Master of Public Health

Master de Santé Publique

Multimorbidity incidence among women in peri-urban Telangana, India: Associated risk factors and disease clusters

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List of abbreviations

APCAPS	Andhra Pradesh Children and Parents Study
BIC	Bayesian Information Criterion
BMI	Body Mass Index
BP	Blood Pressure
CAIC	Consistent Akaike's Information Criterion
CI	Confidence Interval
CIMT	Carotid Intima-Media Thickness
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
COPD	Chronic Obstructive Pulmonary Disease
CSI-D	Community Screening Instrument for Dementia
eGFR	Estimated Glomerular Filtration Rate
FPG	Fasting Plasma Glucose
GAD-7	Generalized Anxiety Disorder-7
HICs	High-income Countries
ICD-10	International Classification of Diseases, 10th Edition
LCA	Latent Class Analysis
LMICs	Low- and Middle-Income Countries
MCAR	Missing Completely At Random
MAQ-PC	Multimorbidity Assessment Questionnaire-Primary Care
NICE	National Institute for Health and Care Excellence
OR	Odds Ratio
PHQ-9	Patient Health Questionnaire-9
TB	Tuberculosis
WHO	World Health Organization

Abstract

Background: The rising burden of multimorbidity (presence of two or more chronic conditions), partly due to epidemiological and demographic transitions in India, necessitates a better understanding of its determinants and patterns. This longitudinal study aimed to assess the cumulative incidence of multimorbidity, identify potential sociodemographic, reproductive and long-term lifestyle predictors and explore common disease clusters among women aged 18 years or older in peri-urban Telangana, India.

Methods: This study assessed 16 chronic conditions in women who participated in the third (2010-12) and fourth follow-up (2021-23) of the prospective Andhra Pradesh Children and Parents' Study (APCAPS) cohort and had complete data on chronic conditions at both time-points. Bivariate and multivariable regression models, stratified by the presence or absence of a chronic condition at third follow-up, were used to investigate the associations of multimorbidity predictors. Latent class analysis (LCA) was used to identify commonly occurring disease patterns.

Results: The study population comprised 814 individuals, among whom 403 (49.5%) developed multimorbidity over a 10-year period. Being aged 45 years or older, primary education, being widowed or divorced or separated, experiencing menopause at late age, having high-risk of waist-hip ratio were significant predictors of multimorbidity incidence for women with one chronic condition at baseline. Among women without a baseline chronic condition, higher odds of multimorbidity incidence were observed in those aged 65 years or older and with poor sleep quality. Three distinct clusters of multimorbidity incidence were found, *metabolic and musculoskeletal*, *psychosomatic* and *cardiovascular and mental health cluster*.

Conclusion: The high incidence of multimorbidity among women in the region warrants the substantial need for comprehensive multimorbidity care. The findings provide insights into the longitudinal determinants that can inform targeted prevention and care strategies. Disease clusters can guide multimorbidity screening and emphasize the need to target a group of diseases instead of individual conditions.

Keywords*:* Multimorbidity incidence, Women, Risk factors, India, Chronic diseases

1. Introduction

1.1. Multimorbidity in India

Multimorbidity, defined as the presence of two or more chronic conditions, is emerging as a significant global health challenge(1). The burden of multimorbidity is associated with not only individual health outcomes such as impaired quality of life and declining physical and mental functionality, it also impacts healthcare systems and social care(2). As multimorbidity continues to rise and is recognised as a serious public health concern in both high-income (HICs) and low and middle-income countries (LMICs), limited data has focused in LMICs to understand the increasing burden (3). The pooled prevalence of multimorbidity in low and middle-income countries (LMICs) was reported to be 36.4% (95% CI: 32.2 – 40.6) in a systematic review (4) .

In India, as one of the largest LMICs, the prevalence estimates of multimorbidity range from 30-83%(5–7). Such large discrepancies in overall estimates can be attributed to various reasons such as; inconsistent definitions of multimorbidity, variations in included conditions, reliance on self-reported measures and the study settings. Multimorbidity as an emerging public health priority in India can be explained by the country's double burden of disease with the rise of both communicable and non-communicable diseases. Furthermore, with rapid socioeconomic developments, India is also experiencing a demographic transition which is characterised by its ageing population, introduction of new risk factors (e.g. lifestyle changes) that contribute to an epidemiological shift towards chronic non-communicable diseases (8). This transition adds further burden to the already fragmented healthcare system of the country with limited access to healthcare services, putting individuals with multimorbidity at significant risk of facing severe healthcare costs and experiencing sub-optimal health and social outcomes (9). Addressing the care gaps in India and the associated challenges with managing multimorbidity necessitates understanding of the burden, determinants and patterns of multimorbidity. Therefore, robust evidence on the complexities underlying multimorbidity can be used by healthcare providers and policy makers to implement integrated care approaches that improve health outcomes and reduce the financial burden on individuals with multimorbidity (10).

1.2. The need to study multimorbidity in women

Higher prevalence of multimorbidity patterns have been reported in women in India than men (3,11). In a multi-country study, survey data from south Asia revealed women reporting significantly poorer health outcomes than men (12). Another study in India found

pronounced gender differences in cognitive health in older women than older men (13). Women have unique healthcare needs and challenges due to a combination of biological, sociocultural and socioeconomic factors that may contribute to this disparity (14). However, there are significant gaps in knowledge that explain the underlying factors which contribute to the high burden of multimorbidity among women in the context of India, making this population a key public heath focus.

Women often experience a higher burden of certain conditions, such as anaemia, depression and osteoarthritis that also tend to occur in multimorbidity (15–17). Investigating the overlapping health conditions that commonly coexist in this population is crucial for understanding these complex interactions and for designing targeted interventions. There is also considerable evidence of gender inequality in access to healthcare, and women suffering more adverse effects of poverty, potentially increasing their burden of multimorbidity (18,19). A study in rural women in Telangana found that sociocultural factors, such as familial relationships and social stigma, also impact women's health seeking behaviours (20). As primary caregivers, women in India often play a crucial role in managing the health of their spouses, children and elderly parents. This interconnectedness of women's health with the overall well-being of the entire family highlights the significant public health implications of women with multimorbidity and the tangible impact of their health on the broader societal context (21). Therefore, the generation of robust evidence on the influence of various factors on the prevalence and management of multimorbidity can inform policymakers and healthcare providers to promote gender equity in healthcare and improve the overall health and well-being of individual patients and the larger community in India.

1.3. The determinants of multimorbidity

Current evidence of multimorbidity has focused on highlighting the prevalence of multimorbidity, though exploration of long-term determinants has been inadequately studied. While the role of age and socio-economic deprivation on multimorbidity has been well-established, there is evidence suggesting that the age of onset of non-communicable chronic diseases is lower in India than many other LMICs and HICs (22–24). Other socioeconomic factors such as education and employment have also been found to impact multimorbidity among women in India (25,26).

There is also a need to study biological differences, such as reproductive health events (for e.g., menopause and parity), which can differentially influence the development and progression of certain health conditions in women (27). These events can be a marker of

accelerated ageing and hormonal fluctuations that impact the onset of multimorbidity. Despite the existence of various health programs aimed at improving health outcomes for women in India, there is a lack of dedicated programs that address the management of chronic health conditions specifically during the reproductive span (13-45) (27). Consequently, there is a pressing need to investigate and understand the onset of chronic conditions among women, not only beyond the reproductive years but also during this crucial period.

The changes in demographic patterns of India has resulted in an interplay of urbanization and existing and emerging lifestyle and cultural behaviours which contribute to an increased prevalence of chronic conditions (8). As such changes continue to advance and would likely increase the scale of multimorbidity, longitudinal analysis of lifestyle behaviours could be valuable to better understand the magnitude of any causal associations and develop targeted interventions to promote healthier lifestyles that can mitigate the development of multiple chronic conditions (1).

1.4. Disease clusters

Multimorbidity is highly heterogenous as it involves various combinations of chronic conditions that often appear to cluster together (28). In concordant multimorbidity, the chronic conditions tend to interact and coexist due to shared pathophysiology and risk factors, while in discordant multimorbidity, the co-existing conditions do not share a common aetiology (29). Due to variations in the type and levels of exposures to potential determinants such as demographic and lifestyle factors, it seems likely that heterogeneity of clusters also exists between different population subgroups (30). There is a paucity of studies that focus on chronic conditions among women in rural India, despite their increasing number and vulnerability to multimorbidity. Therefore, there is a need to study non-random associations between diseases among women in India to understand co-existing conditions and the population subgroups that they tend to most commonly occur together in (31,32).

