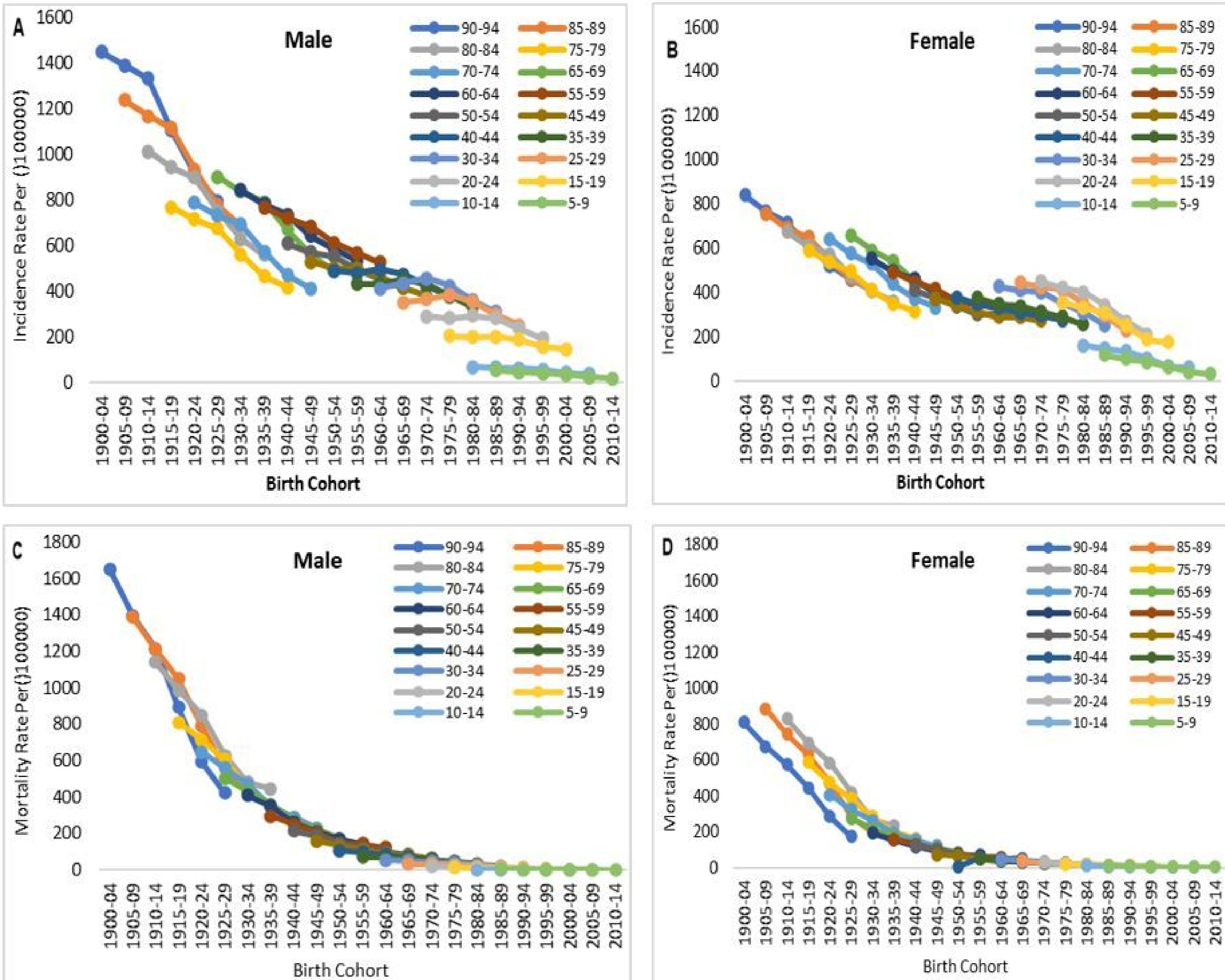

Figure 4

Cohort-based variation in age-specific Tuberculosis incidence and mortality for India in 1990-2019

