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Trajectories of multiple long-term conditions and mortality in older adults: A retrospective cohort study using English Longitudinal Study of Ageing (ELSA)

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Authors' contribution

All authors contributed to the study's conception and design. C.V.C and Cornelia are jointly the first authors. Material preparation and analysis were performed by HDM, C.V.C, and C.S. The first draft of the manuscript was written by C.V.C and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Competing interests

None declared.

Ethics approval

Ethical approval for the study was provided by the Faculty of Medicine Ethics Committee, University Hospital Southampton, (reference number 67953).

Abstract

Objectives

To classify older adults with MLTC into clusters based on accumulating conditions as trajectories over time, characterise clusters and quantify associations between derived cluster and all-cause mortality.

Design

We conducted a retrospective cohort study using the English Longitudinal Study of Ageing (ELSA) over nine years (n=15,091 aged 50 years and older). Group-based trajectory modelling was used to classify people into MLTC clusters based on accumulating conditions over time. Derived clusters were used to quantify the associations between MLTC trajectory memberships, sociodemographic characteristics, and all-cause mortality.

Results

Five distinct clusters of MLTC trajectories were identified and characterised as: "no-LTC" (18.57%), "single-LTC" (31.21%), "evolving MLTC" (25.82%), "moderate MLTC" (17.12%), and "high MLTC" (7.27%). Increasing age was consistently associated with an increased number of MLTC. Female sex (aOR = 1.13; 95%CI 1.01 to 1.27) and ethnic minority (aOR = 2.04; 95%CI 1.40 to 3.00) were associated with the "moderate MLCTC" and "high MLTC" clusters, respectively. Higher education and paid employment were associated with a lower likelihood of progression over time towards an increased number of MLTC. All the clusters had higher all-cause mortality than the "no-LTC" cluster.

Conclusions

The development of MLTC and the increase in the number of conditions over time follow distinct trajectories. These are determined by non-modifiable (age, sex, ethnicity) and modifiable factors (education and employment). Stratifying risk through clustering will enable practitioners to identify older adults with a higher likelihood of worsening MLTC over time to tailor effective interventions.

Keywords

Multiple long-term conditions, trajectories, mortality, English Longitudinal Study on Ageing (ELSA), older.

Strengths and limitations

- The main strength of the current study is the use of a large dataset, assessing longitudinal data to examine MLTC trajectories and a dataset that is nationally representative of people aged 50 years and older, including a wide range of long-term conditions and sociodemographics.
- The measurement of MLTC was limited to ten long-term conditions, which was all of what was available in the English of Longitudinal Study of Ageing, which may not be exhaustive of all possible long-term conditions.

Introduction

Globally, the average life expectancy has risen from 66.8 years in 2000 to 73.4 years in 2019 (1). By 2050, the population over 60 and 80 years will reach 2.1 billion and 426 million, respectively (2,3). This rise in longevity raises the risk of developing multiple long-term conditions (MLTC), which is the co-occurrence of two or more chronic diseases (4). Globally, the prevalence of MLTC among older people is reported to be between 55-98% (5), and in the UK, this is expected to rise from 54% in 2015 to 68% in 2035 (2). MLTC represent an ongoing challenge for healthcare systems because people with MLTC have worse care outcomes, including functional limitation and disability (6,7), higher service utilisation (5), mortality (8) and poorer quality of life (5). Management of MLTC places considerable economic and logistical burdens on services which are traditionally organised around single disease models (6).

While there is ample evidence of identified risk factors (7,9) and adverse care outcomes for MLTC cross-sectionally to help understand the prevalence and patterns of MLTC, they provide little evidence on temporal elements, including patterns of MLTC development over time (8,10,11). There is a paucity of longitudinal approaches examining patterns in the accumulation of diseases over time (12). Understanding the trajectory that an older adult will follow in the progression towards an increased number of MLTC could help predict when intervention is needed and inform targeted and earlier preventive interventions. To address this critical gap in the literature, this study aimed to classify older adults with MLTC into clusters based on the cumulation of conditions as trajectories over time; clusters were then characterised, and associations were quantified between derived clusters and all-cause mortality.

Methods

Data source and study population

The English Longitudinal Study of Aging (ELSA) is a longitudinal cohort of people aged 50 years or older living in England (13). The ELSA cohort profile has been described in detail elsewhere (14). In summary, it included 12,099 people at study entry in 2002 with follow-up every two years with self-report questionnaires on physical and mental health, well-being, finances, and attitudes around ageing over time. Four yearly additional nurse visits collected objective data such as anthropometric data (13,15). The ELSA is an open cohort, and refreshment samples were added depending on the proportional age requirement for ELSA, so the total number of people in this cohort was 15091. Our baseline was wave 2 (2004/5) of the ELSA cohort, the first collecting time point in the study of long-term conditions with a nine-year follow-up to wave 6 (2012/3), the most recent wave with available data on all-cause mortality status.

Multiple Long-Term Conditions

MLTC was defined as the presence of two or more of the following ten conditions: hypertension, diabetes, cancer, lung disease, cardiovascular disease, stroke, mental health disorder, arthritis, Parkinson's disease, and dementia. These are self-reported by patients, relatives or carers and verified by nurse visits (13). These ten conditions were available within the ELSA dataset based on our earlier work to define MLTC (16,17). After statistical consideration due to the small sample size and clinical discussion, we grouped some of the conditions as follows: people with depression were combined with mental health disorders, asthma was combined with lung disease, Alzheimer's within dementia, and finally, those with heart attack, angina, heart murmur, abnormal heart rhythm and congestive heart failure combined into those with cardiovascular disease.

All-cause mortality

All-cause mortality was reported by end-of-life interviews on waves 2, 3, 4 and 6 with relatives and friends after death.

Covariates

Sociodemographic variables included were age, sex, ethnicity (defined as white/non-white), education, employment, and marital status. The education variable was categorised into four groups: less than upper secondary level, upper secondary and vocational level, tertiary level, and others. Employment status was categorised into 'paid employment and 'unemployed'. Marital status was categorised into three groups: never married, married/having a partner, and separated/divorced/widowed. These covariates were based on the baseline. We used data provided in the nearest subsequent waves if they were missing at baseline.

Statistical analysis

Descriptive statistics were used to summarise participants' characteristics. We used group-based trajectory modelling (GBTM) to classify older adults with MLTC into clusters based on the accumulation of conditions as trajectories over time. GBTM is a finite mixture model applying maximum likelihood to identify a cluster of people following similar trajectories by the number of conditions over time (18). This model assumes the same error variance for all clusters and time points and treats missing data as 'missing at random' (19). The procedure for selecting the best model included two steps: identifying the ideal number of trajectory groups and determining polynomial orders to represent the shapes of the trajectories (18,20). Based on the observed distribution, we employed a censored normal model to specify MLTC (21,22). We fitted the models iteratively, starting with one and increasing up to a maximum of six clusters that would be useful in a clinical setting (20). We selected the number of trajectory clusters based on the following criteria: the lowest Bayesian Information Criterion (BIC) value, Average Posterior Probability Assignment (APPA) >70%, Odds of a Correct Classification (OCC) >5, the percentage of participants in each trajectory groups >5% of the total sample (if less than 5% it is unlikely to be conceptually useful for clinical practice) (22–24). We first used cubic polynomials to characterise the shape of the clusters of MLTC trajectories. However, after selecting the number of trajectories, we refitted the model to use lower-order terms when the higher-order terms were insignificant (20). We then assigned individuals to the trajectory group based on the maximum posterior probability (20). Multinomial logistic regression was then performed to test the association between socio-demographic factors and clusters of MLTC trajectory, with the "no-LTC" cluster as the reference. Binary logistic regression was also performed to quantify the association between the clusters of MLTC trajectory membership and all-cause mortality, adjusting for all the covariates mentioned above. A squared term of age was included in the model to account for the non-linear relationship

between age and mortality. The significance level was set at a p-value <0.05, and all analyses were performed using STATA M.P v17.0.