Understanding commonly occurring clusters of diseases could uncover possible shared pathways of causation, genetic predisposition and support the design of appropriate care practices, secondary prevention and treatment approaches (33). Particularly, investigating the disproportionate distribution of chronic conditions can identify patients with a single condition who have the greatest risk of developing a second or additional conditions to inform prevention strategies. Therefore, the present study aims to bridge this gap to identify the clusters of diseases among women with incident multimorbidity in India.

1.5. Objectives

The research objectives are:

1. To determine the age-stratified 10-year incidence of multimorbidity among women in peri-urban Telangana, India
2. To investigate the potential determinants of 10-year incident multimorbidity, stratified by absence or presence of a chronic condition at baseline
3. To explore the common clusters of chronic conditions in 10-year incident multimorbidity among the study population.

2. Methods

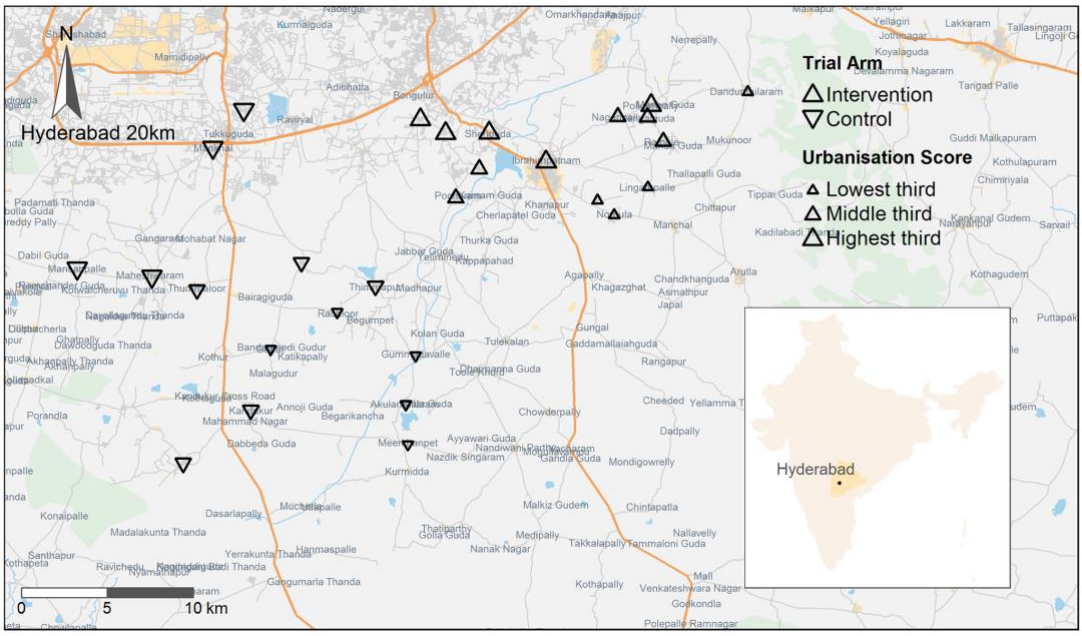
2.1. Study Population and setting

The APCAPS is an ongoing prospective inter-generational cohort that has been gradually built through following-up a nutrition trial (1987-90) in 29 villages (Ranga Reddy district) in the south Indian state of Telangana. The villages are situated 50-100 kms from Hyderabad, the capital of Telangana, and thus have experienced varying rates of urbanisation which have resulted in a combination of rural and urban risk factors (Figure 1). The children born during the original nutrition trial made up the index children and data on chronic disease risk factors and health outcomes have been repeatedly collected between 2003-12 in three follow-ups. In 2010-12, data collection was extended to their parents and siblings (34). The fourth follow-up (2021-23) collected extensive data on mainly adults aged 45 years and above who had participated in a previous APCAPS study.

2.2. Data collection

A cohort tracking exercise was used to inform the eligible adults from the third follow-up to participate in the fourth-follow up. Data collection was performed village-by-village in clinics or household for people with mobility impairments or at the central study office in Hyderabad. Chronic conditions were screened with a combination of self-reported clinical diagnosis, symptom-based questionnaires, physical examinations, and biochemical assays. Data on sociodemographic, behavioural and reproductive risk factors was collected through validated questionnaires and administered by a trained interviewer. The physical assessments covered cardiovascular physiology, anthropometry and physical functioning assessments and were collected by trained professionals using standard protocols. Biochemical assays included fasting blood samples and assays for haemoglobin.

Figure 1: Map of APCAPS villages(35)



2.3. Inclusion and exclusion criteria

Women aged ≥ 18-years at baseline who were present in the third (2010-12) and fourth follow-up (2021-23) of the APCAPS cohort were included. Women with two or more chronic conditions at third follow-up were excluded from the analysis.

2.4. Outcome

The outcome variable was multimorbidity which was defined as the presence of two or more chronic conditions. Third follow-up is considered as baseline and fourth follow-up as follow-up for these analyses. The cumulative incidence of multimorbidity was calculated by dividing the number of newly developed cases of multimorbidity at follow-up by the number of women with one or no chronic conditions at baseline and also stratified for each age category. The calculations of 95% confidence intervals for the cumulative incidence and age-stratified incidence were based on the binomial distribution.

2.4.1. Screened chronic conditions

The included conditions were selected based on their high disease burden unique to women in India and their occurrence in multimorbidity. The conditions were also guided by the Multimorbidity Assessment Questionnaire for Primary Care (MAQ-PC), which has been developed and previously validated in India (36). Moreover, in accordance with the

recommendations from the UK Academy of Medical Sciences, long-term physical non-communicable diseases, long-term mental health conditions and long-term infectious diseases were included (1). The screened health conditions were classified based on guidelines from validated clinical definitions (Appendix 1);

- *Thirteen physical health conditions:* Anaemia, angina, arthritis, asthma, cancer, chronic kidney disease, chronic obstructive pulmonary disease (COPD), dementia, diabetes, hypertension, sarcopenia, stroke, thyroid dysfunction
- *Two mental health conditions:* Anxiety and depression
- *One long-term infectious disease:* Tuberculosis.

While the survey protocols for the follow-up and baseline were aligned where possible, there were some variations in the screening measures of the condition at each timepoint (Table 1). Therefore, a pragmatic approach was adopted to maximize the number of conditions in this analysis.

Diabetes and hypertension were assessed by self-reported diagnosis or standard cut-offs for fasting blood glucose and blood pressure, respectively, at both baseline and follow-up (37,38). Anaemia was assessed by standard threshold for <120 g/dL haemoglobin concentration at both baseline and follow-up (39). Asthma, cancer and thyroid dysfunction were only screened by self-reported diagnosis at both baseline and follow-up. Chronic kidney disease was assessed with Estimated Glomerular Filtration Rate (eGFR) < 60, calculated from serum creatinine-based through chronic kidney disease epidemiology collaboration (CKD-EPI) equation, as well as the age at diagnosis of the condition from the follow-up questionnaire was used to assess the presence of chronic kidney disease at baseline (40). At follow-up, it was assessed only by self-reported diagnosis. Baseline osteoarthritis was assessed through the age at prior diagnosis from follow-up questionnaire and follow-up assessment was based on a validated questionnaire and prior diagnosis (41). Baseline stroke was assessed using previous diagnosis while a symptom-based questionnaire on paralysis and numbness and previous diagnosis was used to assess stroke at follow-up (42). Angina was assessed based on prior diagnosis or the responses from the Rose Angina Questionnaire at both baseline and follow-up (43).

Baseline COPD was assessed using previous diagnosis while threshold of ≤18 from the lung function questionnaire was interpreted at risk of COPD at follow-up (44). Presence of dementia was interpreted with a score of less than 6 on the cognitive scale of CSI-D at follow-up (45). Since dementia was not assessed at the beginning of the study, it was

assumed that participants at baseline did not have dementia. This assumption was made based on the age distribution of the participants, with the average age being 34 years. Considering that the average age of dementia cases at follow-up was 58 years, it was expected that the number of missed dementia cases from the baseline assessment would be small due to the low prevalence of dementia in individuals below the age of 50 (46). Sarcopenia was defined by validated cut-offs for hand grip strength at both baseline and follow-up (47). Depression and anxiety were assessed with a cut-off score of ≥ 10 with PHQ-9 and GAD-7 scales respectively at follow-up (48,49). Anxiety was assessed with a different scale, Brief-PHQ, at baseline where the presence of all symptoms in the questionnaire was assessed as the presence of the condition (50). Baseline tuberculosis was assessed with previous diagnosis while tuberculosis at follow-up was assessed with both previous diagnosis and from a bespoke symptom-based questionnaire that satisfied Government of India's case definition of presumptive TB (51,52).