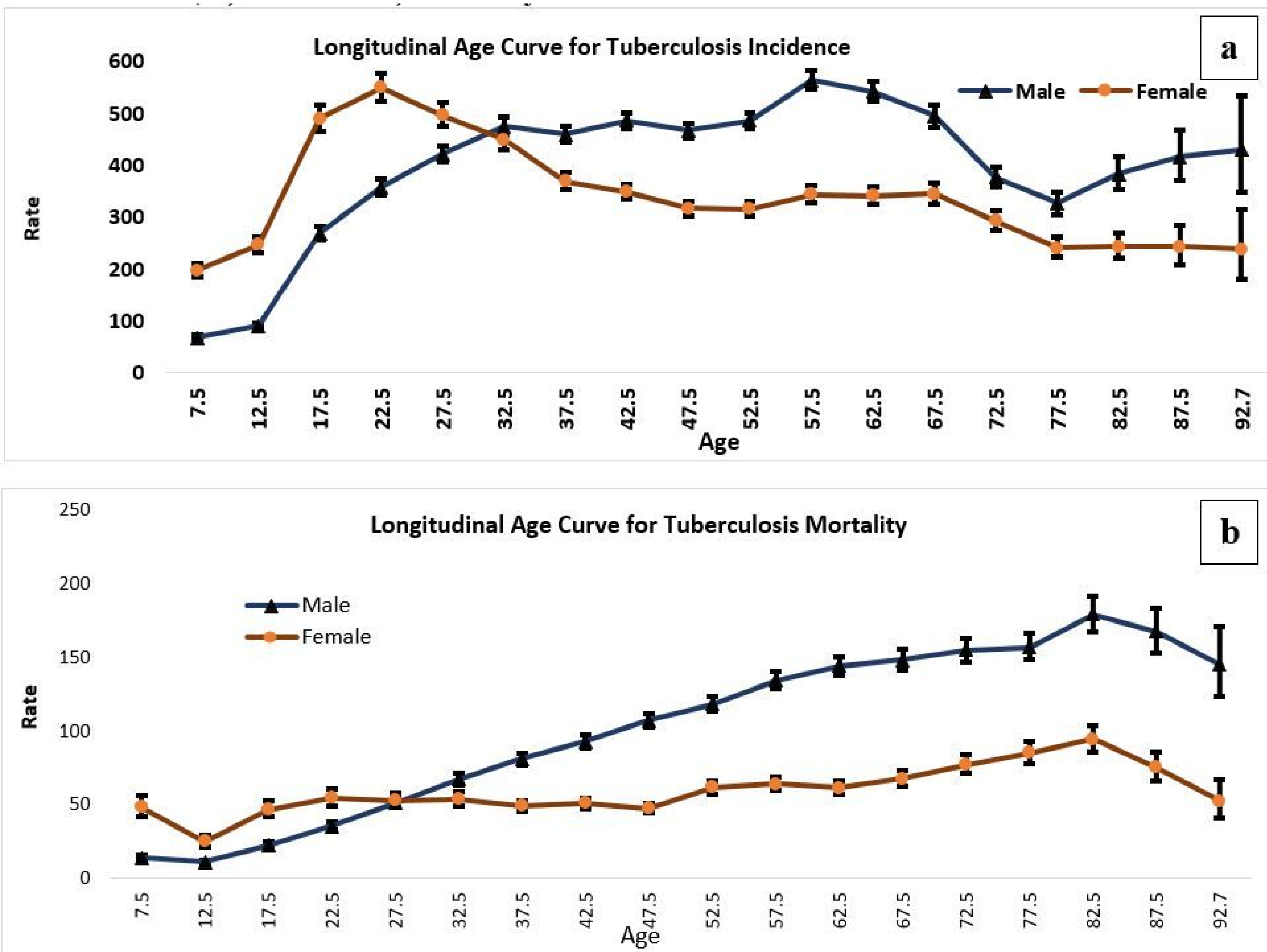

Figure 5

Longitudinal age curve of Tuberculosis incidence and mortality rate under the APC framework; a) incidence b) mortality