Patient and Public Involvement

This study was conducted as part of a wider mixed-methods programme of research exploring the potential of machine learning to address multimorbidity through the 'clustering' of patients based on similarities in clinical and social care needs. Patient and public involvement has been incorporated throughout the wider research programme from the initial inception, design, and dissemination of findings. The initial results and the final written draft of the study submitted in this manuscript were shared with our programme's patient and public representative.

Results

Participants' characteristics

We identified 15,091 individuals participating in at least one wave during the follow-up period (The flow of participants through the study is shown in **Figure 1**). Six participants were excluded, as they had no information on MLTC. After excluding those (n = 123) with missing data on covariates, 14,962 people were included in the final analysis. The mean (SD) age of the cohort was 61.9 (11) years; most were females (53.5%), whites (96.5%), with educational attainment of upper secondary or vocational (43.1%), employed (56.8%), and married or had a partner (72%) (**Table 1**).

Table 1. Participants' characteristics overall and stratified by clusters of MLTC trajectory.

	Total	No-LTC	Single-LTC	Evolving MLTC	Moderate MLTC	High MLTC
	14962 (100%)	2826 (18.9%)	4802 (32.1%)	3739 (25.0%)	2532 (16.9%)	1063 (7.1%)
Age, mean (SD)	61.9 (11)	56.0 (9.1)	60.0 (10.0)	62.9 (10.8)	67.1 (10.7)	69.8 (10.4)
Sex						
Male	6951 (46.5)	1402 (20.2)	2361 (34.0)	1675 (24.1)	1050 (15.1)	463 (6.7)
Female	8011 (53.5)	1424 (17.8)	2441 (30.5)	2064 (25.8)	1482 (18.5)	600 (7.5)
Ethnicity						
White	14440 (96.5)	2726 (18.9)	4629 (32.1)	3618 (25.1)	2451 (17.0)	1016 (7.0)
Non-white	522 (3.5)	100 (19.2)	173 (33.1)	121 (23.2)	81 (15.5)	47 (9.0)
Education						
Less than upper secondary	5107 (34.1)	629 (12.3)	1417 (27.8)	1326 (26.0)	1136 (22.2)	599 (11.7)
Upper secondary, vocational	6444 (43.1)	1399 (21.7)	2186 (33.9)	1609 (25.0)	941 (14.6)	309 (4.8)
Tertiary	2277 (15.2)	626 (27.5)	859 (37.7)	497 (21.8)	227 (10.0)	68 (3.0)
Others	1134 (7.6)	172 (15.2)	340 (30.0)	307 (27.1)	228 (20.1)	87 (7.7)
Employment						
Paid employment	8500 (56.8)	895 (10.5)	2278 (26.8)	2333 (27.5)	2033 (23.9)	961 (11.3)
Unemployed	6462 (43.2)	1931 (30.0)	2524 (39.1)	1406 (21.8)	499 (7.7)	102 (1.6)
Marital status						
Never married	789 (5.3)	148 (18.8)	268 (34.0)	189 (24.0)	131 (16.6)	53 (6.7)
Married/partner	10766 (72.0)	2282 (21.2)	3635 (33.8)	2674 (24.8)	1566 (14.6)	609 (5.7)
Separated/divorced/widowed	3407 (22.8)	396 (11.6)	899 (26.4)	876 (25.7)	935 (27.5)	401 (11.8)

Clusters of MLTC trajectory

We examined one to six clusters in the model to determine the optimal cluster number. Five clusters were selected based on the model fit indicators (**Supplementary Table 1**) and the interpretability of classified trajectories.

Participants displayed high posterior probabilities of belonging to their assigned clusters ranging from 0.88 to 0.97 across the five clusters. The "no-LTC" cluster (18.57%) was dominated by people (95.2%) without any record of the examined long-term condition during the follow-up, and the "single-LTC" cluster (31.21%) consisted of those who did not develop MLTC during the study period but may have had one long-term condition (**Figure 2**). The "evolving MLTC" cluster (25.82%) was characterised by people who progressed from less than two long-term conditions at baseline to two, three, or four by the end of follow-up. Two clusters had MLTC profiles which showed increasing numbers of long-term conditions ("moderate MLTC" (17.12%) and "high MLTC" (7.27%)). Those in these clusters started with MLTC and continued to have higher counts of long-term conditions in the following periods.

Clusters of MLTC trajectory and socio-demographic characteristics

Increasing age was consistently associated with all MLTC clusters, compared to the "no-LTC" cluster (**Table 1 & 2**). Females had higher odds (aOR = 1.13; 95%CI 1.01 to 1.27) of being in the "moderate MLTC" clusters than females. Being non-white increased the odds of belonging to the "high MLTC" cluster by 2.04 times (aOR = 2.04; 95%CI 1.40 to 3) compared to whites. Higher education and paid employment decreased the odds of belonging to any of the four clusters than those with less than upper secondary education and unemployment, respectively.

Table 2. The association between socio-demographic factors and clusters of MLTC trajectories.

Socio-demographics	Adjusted OR (95%CI) (Reference: No-LTC)			
	Single-LTC	**Evolving MLTC**	**Moderate MLTC**	**High MLTC**
Age	1.04 (1.03-1.04)	1.05 (1.05-1.06)	1.07 (1.06-1.08)	1.08 (1.07-1.09)
Sex				
Male	Reference	Reference	Reference	Reference
Female	1.00 (0.91-1.10)	1.11 (0.99-1.23)	1.13 (1.01-1.27)	0.95 (0.81-1.11)
Ethnicity				
White	Reference	Reference	Reference	Reference
Non-white	1.17 (0.91-1.50)	1.13 (0.85-1.49)	1.36 (1.00-1.86)	2.04 (1.40-3.00)
Education				
Less than upper secondary	Reference	Reference	Reference	Reference
Upper secondary, vocational	0.92 (0.81-1.03)	0.87 (0.77-0.99)	0.77 (0.67-0.88)	0.53 (0.45-0.64)
Tertiary	0.84 (0.72-0.97)	0.68 (0.58-0.80)	0.51 (0.42-0.62)	0.33 (0.25-0.45)
Others	1.01 (0.83-1.25)	1.04 (0.84-1.28)	0.99 (0.79-1.25)	0.76 (0.57-1.02)
Employment				
Unemployed	Reference	Reference	Reference	Reference
Paid employment	0.79 (0.70-0.89)	0.54 (0.4 8-0.62)	0.35 (0.31-0.40)	0.17 (0.13-0.21)
Marital status				
Never married	Reference	Reference	Reference	Reference
Married/partner	0.85 (0.69-1.04)	0.90 (0.72-1.14)	0.80 (0.62-1.03)	0.82 (0.58-1.15)
Separated/divorced/widowed	0.97 (0.77-1.23)	1.14 (0.88-1.48)	1.27 (0.96-1.68)	1.41 (0.98-2.04)