2.5. Independent variables

The explanatory variables for the analysis were taken into consideration after an extensive literature review. For any measure taken multiple times, the average was used in the analysis.

The sociodemographic variables were characterised as; age (18-44, 45-64, 65+), education level (none, no formal education, primary, secondary, higher), occupation status (working, not working, retired), and marital status (never married, currently married, widowed/divorced/separated). Socio-economic position was defined by the Standard of Living Index (SLI) which is a house-hold level scale that has been validated in Index to use as a proxy for income data(53). Tertile of SLI was used to classify socioeconomic status as low, medium (27-47) and high and was collected from the baseline assessment to consider its long-term association on the incidence of multimorbidity (54).

For the reproductive exposures, parity (nulliparity, parity 1-2, parity ≥3) was included as a categorical variable. Hysterectomy was included as a binary variable. For women aged 40 years or above, no hysterectomy and having not had periods for more than a year, age of natural menopause was categorised into early (≤ 42 years), normal (42 ± 52 years) and late (≥ 52 years) based on the 10 and 90th percentile (55).

All the lifestyle exposures were collected from the baseline to investigate their association as long-term determinants on the incidence of multimorbidity. Body mass index (BMI) was

calculated by dividing weight (kg) by height^2 (m^2). BMI is characterised as; underweight (<18.5 kg/m^2), normal (18.5–24.9 kg/m^2), overweight (25.0-29.9 kg/m^2) and obese (≥ 30 kg/m^2) (56). Waist-hip ratio was calculated as waist circumference divided by hip circumference. Women with a waist-hip ratio of ≥ .85 were considered as having a high-risk waist-hip ratio (57). Alcohol consumption was classified as ever or never. Based on recommendations, sleep was categorised as good (7-8 hours) or poor (<7 or >8 hours) (58).

Table 1: Screened health conditions, by type of measure at baseline and follow-up

Health condition/state (ICD-10)	**Screening measure**			
	Self-reported clinical diagnosis	**Symptom-based questionnaire**	**Physical examination/ biochemical assay**	**Consistent at baseline and follow-up**
Physical health conditions				
Anaemia (D64.9)			✓	●
Angina (I25.9)	✓	✓		●
Arthritis[a] (M05-M14)	✓	✓		○
Asthma (J45)	✓			●
Cancer (C00-C97)	✓			●
Chronic kidney disease[b] (N18)	✓		✓	⊖
COPD[c] **(**J44)	✓	✓		⊖
Dementia[d] (FO3)		✓		○
Diabetes (E10-E14)	✓		✓	●
Hypertension (I10-I15)	✓		✓	●
Sarcopenia (M62.5)			✓	●
Stroke[e] (I64)	✓	✓		⊖
Thyroid dysfunction (E00-E07)	✓			●
Mental health conditions				
Anxiety[f] (F41)		✓		⊖
Depression (F32-F33)	✓	✓		●
Long-term infectious disease				
Tuberculosis[g] (A15-A19)	✓	✓		⊖

●-collected with same instrument, ⊖-collected with different instrument, ○-not collected at baseline.
ICD-10 International Classification of Diseases, 10th Edition.
COPD Chronic Obstructive Lung Disease.
[a]Age at previous diagnosis used to assess arthritis at baseline.
[b]Self-reported diagnosis at follow-up; eGFR < 60 from serum creatinine at baseline.
[c]Lung function questionnaire at follow-up; self-reported diagnosis at baseline.
[d]Community Screening Instrument for Dementia at follow-up; absence of dementia at baseline.
[e]Symptom-based questionnaire and previous diagnosis at follow-up; previous diagnosis at baseline.
[f]GAD-7 at follow-up; Brief PHQ at baseline.
[g]Symptom-based questionnaire and previous diagnosis at follow-up; previous diagnosis at baseline.

2.7. Statistical analysis

Complete-case analysis was employed to exclude any participants who had missing outcome data in either the baseline or follow-up. Descriptive statistics was used to summarise the characteristics of all participants by incident multimorbidity. Univariate analyses, independent $\chi 2$-test or Fisher's exact test when cell-count was low, were performed to compare the variables of interest as well the presence of one condition at baseline between the incident multimorbidity and the non-multimorbidity group. Bivariate logistic regression analyses were then performed to investigate the independent effects of the sociodemographic, reproductive and lifestyle risk factors on multimorbidity, followed by adding the presence of a condition at baseline and its interaction term with the variable of interest. This was done to assess whether the presence of a condition at baseline acts as an effect modifier and if there is a need to stratify the multivariate logistic regression by the presence or absence of a condition at baseline. Stratified multivariate regression analyses was then used to investigate the relationship of the significant factors from bivariate analysis with incident multimorbidity.

Women with incident multimorbidity (≥ 2 chronic conditions at follow-up but 0 or 1 chronic condition at baseline) were selected for the clustering step. Latent class analysis (LCA) was performed to determine the most commonly occurring disease clusters among these women. LCA identifies unobserved homogenous subgroups within a heterogenous population and thus, is a useful tool in multivariate categorical data(59). LCA categorises participants into discrete and mutually exclusive classes using model-based posterior membership probabilities (i.e. most likely latent class membership) (60). An array of latent class models with 10 iterations were run to find the optimal number of classes. While no definitive criteria exist, the models were determined by Bayesian Information Criterion (BIC), the consistent Akaike Information Criterion (CAIC) and clinical interpretability (61,62). The best fitting model was chosen by lowest values of BIC and CAIC. Each class was then labelled based on the item-response probabilities of the conditions in the cluster. Existing literature recommend that conditions with probability of 0.3 or higher in an identified latent class are strongly associated with that class (60,63,64). Therefore, a threshold of .30 was chosen to determine which conditions should be included in the clusters and the most prevalent conditions were used to label each latent class. The p-value of $<.05$ was considered significant. All analyses were performed using R 4.2.1.

2.8. Ethics

The study was approved by the University of Sheffield Research Ethics Committee.

Signed informed consent or thumbprint if illiterate was collected from participants to participate in the study and all data was anonymized before analysis. The project's protocol and tools were approved by the ethics committees of ICMR-NIN (CR/1/V/2023) and Indian Institute of Public Health Hyderabad (IIPHH/TRCIEC/189/2018), India, and the London School of Hygiene and Tropical Medicine (21771 /RR/19113), UK.

3. Results

3.1. Baseline characteristics of the study population

From the 3280 women at baseline, 1767 of them also participated in the follow-up wave of the study out of which 1062 (60%) had complete data on all the included chronic conditions in this analysis. 248 (23%) of the women were excluded from the analysis as they had multimorbidity at baseline (Appendix 2). Women who had no or one chronic condition at baseline were included, giving a final sample size of 814 women at risk of developing multimorbidity at follow-up. Baseline characteristics of the participants were stratified according to the presence ($n = 403$) and absence of incident multimorbidity ($n = 411$) (Table 2). Majority of the participants were in the 45-64 age group (72.5%) and had no education (74.1%). Among all women, 76.2% belonged to the medium socioeconomic tertile and 78.9% of them were working.

Descriptive statistics also revealed that most of the women were currently married (72.1%), had parity ≥ 3 (81.0%), experienced menopause at normal age (35.7%) and 23.8% of the women had hysterectomy. There was missing data on age at natural menopause (46.7%) and parity (2.5%) as women were only asked questions on these variables at follow-up if either their periods had stopped more than a year ago or they have had been pregnant since baseline respectively. Therefore, a *post hoc* decision was taken to add a category of no natural menopause (46.7%) for the variable on age at natural menopause which represented the women who had not yet experienced natural menopause or were younger than 40 years old. BMI analysis showed that while the majority of participants had normal weight (59.2%), there was a substantial proportion of women who were underweight (23.0%). The waist-hip ratio analysis revealed that 33.5% of participants were at a high risk. Alcohol consumption was reported by 63.8% of the participants, while good sleep quality was reported by 64.0%.

The number of chronic diseases varied, with 55.4% of women having one chronic disease and 44.6% having no chronic disease at baseline.

3.2. Multimorbidity incidence

Over a 10-year follow-up period, 403 (49.5%; 95% CI: 46.0–53.0) of the individuals had developed multimorbidity. The age-stratified incidence revealed that 10-year multimorbidity incidence was the highest in the 65+ age category (75.7%, 95% CI: 64.0–85.2), followed by 53.1% incidence in the 45-64 age category (95% CI: 48.9–57.1) and 24.0% incidence in the youngest age group (95% CI: 17.5-31.6). When stratified by the presence or absence of a chronic condition at third follow-up, cumulative incidence was 55.4% (95% CI: 50.7-60.1) among the women who had a single chronic condition at third follow-up while cumulative incidence was found to be 42.2% (95% CI: 37.0-47.4) among the women with no chronic condition at third-follow-up.