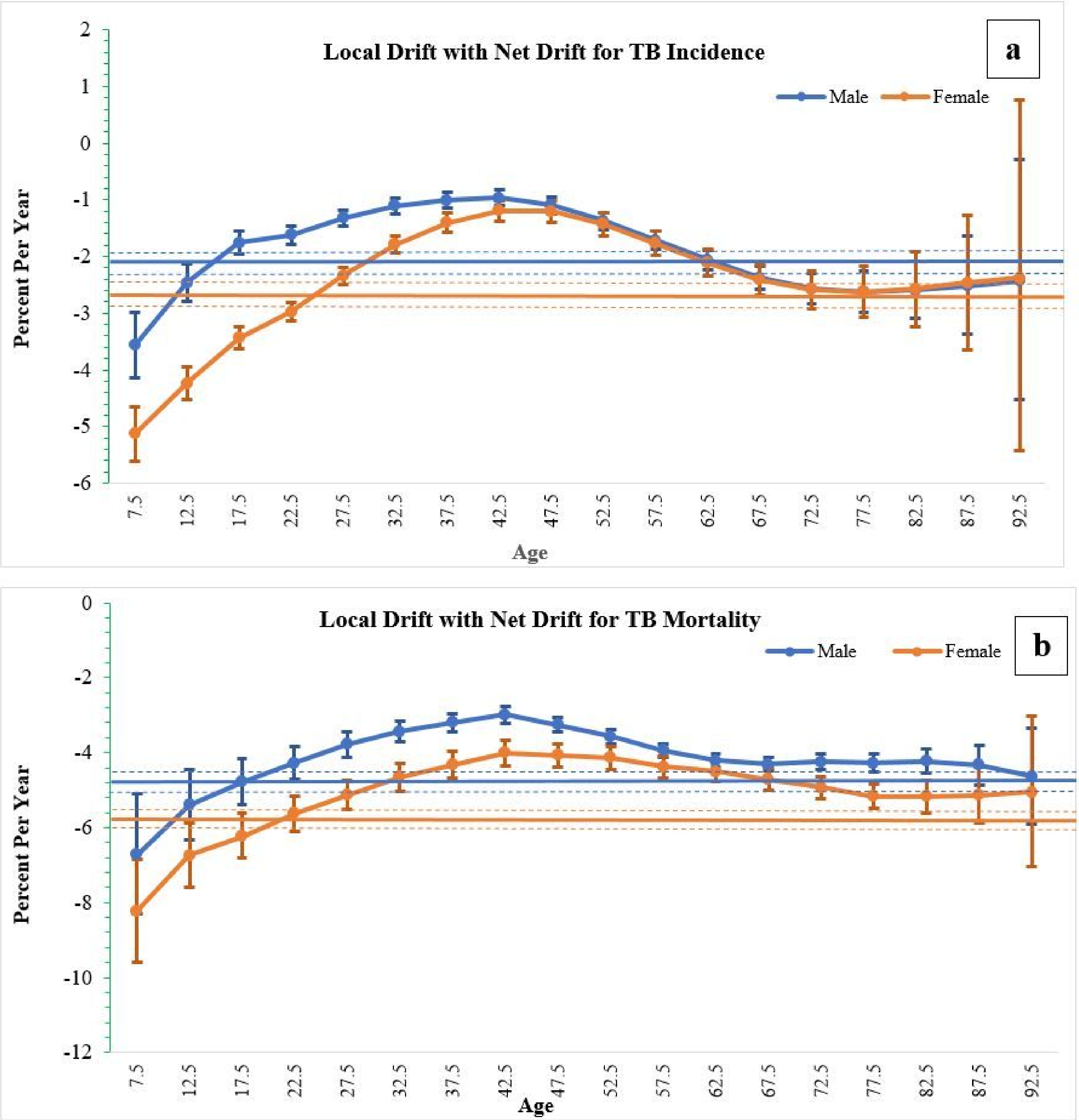

Figure 6

Local drift with net drift with 95% confidence intervals in Tuberculosis incidence & mortality by gender; a) incidence b) mortality

Supplementary Files

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- SupplementaryTable1.docx