Abbreviation: MLTC, Multiple Long-Term Conditions

Clusters of MLTC trajectory and all-cause mortality

The "Single-LTC" (aOR = 1.81; 95% CI 1.21 to 2.73), the "evolving MLTC" (aOR = 2.26; 95% CI 1.51 to 3.38), the "moderate MLTC" (aOR = 2.62; 95% CI 1.75 to 3.94), and the "high MLTC" (aOR = 4.03; 95% CI 2.64 to 6315) clusters were significantly associated with higher all-cause mortality, compared with the people in the "no-LTC" cluster (**Table 3**).

Table 3. Association between clusters of MLTC trajectory and all-cause mortality.

	Alive (14310, 95.6%)	Dead (652, 4.4%)	Unadjusted OR (95%CI)	Adjusted[1] OR (95%CI)	p-value[2]
Trajectory cluster					
No-LTC	2796 (98.9)	30 (1.1)	Reference	Reference	<0.0001
Single-LTC	4668 (97.2)	134 (2.8)	2.69 (1.81-4.01)	1.81 (1.21-2.73)	
Evolving MLTC	3566 (95.4)	174 (4.6)	4.59 (3.10-6.78)	2.26 (1.51-3.38)	
Moderate MLTC	2349 (92.8)	183 (7.2)	7.22 (4.89-10.7)	2.62 (1.75-3.94)	
High MLTC	931 (87.6)	132 (12.4)	13.6 (9.11-20.3)	4.03 (2.64-6.15)	

[1]Adjusted for age, sex, ethnicity, education, employment status, and marital status. Age was included in the model as a squared term.
[2] p-value for trend.
Abbreviation: MLTC, multiple long-term condition.

Discussion

This study examined clusters of MLTC based on the accumulation of conditions as trajectories over time, their associations with sociodemographic factors, and all-cause mortality among older adults in England. We identified five distinct clusters that can be described as "no-LTC", "Single-LTC", "evolving MLTC", "moderate MLTC", and "high MLTC". We observed that the accumulation of MLTC over time progresses differently among older adults with distinction by sex, ethnicity, educational level, and employment status. Specifically, females and ethnic minorities showed faster/steeper progression towards increased numbers of MLTC, whereas higher education and paid employment had a protective effect on the increase of the accumulation of MLTC.

An interesting finding was that clusters with different initial levels and rates of change in MLTC indicating individual differences in the process of health deterioration. This is in line with previous studies that identified different rates of MLTC (25). Those with persistently high levels of multimorbidity have been also similarly identified in other population (26). However, consistent with the literature (25,26), we did not find any trajectories that indicated improvement in health over time (i.e., decreasing levels of MLTC). This may be due to the difficulty of recovery from long-term conditions among older adults.

The faster/steeper progression observed towards increased numbers of MLTC in females is in line with previous literature, which found that the accumulation of long-term conditions was more severe for older females (27). An explanation can be that females tend to live longer than males, and as a result, they are more likely to develop chronic conditions associated with ageing, such as arthritis and dementia. Clinicians should consider that females are at greater likelihood of MLTC. The faster development of MLTC in ethnic minorities can be explained by evidence suggesting that access and engagement with healthcare are limited for some population groups, often on the basis of ethnicity. Specifically, a review from NHS Race and Health Observatory (28) suggests that there are 'clear barriers' for people from minority ethnic backgrounds to seek help for mental health problems, and another research has also found lower access to cancer screening in the UK (29). Socioeconomic risk factors are known to be associated with MLTC (30). Our findings support the role of higher educational attainment, a major socioeconomic risk factor, on MLTC prevention. Targeting education inequality is expected to lead further to the restriction of worsening MLTC. The effect of educational attainment on MLTC is thought to be explained by other risk factors that may mediate this association, such as body mass index and smoking.

Over their life course, individuals develop MLTC. It is necessary to challenge the common statement that MLTC is inevitable in an ageing society. To do this, the focus on MLTC should shift from sole management of high-risk

older individuals to include integrated population-level prevention strategies throughout the life course to address the drivers of MLTC. Programs that bridge multiple clinical specialities and healthcare units should be developed to focus on single individuals, their specific clinical profiles, and their specific clinical trajectories (31). Knowledge of how long-term conditions cluster, and especially how the status of MLTC can change over subsequent years, helps not only in understanding the complexity and dynamic evolution of MLTC clusters but also in supporting clinicians who manage co-occurring long-term conditions and health policymakers who plan care resources use.

This is the first study to examine trajectories of MLTC with a view to stratifying within MLTC to identify those at greatest risk among older adults in England. The main strength of the current study is the use of a large dataset, assessing longitudinal data to examine MLTC trajectories and a dataset that is nationally representative of people aged 50 years and older, including a wide range of long-term conditions and sociodemographics. However, the results of this study should be interpreted with some caution. First, the measurement of MLTC was limited to ten long-term conditions that was all of what was available in ELSA, which may not be exhaustive of all possible long-term conditions. Findings could be different if more long-term conditions are considered. Second, although we examined the correlates of MLTC trajectories using the variables measured at the baseline (wave 2), we cannot conclude on the directionality of the associations. Another limitation is that because our study utilised a longitudinal design that examined age-related changes, there may be inherent confounding of age and period effects. These effects could not be disentangled in this study due to the nature of our data. Lastly, the probability of being in a cluster membership is based on model assignment, which can lead to misclassification bias.

In conclusion, MLTC trajectories of older adults are characterised by dynamism but can still be tracked over time. Considering MLTC clusters will enable future researchers and practitioners to provide evidence in identifying older adults in England at a higher risk of worsening MLTC over time and further tailoring effective interventions for at-risk individuals. Targeting females and ethnic minorities is important for MLTC prevention. Higher levels of education can also lead to a further decrease in the number of long-term conditions. Policymakers should commit to increasing MLTC awareness.