The univariate analyses showed statistically significant differences in age, education, occupation status, marital status, age at natural menopause, parity, BMI, waist-hip ratio, alcohol consumption and the number of chronic diseases at baseline between the incident multimorbidity and non-multimorbidity groups. However, there were no significant differences between incident and non-incident multimorbidity group for socioeconomic status, hysterectomy and sleep type.

Table 2: Baseline characteristics of the study population, by incident multimorbidity

	Total (N=814)	Incident Multimorbidity		*P*-value*
		Yes (N=403)	No (N=411)	
Sociodemographic characteristics				
Age (years)				**<0.001**
18-44	154 (18.9%)	37 (9.2%)	117 (28.5%)	
45-64	590 (72.5%)	313 (77.7%)	277 (67.4%)	
65+	70 (8.6%)	53 (13.2%)	17 (4.1%)	
Education				**<0.001**
None	603 (74.1%)	330 (81.9%)	273 (66.4%)	
No Formal Education	76 (9.3%)	37 (9.2%)	39 (9.5%)	
Primary	38 (4.7%)	12 (3.0%)	26 (6.3%)	
Secondary	57 (7.0%)	14 (3.5%)	43 (10.5%)	
Higher	40 (4.9%)	10 (2.5%)	30 (7.3%)	
Occupation status[a]				**0.003**
Working	642 (78.9%)	332 (82.4%)	310 (75.4%)	
Not working	23 (2.8%)	4 (1.0%)	19 (4.6%)	
Housework	149 (18.3%)	67 (16.6%)	82 (20.0%)	
Socioeconomic status[a]				0.957
Low	114 (14.0%)	55 (13.6%)	59 (14.4%)	
Medium	620 (76.2%)	308 (76.4%)	312 (75.9%)	
High	80 (9.8%)	40 (9.9%)	40 (9.7%)	
Marital status				**0.001**
Currently married	587 (72.1%)	269 (66.7%)	318 (77.4%)	
Never married	10 (1.2%)	4 (1.0%)	6 (1.5%)	
Widowed/Divorced/Separated	217 (26.7%)	130 (32.3%)	87 (21.2%)	
Reproductive factors				
Age at natural menopause				**0.002**
Normal	287 (35.3%)	147 (36.5%)	140 (34.1%)	
Early	98 (12.0%)	55 (13.6%)	43 (10.5%)	
Late	49 (6.0%)	34 (8.4%)	15 (3.6%)	
No natural menopause	380 (46.7%)	167 (41.4%)	213 (51.8%)	
Parity				**<0.001**
Nulliparity	24 (2.9%)	1 (0.2%)	4 (1.0%)	
Parity 1-2	131 (16.1%)	48 (11.9%)	96 (23.4%)	
Parity ≥ 3	659 (81.0%)	344 (85.4%)	301 (73.2%)	
Hysterectomy				0.060
Yes	194 (23.8%)	108 (26.8%)	86 (20.9%)	
No	620 (76.2%)	295 (73.2%)	325 (79.1%)	
Lifestyle factors				
BMI (kg/m²)[a]				**0.0284**
Underweight	187 (23.0%)	82 (20.3%)	105 (25.5%)	
Normal weight	482 (59.2%)	234 (58.1%)	248 (60.3%)	
Overweight	131 (16.1%)	78 (19.4%)	53 (12.9%)	
Obese	14 (1.7%)	9 (2.2%)	5 (1.2%)	
Waist-hip ratio[a]				**<0.001**
Low risk	539 (66.2%)	237 (58.8%)	302 (73.5%)	
High risk	273 (33.5%)	166 (41.2%)	107 (26.0%)	
Missing	2 (0.2%)	0 (0%)	2 (0.5%)	
Alcohol consumption[a]				**0.034**
Never	295 (36.2%)	131 (32.5%)	164 (39.9%)	
Ever	519 (63.8%)	272 (67.5%)	247 (60.1%)	
Sleep type[a]				0.949
Good sleep	521 (64.0%)	257 (63.8%)	264 (64.2%)	
Poor sleep	293 (36.0%)	146 (36.2%)	147 (35.8%)	
Number of chronic diseases[a]				**<0.001**
0	363 (44.6%)	153 (38.0%)	210 (51.1%)	
1	451 (55.4%)	250 (62.0%)	201 (48.9%)	

*Using independent χ2-test and Fisher's exact test, *P*-value in bold is <0.05 (significant)
BMI Body Mass Index
[a]At Baseline

3.3. Regression analyses

After independent assessment of each predictor, the number of chronic conditions at baseline was included in the bivariate analysis and the interaction term was found to be statistically significant for several variables of interest. Therefore, bivariate and multivariate regression analyses were stratified by none or one chronic condition at baseline with the unadjusted and adjusted Odds Ratio (OR) with their corresponding 95% confidence interval (CI) reported (Table 3). In the unadjusted bivariate analysis, being 65 years or older was the strongest predictor of multimorbidity incidence in both the presence (OR: 11.3, 95% CI: 4.59 – 31.1) and absence (OR: 9.48, 95% CI: 3.74 – 25.8) of a chronic condition at baseline. Belonging to the age category of 45-64 years old (OR: 3.53, 95% CI: 1.89 – 7.01) was the only other predictor associated with a significant increase in the odds of incident multimorbidity when no chronic condition was present at baseline. Having secondary (OR: 0.29, 95% CI: 0.11– 0.70) or higher education (OR: 0.26, 95% CI: 0.06– 0.83) was found to significantly lower the odds of having incident multimorbidity in in the absence of a chronic condition at baseline.

Among the participants with one chronic condition at baseline, working either professionally (OR: 5.86, 95% CI: 1.85 – 25.9) or doing housework (OR: 5.02, 95% CI: 1.48 – 23.1), experiencing late menopause (OR: 3.94, 95% CI: 1.42 – 14.0), having a high risk waist-hip ratio (OR: 2.84, 95% CI: 1.87 – 4.37) and being widowed, divorced or separated (OR: 2.46, 95% CI: 1.58 – 3.89) significantly increased the risk of multimorbidity incidence compared to their reference groups. Being underweight (OR: 2.31, 95% CI: 1.33 – 4.17) and having ever consumption of alcohol (OR: 1.66, 95% CI: 1.13 – 2.44) also significantly increased the odds of having incident multimorbidity. Socioeconomic status, parity, hysterectomy and type of sleep were not associated with a significant increase in the odds of incident multimorbidity. Having primary (OR: 0.29, 95% CI: 0.09 - 0.83), secondary (OR: 0.26, 95% CI: 0.10 - 0.58), or higher education (OR: 0.27, 95% CI: 0.10 – 0.64) significantly lowered the odds of having incident multimorbidity compared to no education. No further statistically significant predictors of multimorbidity incidence were identified in this stratum.

The stratified multivariable models combined the sociodemographic, reproductive and lifestyle risk factors. Among the women with no chronic conditions at baseline, after adjusting for other variables, being 65 years old or above remained a significant predictor (OR: 7.27, 95% CI: 1.74 – 32.6) of multimorbidity incidence compared to being 18-44 years old. While insignificant in the unadjusted model, poor sleep (OR: 1.84, 95% CI: 1.13 – 3.02) was significantly related to multimorbidity incidence at follow-up. No other statistically significant

predictors of multimorbidity incidence were identified among women with no chronic conditions at baseline.

Reproductive factors, such as age at natural menopause, parity, and hysterectomy, also showed some associations with chronic conditions. However, the results were not consistent across all categories and did not reach statistical significance in most cases.
Lifestyle factors, including body mass index (BMI) and waist-hip ratio, did not show a significant association with chronic conditions. Similarly, alcohol consumption and sleep type did not demonstrate a clear association with the presence of chronic conditions.

Among women who had one chronic condition at baseline, those aged 65 years or older were the most likely to be affected by multimorbidity (OR: 11.9, 95% CI: 3.18 – 48.9), even after adjusting for all other variables. Women aged 45-64 years were also significantly associated with increased odds of incident multimorbidity (OR: 3.25, 95% CI: 1.22 – 9.22) than women aged 18-44 years old. Marital status was also found to be a significant predictor as women who were widowed, divorced, or separated had a higher odds of incident multimorbidity (OR = 2.03, 95% CI: 1.23 - 3.41) compared to those who were currently married, even after adjustment. Compared to women with no level of education, having primary education significantly lowered the odds of incident multimorbidity (OR = 0.32, 95% CI: 0.08 – 1.12) in the final adjusted model. Among the reproductive factors investigated, only late age at natural menopause (OR = 3.78, 95% CI: 1.28 – 14.0) compared to normal age stayed significantly associated with incident multimorbidity in the adjusted analysis. None of the other reproductive factors showed significance in either the adjusted or the unadjusted analyses.

Regarding the lifestyle factors, a high risk of waist-hip ratio was significantly associated with an increased odds of incident multimorbidity among individuals with one chronic condition (OR = 2.4, 95% CI: 1.46 - 3.99). Women who were overweight (OR = 2.09, 95% CI: 1.10 - 4.12) also were significantly associated with incident multimorbidity compared to women with normal weight. Lifestyle factors, including other categories of BMI, alcohol consumption, and sleep type, did not show significant associations with incident MM in this stratum.

Table 3: Crude and adjusted odds ratios (OR) from logistic regression analyses of potential predictors for multimorbidity, by the absence or presence of chronic condition at baseline.

	Unadjusted		Adjusted[1]	
	No chronic condition (*N* = 363)	One chronic condition (*N* = 451)	No chronic condition (*N* = 363)	One chronic condition (*N* = 451)
Predictor of interest	**OR (95% CI)[2]**	**OR (95% CI)[2]**	**OR (95% CI)[2]**	**OR (95% CI)[2]**
Sociodemographic characteristics				
Age (years)				
18-44	—	—	—	—
45-64	3.53 (1.89 - 7.02)***	3.73 (2.24 - 6.37)***	2.48 (0.76 - 8.61)	3.25 (1.22 - 9.22)*
65+	9.48 (3.74 - 25.8)***	11.3 (4.59 - 31.1)***	7.27 (1.74 - 32.6)**	11.9 (3.18 - 48.9)***
Education				
None	—	—	—	—
No Formal Education	0.79 (0.38 - 1.62)	0.78 (0.41 - 1.51)	0.81 (0.36 - 1.78)	0.89 (0.43 - 1.83)
Primary	0.53 (0.20 - 1.29)	0.29 (0.09 - 0.83)*	0.79 (0.26 - 2.29)	0.32 (0.08 - 1.12)*
Secondary	0.29 (0.11 - 0.70)*	0.26 (0.10 - 0.58)**	0.36 (0.08 - 1.44)	1.11 (0.33 - 3.71)
Higher	0.26 (0.06 - 0.83)*	0.27 (0.10 - 0.64)**	0.28 (0.03 - 2.07)	2.13 (0.47 - 9.51)
Occupation status				
Not working	—	—	—	—
Working	4.84 (0.81 - 92.0)	5.86 (1.85 - 25.9)**	3.84 (0.35 - 131)	3.24 (0.62 - 20.3)
Housework	3.14 (0.49 - 61.1)	5.02 (1.48 - 23.1)*	3.93 (0.36 - 135)	3.35 (0.64 - 21.3)
Socioeconomic status				
Medium	—	—	—	—
Low	0.83 (0.44 - 1.54)	1.03 (0.60 - 1.78)	0.8 (0.39 - 1.61)	1 (0.54 - 1.88)
High	1.17 (0.59 - 2.29)	0.93 (0.49 - 1.79)	1.5 (0.70 - 3.22)	0.95 (0.45 - 2.01)
Marital status				
Currently married	—	—	—	—
Never married	1.46 (0.17 - 12.3)	0.5 (0.07 - 2.60)	5.5 (0.31 - 184)	0.57 (0.03 - 7.81)
Widowed/Divorced/Separated	1.23 (0.77 - 1.98)	2.46 (1.58 - 3.89)***	1.07 (0.62 - 1.86)	2.03 (1.23 - 3.41)**
Reproductive factors				
Age at natural menopause				
Normal	—	—	—	—
No natural menopause	0.78 (0.49 - 1.25)	0.72 (0.48 - 1.09)	1.01 (0.41 - 2.47)	1.37 (0.61 - 3.21)
Early	1.23 (0.60 - 2.50)	1.19 (0.65 - 2.24)	1.1 (0.51 - 2.33)	1.45 (0.74 - 2.88)
Late	1.53 (0.63 - 3.73)	3.94 (1.42 - 14.0)*	1.12 (0.43 - 2.89)	3.78 (1.28 - 14.0)*
Parity				
Nulliparity	—	—	—	—
Parity 1-2	0.51 (0.13 - 2.18)	0.9 (0.27 - 3.05)	0.16 (0.02 - 1.55)	0.36 (0.06 - 2.14)
Parity ≥ 3	1.52 (0.45 - 5.92)	1.61 (0.53 - 5.09)	0.34 (0.04 - 3.27)	0.37 (0.06 - 2.14)
Hysterectomy				
No	—	—	—	—
Yes	1.56 (0.95 - 2.56)	1.24 (0.81 - 1.93)	1.54 (0.62 - 3.85)	1.04 (0.45 - 2.37)
Lifestyle factors				
BMI (kg/m²)				
Normal weight	—	—	—	—
Underweight	0.73 (0.43 - 1.21)	0.93 (0.59 - 1.46)	0.72 (0.39 - 1.34)	1.09 (0.64 - 1.87)
Overweight	1.06 (0.59 - 1.88)	2.31 (1.33 - 4.17)**	1.25 (0.65 - 2.43)	2.09 (1.10 - 4.12)*
Obese	1.29 (0.15 - 10.9)	2.12 (0.58 - 9.99)	1.04 (0.11 - 10.3)	2.01 (0.45 - 11.4)
Waist-hip ratio				
Low risk	—	—	—	—
High risk	1.36 (0.88 - 2.11)	2.84 (1.87 - 4.37)***	0.84 (0.48 - 1.45)	2.4 (1.46 - 3.99)***
Alcohol consumption				
Never	—	—	—	—
Ever	1.14 (0.74 - 1.78)	1.66 (1.13 - 2.44)*	0.65 (0.38 - 1.12)	0.96 (0.59 - 1.56)
Sleep type				
Good sleep	—	—	—	—
Poor sleep	1.33 (0.86 - 2.06)	0.8 (0.55 - 1.18)	1.84 (1.13 - 3.02)*	0.71 (0.46 - 1.10)

Dashed line - refers to Reference group

[1]Adjusted model includes the other variables in the analysis.

[2]Odds ratio (95% Confidence Interval)

*p<0.05

**p<0.01

***p<0.001

BMI Body Mass Index

3.4. Clusters

A three-class model was chosen as the optimal class based on the lowest BIC and AIC values that showed parsimony. The selected model had 401 observations which were the number of incident multimorbidity cases. Each class represents a cluster of individuals with similar disease profiles. The results from class proportion and item-response probabilities are displayed in Table 4. The item-response probabilities of diabetes (0.29 in class 3) and anxiety (0.29 in class 2) were rounded off to one decimal and considered as 0.30. Class 1 comprised 64% of the study population who had high probabilities of sarcopenia (0.55), hypertension (0.51) and anaemia (0.33). This group was labelled as *metabolic and musculoskeletal cluster* and there was an average of 2.58 conditions at follow-up in this class. Class 2 comprised of 23% of the individuals and reported high probabilities for depression (0.92), for anaemia (0.40), sarcopenia (0.40) and anxiety (0.30), therefore it was labelled as *psychosomatic health cluster.* The average number of chronic conditions in this group was 2.91. Class 3 represented the remaining 13% of the study population who had high probabilities of having depression (0.71), hypertension (0.66), anxiety (0.50), sarcopenia (0.47) and diabetes (0.30), suggesting that individuals in this class are more likely to have all five diseases. This class was labelled as *cardiovascular and mental health cluster* and the mean number of chronic conditions was 3.67.

Table 4: Class proportions and item-response probabilities of chronic conditions from the three-latent class model

Latent class	Class 1	Class 2	Class 3
Assigned label	Metabolic and musculoskeletal	Psychosomatic health	Cardiovascular and mental health
Class proportion (%)	64	23	13
Physical health conditions			
Anaemia	**0.33**	**0.40**	0.00
Angina	0.06	0.15	0.00
Arthritis	0.15	0.08	0.10
Cancer	0.01	0.00	0.00
Chronic Kidney Disease	0.03	0.00	0.09
COPD*	0.03	0.08	0.02
Dementia	0.19	0.09	0.22
Diabetes	0.27	0.14	**0.30**
Hypertension	**0.51**	0.11	**0.66**
Sarcopenia	**0.55**	**0.40**	**0.47**
Stroke	0.21	0.24	0.00
Thyroid Dysfunction	0.12	0.00	0.24
Mental health conditions			
Anxiety	0.02	**0.30**	**0.50**
Depression	0.00	**0.92**	**0.71**
Long-term infectious disease			
Tuberculosis	0.09	0.03	0.07
Average number of diseases	2.58	2.91	3.67

4. Discussion

The analyses of this large intergenerational cohort identified a number of sociodemographic and long-term determinants associated with 10-year incident multimorbidity in women in India and identified three distinct incident disease clusters. To the best of the author's knowledge, this is the first longitudinal study to analyse determinants and patterns of incident multimorbidity among women in peri-urban Telangana, India.