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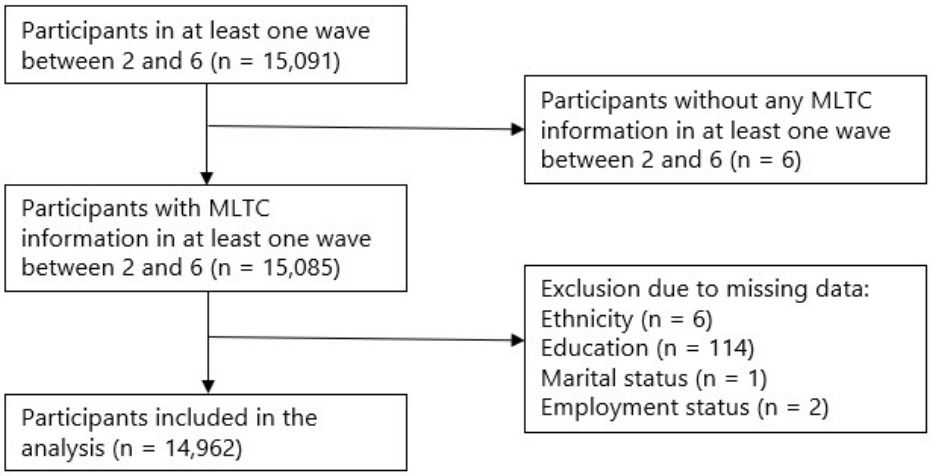
Figure legends

Figure 1. Flow chart of participants selection. MLTC, multiple long-term conditions.

Figure 2. Clusters of MLTC trajectories over time (wave 2 to 6) in the English Longitudinal Study of Aging (ELSA) study. The solid lines represent the estimated mean count of MLTC profiles for the five clusters. The "no-LTC" cluster included people who did not have any of the examined long-term conditions; the "single-LTC" cluster included those who did not develop MLTC but may have had one long-term condition; the ''evolving MLTC'' cluster included those who developed MLTC lately; the ''moderate MLTC'' cluster included those who started with the lower number of MLTC and developed further long-term conditions; the ''high MLTC'' cluster consisted of those who started with the higher number of MLTC and developed additional long-term conditions. Abbreviation: MLTC, Multiple long-term conditions.



Flow chart of participants selection. MLTC, multiple long-term conditions.

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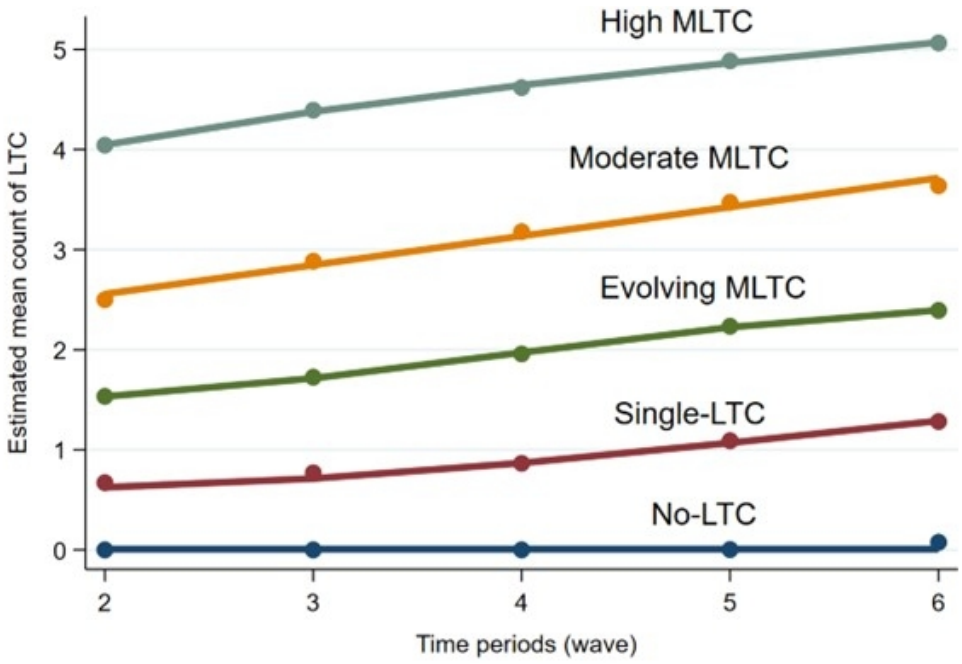

Clusters of MLTC trajectories over time (wave 2 to 6) in the English Longitudinal Study of Aging (ELSA) study. The solid lines represent the estimated mean count of MLTC profiles for the five clusters. The "no-LTC" cluster included people who did not have any of the examined long-term conditions; the "single-LTC" cluster included those who did not develop MLTC but may have had one long-term condition; the "evolving MLTC" cluster included those who developed MLTC lately; the "moderate MLTC" cluster included those who started with the lower number of MLTC and developed further long-term conditions; the "high MLTC" cluster consisted of those who started with the higher number of MLTC and developed additional long-term conditions. Abbreviation: MLTC, Multiple long-term conditions.

155x102mm (96 x 96 DPI)

Trajectories of multiple long-term conditions and mortality in older adults: A retrospective cohort study using English Longitudinal Study of Ageing (ELSA)

Christos V. Chalitsios[1], Cornelia Santoso[1], Yvonne Nartey[1], Nusrat Khan[1], Glenn Simpson[1], Nazrul Islam[1], Beth Stuart[2], Andrew Farmer[3], Hajira Dambha-Miller[1]

Supplements

Supplementary Table 1. Statistical parameters of the optimal number of clusters selection.

Number of groups	Group membership		Trajectory shapes	BIC (sample size=15085)	APPA	OCC
1	(1)	100	3	-85493.21	1	N/A
2	(1)	53.49	33	-73870.19	0.94	12.80
	(2)	46.51			0.94	17.71
3	(1)	21.77	333	-63524.35	0.97	105.25
	(2)	53.83			0.96	18.03
	(3)	24.40			0.95	67.92
4	(1)	19.24	3333	-59262.14	0.96	93.69
	(2)	36.07			0.93	24.44
	(3)	32			0.90	19.03
	(4)	12.69			0.96	172.34
5	(1)	19.35	33333	-56474.28	0.97	119.07
	(2)	30.77			0.90	18.95
	(3)	25.43			0.88	23.76
	(4)	17.15			0.90	44.02
	(5)	7.31			0.95	284.50
5	(1)	18.57	03311	-57000.83	0.96	109.69
	(2)	31.21			0.90	19.32
	(3)	25.82			0.87	20.91
	(4)	17.12			0.90	44.32
	(5)	7.27			0.95	259.29

Note: Trajectory shapes (0=intercept, 1=linear, 2=quadratic, 3=cubic); BIC = Bayesian Information Criterion; APPA = average posterior probability assignment; OCC = odds of a correct classification according to maximum posterior probability group.