In multivariable analyses, being aged 44 or above, having no education, being widowed or divorced or separated, experiencing natural menopause at a late age, having a high-risk waist-hip ratio and having poor sleep at baseline were significantly associated with incident multimorbidity. The manifestation of multimorbidity differently across individuals was revealed by the different disease profiles of women who developed incident multimorbidity through three different clusters of conditions, including *metabolic and musculoskeletal cluster, psychosomatic health cluster* and *cardiovascular and mental health cluster*.

Age-stratified incidence revealed that the cumulative incidences varied largely as 75.7% of women aged 65 or above developed multimorbidity over a 10-year period while cumulative incidence was 24.0% among the women aged 18-44 years. This finding is consistent with the substantial evidence on the increase of multimorbidity with age and the accumulation of chronic conditions with ageing (27,65).

4.1. Comparison with existing literature

Due to the paucity of literature on multimorbidity incidence among women in India, the comparability of the findings of this analysis were challenging. Cumulative incidence was found to be high (49.5%) for the entire study population. A study among Korean participants aged 65 years and older found a 10-year follow-up found a cumulaiive incidence of 31.8% which is much lower than the cumulative incidence of 65 years and older women in this study (66). However, large disparities in cumulative incidences exist, which may be attributable to differences in geographic settings, study population and size, follow-up time, conditions included and operational definition of multimorbidity (67).

Stratified cumulative incidence found that women with one chronic condition at baseline had a higher likelihood of developing multimorbidity at follow-up compared to those without any chronic condition initially. This finding has been reported by several studies that investigated the incidence of multimorbidity (68,69). This observation can be attributed to several factors. Firstly, underlying genetic mechanisms can contribute to the development of multiple chronic

diseases (70). Individual with a baseline chronic condition might be more likely to seek medical assistance, leading to a higher likelihood of being diagnosed with other (71). The overall health impact from a single chronic condition in women can also increase their susceptibility to acquiring additional unrelated illnesses.

The findings of this study from the multivariable analyses revealed marital status and education as significant predictors of incident multimorbidity among women who had a single chronic condition at baseline, when other variables were kept constant. Having no education compared to primary education increased the odds of development of multimorbidity is consistent with previous research findings that have found education as a relevant risk factor for multimorbidity. A cross-sectional study on the effect of unhealthy lifestyle behaviours on multimorbidity among adult women in India found an inverse association of education with multimorbidity while another study reported higher odds of multimorbidity (72). This may in partly be due to education acting as a proxy for socioeconomic status (73). However, no significant association was found between incident multimorbidity and socioeconomic tertile or occupation status, another common proxy for social gradient in health among women in this study. This is in contrast with another cross-sectional study on middle-aged Indian women which found a positive association of multimorbidity with higher socio-economic status (26). The relationship between socioeconomic status and multimorbidity is complex and differs significantly across different contexts. These variations are influenced by factors such as demographic and epidemiological trends, which can predispose to chronic diseases, as well as higher health-seeking behaviour or access to unhealthy lifestyle behaviours such as consuming high-calorie foods, alcohol, that contribute to the development of multiple chronic conditions (1). Among women who had a single chronic condition at baseline, the finding of higher incidence of multimorbidity among widowed, divorced or separated women compared to married women is in accordance with another longitudinal study that also found higher odds of cardiovascular multimorbidity among Australian women (74). The lack of social support and elevated psychosocial stress associated with disrupted marital relations may contribute to the higher incidence of multimorbidity in this population (75).

Regarding the reproductive factors, the findings revealed that women with a single chronic condition at baseline and who experienced menopause at a later age were found to have a significantly higher odds of incident multimorbidity compared to those with normal menopause, when other variables kept constant. This contrasts with a cohort study conducted on Australian women which reported lower odds of developing multimorbidity among women who experienced menopause a later age (76). Menopause, whether induced through hysterectomy or naturally occuring, can lead to premature loss of estrogen, which

has been linked to an increased epigenetic age of blood and saliva, indicating an acceleration of biological ageing (77). This accelerated aging process is a strong predictor of multimorbidity (78). Although, women who had undergone hysterectomy were positively associated with incident multimorbidity, the findings of this study did not show statistical significance. While also not statistically significant, our findings suggest that women with a high parity (high number of live births) had lower odds of developing multimorbidity compared to women who had never given birth to live children (nulliparity). This is in contrast with a study on multimorbidity among middle-aged women in China which found conclusive evidence on high parity being significantly associated with an increased risk of multimorbidity (79). Therefore, further evidence is needed to generate conclusive evidence on this among women in India.

In relation to lifestyle factors, women who were overweight, as indicated by BMI, and who were obese, as indicated by high-risk waist-hip ratio, had significantly higher odds of developing multimorbidity than women with normal weight and low-risk waist-hip ratio, in the stratum for women with a single chronic condition at baseline and adjusted for other variables. Waist-hip ratio has been found to be a better metric to capture obesity and obesity-related disorders than BMI as it captures regional abdominal adiposity (80). These findings are consistent with cross-sectional studies that reported a higher prevalence of multimorbidity among women who were overweight or obese, through the use of BMI and waist-hip ratio, in India (13,26,72). The findings are also in agreement with a longitudinal study conducted on Chilean women that found obesity to be the strongest risk factor for multimorbidity and a large 10-year study of over 120 thousand individuals that found a two-fold risk of multimorbidity in individuals who were overweight (11,81). Women with no condition at baseline and who had poor sleep at baseline had increased odds of multimorbidity than women with good sleep. While good sleep was treated as a dichotomous variable and defined by 7-8 hours of sleep in this study, a longitudinal study among middle-aged and elder participants in China revealed a U-shaped association in which both shorter and longer sleep were significantly associated with a higher likelihood of multimorbidity in women (82). Insignificant findings were observed regarding the association between alcohol consumption and multimorbidity. This disagrees with other studies, some of which have reported a significant association based on frequent consumption of alcohol (72,83,84). Therefore, the inconsistent finding may be attributable to the dichotomous nature of alcohol in this study as it captured only ever use of alcohol.

The three latent classes revealed that three distinct clusters of conditions were found among women with incident multimorbidity namely, including *metabolic* and *musculoskeletal cluster,*

psychosomatic health cluster and *cardiovascular and mental health cluster*. As *metabolic* and *musculoskeletal cluster* comprised of majority of the women (64%), some of the conditions in the cluster have frequently been associated together. A cross-sectional study found sarcopenia associated with increased risk of anaemia and their additive effect on the 10-year cardiovascular disease risk among type-2 diabetes patients (85). Sarcopenia has also been associated with cardiovascular risk factors such as hypertension (86). Some of the conditions in the *psychosomatic health cluster,* such as depression and sarcopenia, also have substantial evidence on association and may share several common risk factors, such as physical activity and dysregulation of hormones (87). This cluster with some similar conditions has also been found in a longitudinal study among Australian women (88). While there is limited evidence on multimorbidity clusters in India, cardiovascular and metabolic disorders are commonly observed in the country (88). Lastly, evidence exists on the complex interplay between cardiovascular and mental health conditions. Individuals with cardiovascular diseases often experience psychological distress, such as symptoms of depression and anxiety while individuals with mental health conditions may have an increased risk of developing cardiovascular diseases due to risk factors and shared biological pathways (89–91).

4.2. Strengths and limitations

The study's major strength was the use of longitudinal design to generate empirical evidence on multimorbidity for women in peri-urban India. While most studies in India so far have used cross-sectional data, this longitudinal analysis provided data on development of multimorbidity in 10-years follow-up period and revealed temporal evidence on predictors of incident multimorbidity. Studies have either been restricted to women of reproductive age or older post-menopausal women while multimorbidity has been to occur at earlier ages in LMICs than HICs (1,10,27,92). However, the growing scale of multimorbidity across all ages among women have not been studied in the Indian context, therefore this present study provided valuable insights into the burden, determinants and patterns of incident multimorbidity.

Another strength of the study is the inclusion of sixteen chronic conditions which were screened with a combination of self-reported clinical diagnosis, symptom-based questionnaires, physical examinations, and biochemical assays. Most studies on multimorbidity in South Asia have relied solely on self-reported previous clinical diagnosis which can be subject to measurement errors and lack of accuracy, leading to inconsistencies in the assessment of multimorbidity (7). The study also followed recommendations from the

UK Academy of Medical Sciences to include physical non-communicable diseases, mental health conditions and long-term infectious diseases in multimorbidity analyses and using a standard classification scheme, the International Classification of Diseases 10th Edition (ICD-10), for reporting them (1). Another systematic review suggested to use at least 12 chronic conditions to measure multimorbidity (67). Therefore, the study included conditions based on their high disease burden unique to women in India and their occurrence in multimorbidity.

Despite the strengths of the study, there are several limitations that need to be considered. Firstly, complete case analyses, which excludes observations with missing data on chronic conditions, was employed in this study. While this approach is commonly used and allows for the utilisation of all available data without imputation or estimation, it may introduce biases if the missing data are not missing completely at random (MCAR) (93). Additionally, it reduces statistical power which may not have been sufficient to capture less commonly occurring disease patterns. This method was employed by another multimorbidity study to investigate multimorbidity clusters through LCA which found similar results in the sensitivity analysis between complete case analyses and multiple imputation (94).

The study population being based in a specific geographical region is another limitation because it may not fully represent the diversity of the women in India. Multimorbidity estimates from a nationally representative data In India highlighted sub-national variations in patterns in the burden of multimorbidity among women (26). Therefore, given the geographical and contextual differences in disease burden and profiling, the findings of this study may not be applicable to the entire Indian population and the multimorbidity clusters specific to other Indian settings may have not been captured. Nonetheless, the findings build on the evidence on burden and determinants of multimorbidity in peri-urban India which may have relevance to other rural and urban settings which are undergoing similar epidemiological trends (10).

Another major limitation pertains to the use of different screening measure for certain chronic conditions which differed at the two time points. This discrepancy in measurement methods may introduce variability and affect the comparability of the results, potentially leading to misclassification bias. However, a pragmatic approach was adopted to ensure consistency where possible to maximise the number of conditions that could be analysed longitudinally. The use of LCA also has its methodological limitations. Class assignment is based on probability-based classification, which can introduce bias, and the designation of class labels is subjective to the author and subject to naming fallacy (60). The results should be interpreted with care due to uncertainty related with latent class membership.

4.3. Implications for public health

The findings of this study provide invaluable insights that can have significant implications for reducing the incidence and thereafter, burden of multimorbidity among women. The evidence for a temporal association between certain modifiable risk factors, such as overweight/obesity and type of sleep, highlight the importance of designing new and evaluating current interventions to include evidence-based components that promote healthy lifestyles as an approach to reduce the burden of multiple diseases. While most approaches aim to improve outcomes of people with multimorbidity, these findings suggest the opportunity for prevention strategies, employing behavior-change interventions, as the risk factors are amenable to change (95,96). With the lack of complex interventions in LMICs with low-resource settings such as India, existing programs aimed to implement and deliver evidence-based components for behavior change should be prioritized in health policy and clinical practice. Furthermore, such interventions also empower patients by fostering an internal health-related locus of control to actively pursue and sustain positive changes, further enhancing the outcomes of the interventions.

The analyses revealed women aged 45 or older, those who had underlying chronic condition at baseline, those who were widowed, divorced or separated, those who experienced menopause at late age, or those with no education were found to have a higher risk of incident multimorbidity. The identification of these high-risk categories of developing multimorbidity can inform future work on tailored early interventions to focus on primary prevention and management of multimorbidity among these groups. Moreover, considering the ongoing demographic transition in India, the survival of older women and the number of women experiencing menopause is set to increase further. Since the scale of the problem is likely going to rise, a multi-faceted approach is required to potentially prevent or delay the onset of multimorbidity and improve overall health outcomes. The presence of commonly occurring clusters of diseases showed non-random associations between certain chronic condition and distinct patterns in accumulation of chronic conditions. This finding warrants the need to adopt a holistic approach in clinical practice to target multiple diseases rather than the treating diseases as single entities.

Looking ahead, it is imperative to integrate these findings into the development of programs and evidence-based policymaking that promote health, foster social engagement and establish comprehensive primary care systems that can identify women at risk in India.

4.4. Recommendations for future research

Further research is crucial to gain a deeper understanding of the underlying mechanisms and pathways through which risk factors contribute to incident multimorbidity in women in India.

Identifying specific temporal patterns in the development of multimorbidity was beyond the scope of this study. Evidence on disease trajectories can help understand the accumulation and progression of chronic conditions. It is also paramount to expand the scope of research and understand the relevant mechanisms of co-occuring diseases in multimorbidity clusters, such as clarity on shared pathophysiology or shared risk factors. This can inform clinicians to anticipate the likelihood of disease progression, identifying potential aggravating factors, and predict future healthcare needs of patients with multimorbidity. Furthermore, research analyses should maintain consistency in the screening approaches for conditions across different time points to ensure the validity and reliability of longitudinal multimorbidity studies. Future studies should also consider the severity of diseases as well as impact measures, such as quality of life, as it can provide a more meaningful insight on the burden of multimorbidity.

5. Conclusion

This study found a high incidence of multimorbidity among women in India over a period of 10 years, especially in those with a chronic condition at baseline. The findings added to existing knowledge on age as a strong predictor of incident multimorbidity and generated new evidence on the role of reproductive and lifestyle factors as predictors. These findings can inform about the identification of at-risk groups among women to develop multimorbidity who should receive attention to reduce the burden of incident multimorbidity through effective prevention strategies. These findings can also be relevant to other settings with similar epidemiological trends and rural-urban areas.

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List of appendices

Appendix 1: Screened chronic conditions by clinical definition and classification in the analysis, at follow-up and baseline

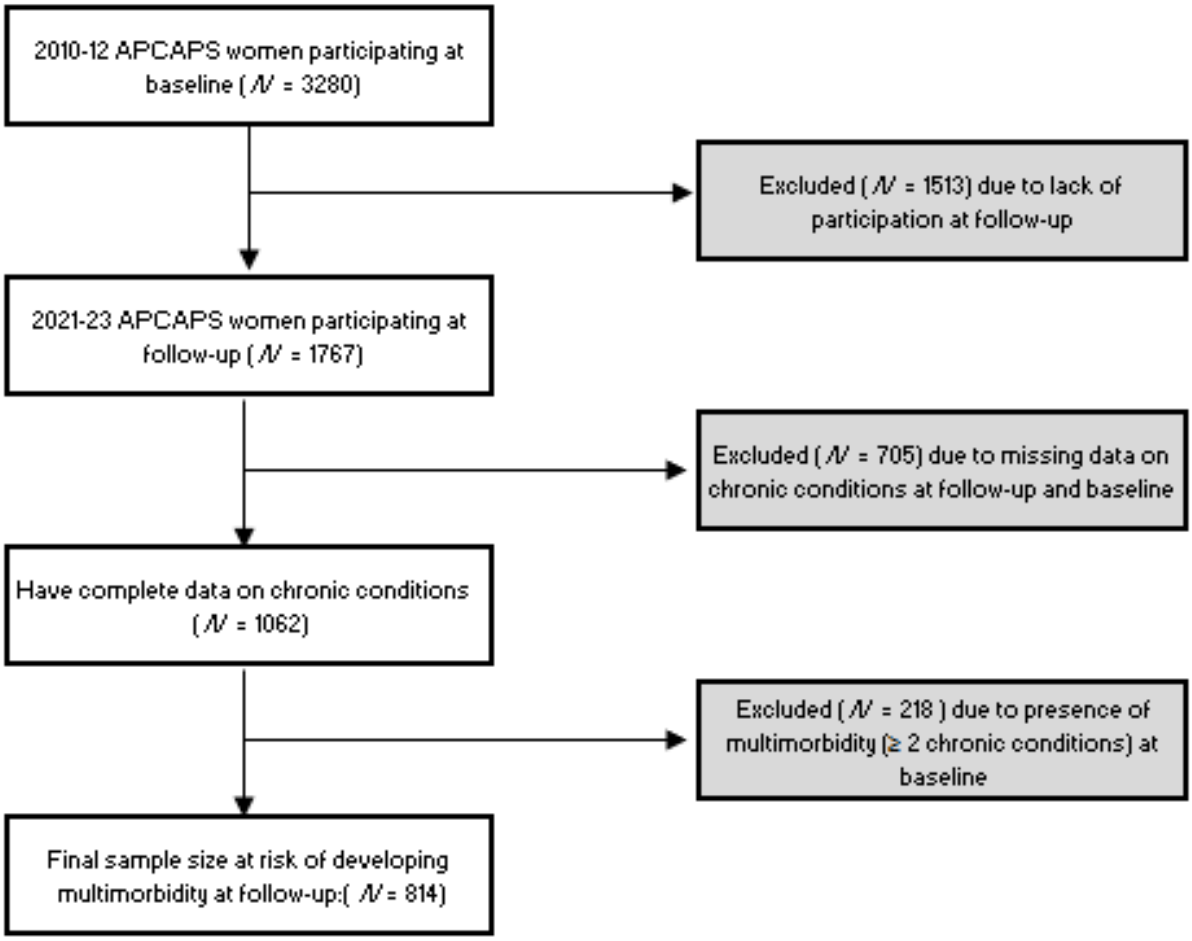
Condition (ICD-10 code)	**Clinical definition**	**Classification in the analysis**
Anaemia (D64.9)	Pregnant women ≤109 g/dL Non-pregnant women ≤ 119 g/dL 2011 WHO; Haemoglobin concentrations for the diagnosis of anaemia and assessment of severity(1)	*Follow-up and baseline:* Same as clinical definition
Angina (I25.9)	Chest pain that limits exertion, is situated over the sternum or in the left chest and left arm, and is relieved within 10 minutes by rest 1962 WHO; Rose Questionnaire(2)	*Follow-up and baseline:* Previously diagnosed OR Rose questionnaire
Arthritis (M05-M14)	Patients ≥ 45 years old and having activity-related joint pain and having either no morning joint-related stiffness or morning stiffness that lasts no longer than 30 minutes. 2022 National Institute for Health and Care Excellence (NICE); Osteoarthritis in over 16s: Diagnosis and Management(3)	*Follow-up:* Previously diagnosed OR diagnosis from an algorithm by the WHO SAGE survey (If responses to questions 1 and/or 2 are 'yes' and question 3 are 'yes', and question 4 is 'non', then the participant is categorised as having arthritis)(4) *Baseline:* Age at previous diagnosis to assess presence or absence at baseline