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	6
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6, 7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*6*
Bias	9	Describe any efforts to address potential sources of bias	6, 7
Study size	10	Explain how the study size was arrived at	NA
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	7
		(*c*) Explain how missing data were addressed	7
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	7
		(*e*) Describe any sensitivity analyses	7

Continued on next page

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9
		(b) Give reasons for non-participation at each stage	9
		(c) Consider use of a flow diagram	9
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9, 10
		(b) Indicate number of participants with missing data for each variable of interest	9, 10
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	NA
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	*NA*
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	*13*
		Cross-sectional study—Report numbers of outcome events or summary measures	*NA*
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	13
		(*b*) Report category boundaries when continuous variables were categorized	13
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	14
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	15
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14, 15
Generalisability	21	Discuss the generalisability (external validity) of the study results	14, 15
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	2

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Trajectories in long-term conditions accumulation and mortality in older adults: A group-based trajectory modelling approach using the English Longitudinal Study of Ageing

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Trajectories in long-term conditions accumulation and mortality in older adults: A group-based trajectory modelling approach using the English Longitudinal Study of Ageing

Christos V. Chalitsios[1], Cornelia Santoso[1], Yvonne Nartey[1], Nusrat Khan[1], Glenn Simpson[1], Nazrul Islam[1], Beth Stuart[2], Andrew Farmer[3], Hajira Dambha-Miller[1]

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Authors' contribution

All authors (CVC, CS, YN, NK, GS, NI, BS, AF, and HDM) contributed to the study's conception and design. Data acquisition, data management, and analysis were performed by CVC, CS, and YN. All authors (CVC, CS, YN, NK, GS, NI, BS, AF, and HDM) contributed to the interpretation of the fundings. The first draft of the manuscript was written by CVC, and all authors (CS, YN, NK, GS, NI, BS, AF, and HDM) commented on previous versions of the manuscript. All authors (CVC, CS, YN, NK, GS, NI, BS, AF, and HDM) read and approved the final manuscript.

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Competing interests

None declared.

Ethics approval

Ethical approval for the study was provided by the Faculty of Medicine Ethics Committee, University Hospital Southampton, (reference number 67953).

Data availability statement

ELSA data were available through the UK Data Archive and are widely available to access in this way; as such, our study data will not be made available for access.

Abstract

Objectives

To classify older adults into clusters based on accumulating long-term conditions (LTC) as trajectories, characterise clusters, and quantify their associations with all-cause mortality.

Design

We conducted a cross-sectional study using the English Longitudinal Study of Ageing (ELSA) over nine years (n=15,091 aged 50 years and older). Group-based trajectory modelling was used to classify people into clusters based on accumulating LTC over time. Derived clusters were used to quantify the associations between trajectory memberships, sociodemographic characteristics, and all-cause mortality by conducting regression models.

Results

Five distinct clusters of accumulating LTC trajectories were identified and characterised as: "no-LTC" (18.57%), "single-LTC" (31.21%), "evolving multimorbidity" (25.82%), "moderate multimorbidity" (17.12%), and "high multimorbidity" (7.27%). Increasing age was consistently associated with a larger number of LTC. Ethnic minorities (aOR = 2.04; 95%CI 1.40 to 3.00) were associated with the "high multimorbidity" cluster. Higher education and paid employment were associated with a lower likelihood of progression over time towards an increased number of LTC. All the clusters had higher all-cause mortality than the "no-LTC" cluster.

Conclusions

The development of multimorbidity in the number of conditions over time follows distinct trajectories. These are determined by non-modifiable (age, ethnicity) and modifiable factors (education and employment). Stratifying risk through clustering will enable practitioners to identify older adults with a higher likelihood of worsening LTC over time to tailor effective interventions to prevent mortality.

Keywords

Multimorbidity, trajectories, mortality, English Longitudinal Study on Ageing (ELSA), older adults.

Strengths and limitations

- The main strength of the current study is the use of a large and nationally representative dataset of people aged 50 years and older assessing longitudinal data to examine long-term conditions (LTC) trajectories.
- The measurement was limited to ten long-term conditions, based on what was available in the English Longitudinal Study of Ageing, which may not be exhaustive of all possible long-term conditions.

Introduction

Globally, the average life expectancy has risen from 66.8 years in 2000 to 73.4 years in 2019 (1). By 2050, the population over 60 and 80 years will reach 2.1 billion and 426 million, respectively (2,3). This rise in longevity raises the risk of developing multimorbidity, which is the co-occurrence of two or more chronic diseases (4). The worldwide prevalence of multimorbidity among older people is reported to be between 55-98% (5), and in the UK, this is expected to rise from 54% in 2015 to 68% in 2035 (2). Multimorbidity represents an ongoing challenge for healthcare systems because people with multimorbidity have worse care outcomes, including functional limitation and disability (6,7), higher service utilisation (5), mortality (8) and poorer quality of life (5). Management of multimorbidity places considerable economic and logistical burdens on services traditionally organised around single disease models (6).

While there is ample evidence of identified risk factors (7,9) and adverse care outcomes for multimorbidity cross-sectionally to help understand the prevalence and patterns of LTC, they provide little evidence on temporal elements, including patterns of LTC development over time (8,10,11). There is a paucity of longitudinal approaches examining patterns in the accumulation of diseases (12). Understanding the trajectory that an older adult will follow in the progression towards an increased number of LTC could help predict when intervention is needed and inform targeted and earlier preventive interventions. To address this gap in the literature, this study aimed to classify older adults with LTC into clusters based on the accumulation of conditions as trajectories over time, characterise these clusters, and quantify the association between derived clusters and all-cause mortality.

Methods

Data source and study population

The English Longitudinal Study of Aging (ELSA) is a longitudinal cohort of people aged 50 years or older living in England (13). The ELSA cohort profile has been described in detail elsewhere (14). In summary, it included 12,099 people at study entry in 2002 with follow-up every two years with self-report questionnaires on physical and mental health, well-being, finances, and attitudes around ageing over time. Four yearly additional nurse visits collected objective data such as anthropometric data (13,15). The ELSA is an open cohort, and refreshment samples were added depending on the proportional age requirement for ELSA, so the total number of people in this cohort was 15,091. Our baseline was wave 2 (2004/5) of the ELSA cohort, the first collecting time point in the study of long-term conditions with a nine-year follow-up to wave 6 (2012/3), the most recent wave with available data on all-cause mortality status.

Multimorbidity

Multimorbidity was defined as the presence of two or more of the following ten conditions: hypertension, diabetes, cancer, lung disease, cardiovascular disease, stroke, mental health disorder, arthritis, Parkinson's disease, and dementia. These are self-reported by patients, relatives or carers and verified by nurse visits (13). These ten conditions were available within the ELSA dataset based on our earlier work to define multimorbidity (16,17). After statistical consideration due to the small sample size and clinical discussion, we grouped some of the conditions as follows: people with depression were combined with mental health disorders, asthma was combined with lung disease, Alzheimer's within dementia, and finally, those with heart attack, angina, heart murmur, abnormal heart rhythm and congestive heart failure combined into those with cardiovascular disease.

All-cause mortality

All-cause mortality was reported by end-of-life interviews on waves 2, 3, 4 and 6 with relatives and friends after death.

Covariates

Sociodemographic variables included were age, sex, ethnicity (defined as white/non-white), education, employment, and marital status. The education variable was categorised into four groups: less than upper secondary level, upper secondary and vocational level, tertiary level, and others. Employment status was categorised into 'paid employment and 'unemployed'. Marital status was categorised into three groups: never married, married/having a partner, and separated/divorced/widowed. These covariates were based on the baseline. We used data provided in the nearest subsequent waves if they were missing at baseline.

Statistical analysis

Descriptive statistics were used to summarise participants' characteristics. We used group-based trajectory modelling (GBTM) to classify older adults with LTC into clusters based on accumulating conditions as trajectories over time. GBTM is a finite mixture model applying maximum likelihood to identify a cluster of people following similar trajectories by the number of conditions over time (18). This model assumes the same error variance for all clusters and time points and treats missing data as 'missing at random' (19). The procedure for selecting the best model included two steps: identifying the ideal number of trajectory groups and determining polynomial orders to represent the shapes of the trajectories (18,20). Based on the observed distribution, we employed a censored normal model to specify LTC (21,22). We fitted the models iteratively, starting with one and increasing up to a maximum of six clusters that would be useful in a clinical setting (20). We selected the number of trajectory clusters based on the following criteria: the lowest Bayesian Information Criterion (BIC) value, Average Posterior Probability Assignment (APPA) >70%, Odds of a Correct Classification (OCC) >5, the percentage of participants in each trajectory groups >5% of the total sample (if less than 5% it is unlikely to be conceptually useful for clinical practice) (22–24). We first used cubic polynomials to characterise the shape of the clusters of LTC trajectories. However, after selecting the number of trajectories, we refitted the model to use lower-order terms when the higher-order terms were insignificant (20). We then assigned individuals to the trajectory group based on the maximum posterior probability (20). Multinomial logistic regression was then performed to test the association between socio-demographic factors and clusters of LTC trajectory, with the "no-LTC" cluster as the reference. Binary logistic regression was also performed to quantify the association between the clusters of LTC trajectory membership and all-cause mortality, adjusting for all the covariates mentioned above. A squared term of age was included in the model to account for the non-linear relationship between age and mortality. The significance level was set at a p-value <0.05, and all analyses were performed using STATA M.P v17.0.

Patient and Public Involvement

This study was conducted as part of a wider mixed-methods programme of research exploring the potential of machine learning to address multimorbidity through the 'clustering' of patients based on similarities in clinical and social care needs. Patient and public involvement has been incorporated throughout the wider research programme from the initial inception, design, and dissemination of findings. The initial results and the final written draft of the study submitted in this manuscript were shared with our programme's patient and public representative.

Results

Participants' characteristics

There were 9,170 participants in wave 2 and we identified 15,091 individuals participating in at least one wave during the follow-up period (The flow of participants through the study is shown in **Figure 1**). Six participants were excluded, as they had no information on LTC. After excluding those (n = 123) with missing data on covariates, 14,962 people were included in the final analysis. The mean (SD) age of the cohort was 61.9 (11) years; most were females (53.5%), whites (96.5%), with educational attainment of upper secondary or vocational (43.1%), employed (56.8%), and married or had a partner (72%) (**Table 1**).

Table 1. Participants' characteristics overall and stratified by clusters of LTC trajectories.

	Total	No-LTC	Single-LTC	Evolving multimorbidity	Moderate multimorbidity	High multimorbidity
	14962 (100%)	2826 (18.9%)	4802 (32.1%)	3739 (25.0%)	2532 (16.9%)	1063 (7.1%)
Age, mean (SD)	61.9 (11)	56.0 (9.1)	60.0 (10.0)	62.9 (10.8)	67.1 (10.7)	69.8 (10.4)
Sex						
Male	6951 (46.5)	1402 (20.2)	2361 (34.0)	1675 (24.1)	1050 (15.1)	463 (6.7)
Female	8011 (53.5)	1424 (17.8)	2441 (30.5)	2064 (25.8)	1482 (18.5)	600 (7.5)
Ethnicity						
White	14440 (96.5)	2726 (18.9)	4629 (32.1)	3618 (25.1)	2451 (17.0)	1016 (7.0)
Non-white	522 (3.5)	100 (19.2)	173 (33.1)	121 (23.2)	81 (15.5)	47 (9.0)
Education						
Less than upper secondary	5107 (34.1)	629 (12.3)	1417 (27.8)	1326 (26.0)	1136 (22.2)	599 (11.7)
Upper secondary, vocational	6444 (43.1)	1399 (21.7)	2186 (33.9)	1609 (25.0)	941 (14.6)	309 (4.8)
Tertiary	2277 (15.2)	626 (27.5)	859 (37.7)	497 (21.8)	227 (10.0)	68 (3.0)
Others	1134 (7.6)	172 (15.2)	340 (30.0)	307 (27.1)	228 (20.1)	87 (7.7)
Employment						
Paid employment	8500 (56.8)	895 (10.5)	2278 (26.8)	2333 (27.5)	2033 (23.9)	961 (11.3)
Unemployed	6462 (43.2)	1931 (30.0)	2524 (39.1)	1406 (21.8)	499 (7.7)	102 (1.6)
Marital status						
Never married	789 (5.3)	148 (18.8)	268 (34.0)	189 (24.0)	131 (16.6)	53 (6.7)
Married/partner	10766 (72.0)	2282 (21.2)	3635 (33.8)	2674 (24.8)	1566 (14.6)	609 (5.7)
Separated/divorced/widowed	3407 (22.8)	396 (11.6)	899 (26.4)	876 (25.7)	935 (27.5)	401 (11.8)

Note: The percentages in the "total" column are presented vertically, whereas in the other five columns horizontally.

Clusters of LTC trajectory

We examined one to six clusters in the model to determine the optimal cluster number. Five clusters were selected based on the model fit indicators (**Supplementary Table 1**) and the interpretability of classified trajectories.

Participants displayed high posterior probabilities of belonging to their assigned clusters ranging from 0.88 to 0.97 across the five clusters. The "no-LTC" cluster (18.57%) was dominated by people (95.2%) without any record of the examined long-term condition during the follow-up, and the "single-LTC" cluster (31.21%) consisted of those who did not develop multimorbidity during the study period but may have had one long-term condition (**Figure 2**). The "evolving multimorbidity" cluster (25.82%) was characterised by people who progressed from less than two long-term conditions at baseline to two, three, or four by the end of follow-up. Two clusters had multimorbidity profiles which showed increasing numbers of long-term conditions ("moderate multimorbidity" (17.12%) and "high multimorbidity" (7.27%)). Those in these clusters started with multimorbidity and continued to have higher counts of long-term conditions in the following periods.

Clusters of LTC trajectory and socio-demographic characteristics

Increasing age was consistently associated with all LTC clusters, compared to the "no-LTC" cluster (**Table 1 & 2**). Females had higher odds (aOR = 1.13; 95%CI 1.01 to 1.27) of being in the "moderate multimorbidity" clusters than males. Being non-white increased the odds of belonging to the "high multimorbidity" cluster by 2.04 times (aOR = 2.04; 95%CI 1.40 to 3) compared to whites. Higher education and paid employment decreased the odds of belonging to any of the four clusters than those with less than upper secondary education and unemployment, respectively.

Table 2. The association between socio-demographic factors and clusters of LTC trajectories.