Asthma (J45)	The presence of symptoms (more than one of wheeze, breathlessness, chest tightness, cough) and of variable airflow obstruction. 2014 British Thoracic Society; British guideline on the management of asthma(5)	*Follow-up and baseline:* Previously diagnosed
Cancer (C00-C97)	Large group of diseases in which abnormal cells grow beyond their usual boundaries, and can then invade adjoining parts of the body and spread to other organs 2021 National Cancer Institute; What is cancer?(6)	*Follow-up and baseline:* Previously diagnosed
Chronic kidney disease (N18)	The presence of a marker of kidney damage, such as proteinuria or a decreased glomerular filtration rate for three or more months. 2002 The Kidney Disease Outcome Quality Initiative of the National Kidney Foundation; Clinical Practice Guidelines for Chronic Kidney Disease(7)	*Follow-up:* Previously diagnosed *Baseline:* eGFR < 60 from serum creatinine
Chronic Obstructive Lung Disease **(**J44)	The presence of dyspnoea, chronic cough or sputum production, and/or a history of exposure to risk factors for the disease. 2017 Global Initiative for Chronic Obstructive Lung Disease (GOLD)(8)	*Follow-up:* A total score of ≤18 from lung faction questionnaire, age and years of smoking would be at risk of COPD(9) *Baseline:* Previously diagnosed
Dementia (F03)	Dementia is a term for several diseases that result in the loss of cognitive functioning and the ability to perform daily activities. 2021 National Institute on Ageing(10)	*Follow-up:* Optimal cut-off < 6 for the cognitive scale of the Community Screening Instrument for Dementia (CSI-D)(11) *Baseline:* Absence of dementia
Diabetes	Fasting plasma glucose concentration ≥ 126 mg/dL	*Follow-up and baseline:*

(E10-E14)	2006 WHO; Definition and Diagnosis of Diabetes Mellitus and Intermediate Hyperglycaemia(12)	Previously diagnosed OR FPG ≥ 126 mg/dL
Hypertension (I10/I15)	Systolic 140+ and/or diastolic 90+ 2020 International Society of Hypertension; Global Hypertension Practice Guidelines(13)	*Follow-up and baseline:* Previously diagnosed OR average systolic ≥140 OR average diastolic ≥90
Sarcopenia (M62.5)	Age-related loss of muscle mass, and low muscle strength, and/or low physical performance Asian Working Group for Sarcopenia; 2019 Consensus Update on Sarcopenia Diagnosis and Treatment(14)	*Follow-up and baseline:* Low muscle strength: Handgrip strength <10.76 kg for women(15)
Stroke (I64)	An episode of acute neurological dysfunction presumed to be caused by ischemia or haemorrhage, persisting ≥24 hours 2013 The American Heart Association/American Stroke Association; An Updated Definition of Stroke for the 21st Century(16)	*Follow-up:* Previously diagnosed OR paralysis and/or numbness is present from the questionnaire. If no paralysis AND no numbness, then no stroke. *Baseline:* Previously diagnosed
Thyroid dysfunction (E00-E07)	Conditions causing thyroid dysfunction can be broadly divided into those that result in thyroid gland underactivity (overt and subclinical hypothyroidism) or overactivity (thyrotoxicosis). 2019 NICE; Thyroid disease: assessment and management	*Follow-up and baseline:* Previously diagnosed
Anxiety (F41)	Scores range from 0-21 with a score of 10 or higher indicating the presence of moderate to severe anxiety.	*Follow-up:* A score of 10 or higher in GAD-7

	GAD-7(17)	*Baseline:* Response of yes to all questions in the anxiety component of Brief-PHQ
Depression (F32-F33)	Scores range from 0-27 with a score of 10 or higher being indicative of depression. PHQ-9(18)	*Follow-up:* A score of 10 or higher in PHQ-9 *Baseline:* Previously diagnosed or a score of 10 or higher in PHQ-9
Tuberculosis (A15-A19)	Active lung TB ≥ 2 weeks of cough with sputum and blood at times OR chest pains OR weakness OR weight loss OR fever OR night sweats 2022 WHO(19)	*Follow-up:* Previously diagnosed OR satisfying Government of India's case definition of presumptive TB and/or night sweats(20) *Baseline:* Previously diagnosed

Appendix 2: Flowchart of study sample



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Résumé

Introduction: Le fardeau croissant de la multimorbidité (présence de deux ou plusieurs maladies chroniques), en partie dû aux transitions épidémiologiques et démographiques en Inde, nécessite une meilleure compréhension de ses déterminants et de ses schémas. Cette étude longitudinale visait à évaluer l'incidence cumulative de la multimorbidité, à identifier les prédicteurs potentiels sociodémographiques, reproductifs et liés au mode de vie à long terme, et à explorer les regroupements fréquents de maladies chez les femmes âgées de 18 ans ou plus dans la région péri-urbaine de Telangana, en Inde.

Méthodes: Cette étude a évalué 16 maladies chroniques chez les femmes qui ont participé au troisième (2010-2012) et quatrième suivi (2021-2023) de la cohorte prospective de l'étude des enfants et des parents d'Andhra Pradesh (APCAPS) et qui disposaient de données complètes sur les maladies chroniques aux deux périodes. Des modèles de régression bivariée et multivariée, stratifiés en fonction de la présence ou de l'absence d'une maladie chronique au troisième suivi, ont été utilisés pour étudier les associations avec les prédicteurs de la multimorbidité. L'analyse de classes latentes (ACL) a été utilisée pour identifier les schémas de maladies fréquents.

Résultats: La population de l'étude comprenait 814 personnes, parmi lesquelles 403 (49,5 %) ont développé une multimorbidité sur une période de 10 ans. Être âgé de 45 ans ou plus, avoir une éducation primaire, être veuve, divorcée ou séparée, connaître une ménopause tardive et présenter un indice taille-hanche à haut risque étaient des prédicteurs significatifs de l'incidence de la multimorbidité chez les femmes ayant une maladie chronique initiale. Chez les femmes sans maladie chronique initiale, une probabilité plus élevée d'incidence de la multimorbidité a été observée chez celles âgées de 65 ans ou plus et ayant une mauvaise qualité de sommeil. Trois clusters distincts d'incidence de la multimorbidité ont été identifiés : métabolique et musculo-squelettique, psychosomatique et cardiovasculaire, et santé mentale.

Conclusion: La forte incidence de la multimorbidité chez les femmes dans la région justifie la nécessité d'une prise en charge globale de la multimorbidité. Les résultats fournissent des informations sur les déterminants longitudinaux qui peuvent orienter les stratégies de prévention et de prise en charge ciblées. Les regroupements de maladies peuvent guider le dépistage de la multimorbidité et souligner la nécessité de cibler un groupe de maladies plutôt que des affections individuelles.