	Adjusted OR (95%CI) (Reference: No-LTC)			
Socio-demographics	**Single-LTC**	**Evolving multimorbidity**	**Moderate multimorbidity**	**High multimorbidity**
Age	1.04 (1.03-1.04)	1.05 (1.05-1.06)	1.07 (1.06-1.08)	1.08 (1.07-1.09)
Sex				
Male	Reference	Reference	Reference	Reference
Female	1.00 (0.91-1.10)	1.11 (0.99-1.23)	1.13 (1.01-1.27)	0.95 (0.81-1.11)
Ethnicity				
White	Reference	Reference	Reference	Reference
Non-white	1.17 (0.91-1.50)	1.13 (0.85-1.49)	1.36 (1.00-1.86)	2.04 (1.40-3.00)
Education				
Less than upper secondary	Reference	Reference	Reference	Reference
Upper secondary, vocational	0.92 (0.81-1.03)	0.87 (0.77-0.99)	0.77 (0.67-0.88)	0.53 (0.45-0.64)
Tertiary	0.84 (0.72-0.97)	0.68 (0.58-0.80)	0.51 (0.42-0.62)	0.33 (0.25-0.45)
Others	1.01 (0.83-1.25)	1.04 (0.84-1.28)	0.99 (0.79-1.25)	0.76 (0.57-1.02)
Employment				
Unemployed	Reference	Reference	Reference	Reference
Paid employment	0.79 (0.70-0.89)	0.54 (0.4 8-0.62)	0.35 (0.31-0.40)	0.17 (0.13-0.21)
Marital status				
Never married	Reference	Reference	Reference	Reference
Married/partner	0.85 (0.69-1.04)	0.90 (0.72-1.14)	0.80 (0.62-1.03)	0.82 (0.58-1.15)
Separated/divorced/widowed	0.97 (0.77-1.23)	1.14 (0.88-1.48)	1.27 (0.96-1.68)	1.41 (0.98-2.04)

Abbreviation: LTC, Long-Term Conditions

Clusters of LTC trajectory and all-cause mortality

The "Single-LTC" (aOR = 1.81; 95% CI 1.21 to 2.73), the "evolving multimorbidity" (aOR = 2.26; 95% CI 1.51 to 3.38), the "moderate multimorbidity" (aOR = 2.62; 95% CI 1.75 to 3.94), and the "high multimorbidity" (aOR = 4.03; 95% CI 2.64 to 6315) clusters were significantly associated with higher all-cause mortality, compared with the people in the "no-LTC" cluster (**Table 3**).

Table 3. Association between clusters of LTC trajectory and all-cause mortality.

	Alive (14310, 95.6%)	Dead (652, 4.4%)	Unadjusted OR (95%CI)	Adjusted[1] OR (95%CI)	p-value[2]
Trajectory cluster					
No-LTC	2796 (98.9)	30 (1.1)	Reference	Reference	<0.0001
Single-LTC	4668 (97.2)	134 (2.8)	2.69 (1.81-4.01)	1.81 (1.21-2.73)	
Evolving multimorbidity	3566 (95.4)	174 (4.6)	4.59 (3.10-6.78)	2.26 (1.51-3.38)	
Moderate multimorbidity	2349 (92.8)	183 (7.2)	7.22 (4.89-10.7)	2.62 (1.75-3.94)	
High multimorbidity	931 (87.6)	132 (12.4)	13.6 (9.11-20.3)	4.03 (2.64-6.15)	

[1]Adjusted for age, sex, ethnicity, education, employment status, and marital status. Age was included in the model as a squared term.

[2] p-value for trend.

Abbreviation: LTC, long-term condition.

Discussion

This study examined clusters of LTC based on the accumulation of conditions as trajectories over time, their associations with sociodemographic factors, and all-cause mortality among older adults in England. We identified five distinct clusters that can be described as "no-LTC", "single-LTC", "evolving multimorbidity", "moderate multimorbidity", and "high multimorbidity". We observed that the accumulation of LTC over time progresses differently among older adults with distinction by ethnicity, educational level, and employment status. Specifically, ethnic minorities showed faster/steeper progression towards increased numbers of LTC, whereas higher education and paid employment had a protective effect on the increase in the accumulation of LTC.

An interesting finding was that clusters with different initial levels and rates of change in LTC indicating individual differences in the process of health deterioration. This is in line with previous studies that identified different rates of LTC (25). Those with persistently high levels of multimorbidity have also been similarly identified in other populations (26). However, consistent with the literature (25,26), we did not find any trajectories that indicated improvement in health over time (i.e., decreasing levels of LTC). This may be due to the difficulty of recovery from long-term conditions among older adults or due to the older population as it is anticipated that the mean number of conditions will increase as we follow them over time (waves).

The faster/steeper progression observed towards increased numbers of LTC in females is in line with previous literature, which found that the accumulation of long-term conditions was more severe for older females (27). An explanation can be that females tend to live longer than males, and as a result, they are more likely to develop chronic conditions associated with ageing, such as arthritis and dementia. The faster development of MLTC in ethnic minorities can be explained by evidence suggesting that access and engagement with healthcare are limited for some population groups, often on the basis of ethnicity. Specifically, a review from NHS Race and Health Observatory (28) suggests that there are 'clear barriers' for people from minority ethnic backgrounds to seek help for mental health problems, and another research has also found lower access to cancer screening in the UK (29). Socioeconomic risk factors are known to be associated with MLTC (30). Our findings support the role of higher educational attainment, a major socioeconomic risk factor, on MLTC prevention. Targeting education inequality is expected to lead further to the restriction of worsening MLTC. The effect of educational attainment on MLTC is thought to be explained by other risk factors that may mediate this association, such as body mass index and smoking.

Over their life course, individuals develop MLTC. It is necessary to challenge the common statement that MLTC is inevitable in an ageing society. To do this, the focus on MLTC should shift from sole management of high-risk

older individuals to include integrated population-level prevention strategies throughout the life course to address the drivers of MLTC. Programs that bridge multiple clinical specialities and healthcare units should be developed to focus on single individuals, their specific clinical profiles, and their specific clinical trajectories (31). Knowledge of how long-term conditions cluster, and especially how the status of MLTC can change over subsequent years, helps not only in understanding the complexity and dynamic evolution of MLTC clusters but also in supporting clinicians who manage co-occurring long-term conditions and health policymakers who plan care resources use.

This is the first study to examine trajectories of MLTC with a view to stratifying within MLTC to identify those at greatest risk among older adults in England. The main strength of the current study is the use of a large dataset, assessing longitudinal data to examine MLTC trajectories and a dataset that is nationally representative of people aged 50 years and older, including a wide range of long-term conditions and sociodemographics. However, the results of this study should be interpreted with some caution. First, the measurement of MLTC was limited to ten long-term conditions that was all of what was available in ELSA, which may not be exhaustive of all possible long-term conditions. Findings could be different if more long-term conditions are considered. Second, although we examined the correlates of MLTC trajectories using the variables measured at the baseline (wave 2), we cannot conclude on the directionality of the associations. Another limitation is that because our study utilised a longitudinal design that examined age-related changes, there may be inherent confounding of age and period effects. These effects could not be disentangled in this study due to the nature of our data. Lastly, the probability of being in a cluster membership is based on model assignment, which can lead to misclassification bias.

In conclusion, LTC trajectories of older adults are characterised by dynamism but can still be tracked over time. Considering LTC clusters has potential to enable future researchers and practitioners to provide evidence in identifying older adults in England at a higher risk of worsening MLTC over time and further tailoring effective interventions for at-risk individuals. Targeting ethnic minorities is important for multimorbidity prevention. Higher levels of education can also lead to a further decrease in the number of long-term conditions. Policymakers should commit to increasing MLTC awareness.

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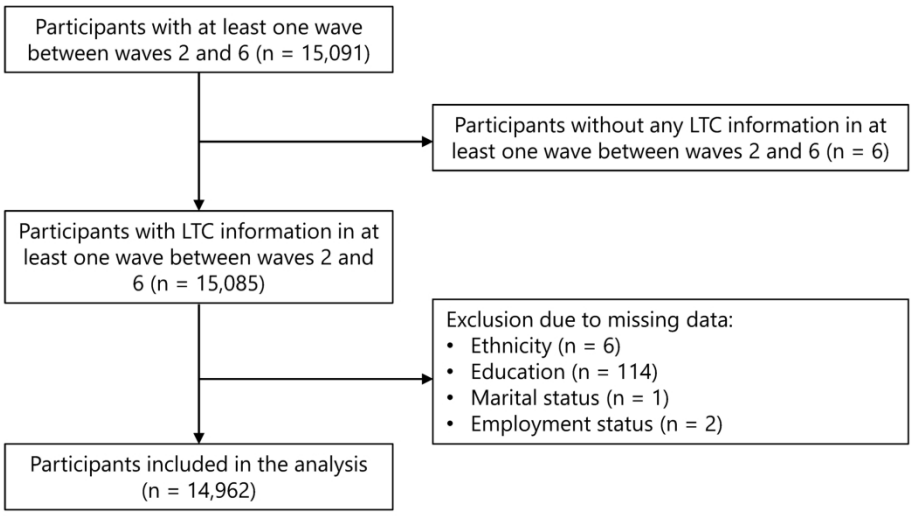
Figure legends

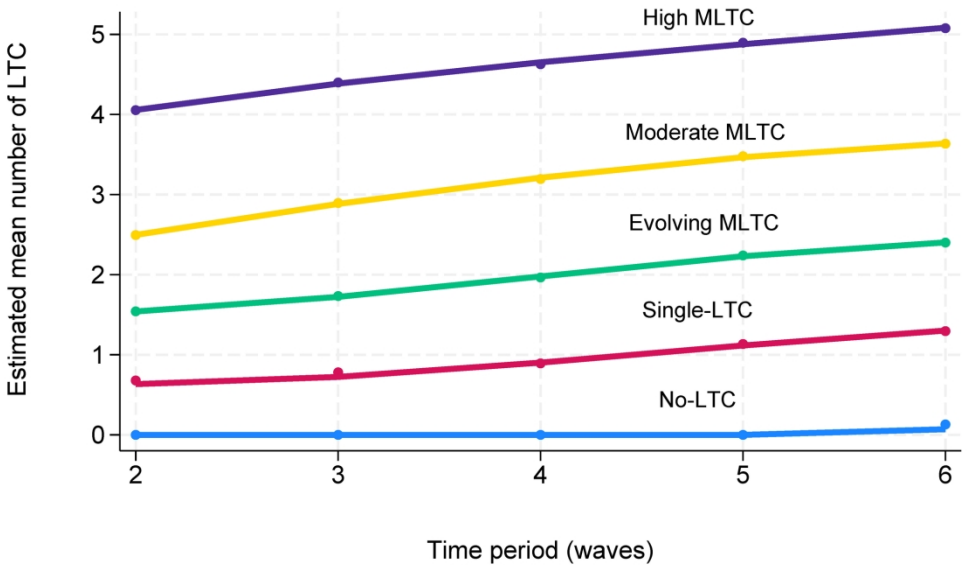
Figure 1. Flow chart of participants selection. MLTC, multiple long-term conditions.

Figure 2. Clusters of long-term condition (LTC) trajectories over time (wave 2 to 6) in the English Longitudinal Study of Aging study. The solid lines represent the estimated mean count of LTC profiles for the five clusters. The "no-LTC" cluster included people who did not have any of the examined LTC; the "single-LTC" cluster included those who did not develop MLTC but may have had one LTC; the ''evolving MLTC'' cluster included those who developed MLTC lately; the ''moderate MLTC'' cluster included those who started with the lower number of MLTC and developed further long-term conditions; the ''high MLTC'' cluster consisted of those who started with the higher number of MLTC and developed additional long-term conditions. Abbreviation: MLTC, Multiple long-term conditions.



Flow chart of participants selection. MLTC, multiple long-term conditions.

195x107mm (300 x 300 DPI)



Clusters of long-term condition (LTC) trajectories over time (wave 2 to 6) in the English Longitudinal Study of Aging study. The solid lines represent the estimated mean count of LTC profiles for the five clusters. The "no-LTC" cluster included people who did not have any of the examined LTC; the "single-LTC" cluster included those who did not develop MLTC but may have had one LTC; the "evolving MLTC" cluster included those who developed MLTC lately; the "moderate MLTC" cluster included those who started with the lower number of MLTC and developed further long-term conditions; the "high MLTC" cluster consisted of those who started with the higher number of MLTC and developed additional long-term conditions. Abbreviation: MLTC, Multiple long-term conditions.

190x114mm (300 x 300 DPI)

Trajectories in long-term conditions accumulation and mortality in older adults: A group-based trajectory modelling approach using the English Longitudinal Study of Ageing

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Supplements

Supplementary Table 1. Statistical parameters of the optimal number of clusters selection.

Number of groups	Group membership		Trajectory shapes	BIC (sample size=15085)	APPA	OCC
1	(1)	100	3	-85493.21	1	N/A
2	(1)	53.49	33	-73870.19	0.94	12.80
	(2)	46.51			0.94	17.71
3	(1)	21.77	333	-63524.35	0.97	105.25
	(2)	53.83			0.96	18.03
	(3)	24.40			0.95	67.92
4	(1)	19.24	3333	-59262.14	0.96	93.69
	(2)	36.07			0.93	24.44
	(3)	32			0.90	19.03
	(4)	12.69			0.96	172.34
5	(1)	19.35	33333	-56474.28	0.97	119.07
	(2)	30.77			0.90	18.95
	(3)	25.43			0.88	23.76
	(4)	17.15			0.90	44.02
	(5)	7.31			0.95	284.50
6	(1)	15.57	333333	-57000.83	0.96	109.69
	(2)	29.21			0.90	19.32
	(3)	23.82			0.87	20.91
	(4)	15.12			0.90	44.32
	(5)	6.27			0.95	259.29
	(6)	10.6			0.92	221.23

Note: Trajectory shapes (0=intercept, 1=linear, 2=quadratic, 3=cubic); BIC = Bayesian Information Criterion; APPA = average posterior probability assignment; OCC = odds of a correct classification according to maximum posterior probability group.

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	6
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6, 7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*6*
Bias	9	Describe any efforts to address potential sources of bias	6, 7
Study size	10	Explain how the study size was arrived at	NA
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	7
		(*c*) Explain how missing data were addressed	7
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	7
		(*e*) Describe any sensitivity analyses	7

Continued on next page

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9
		(b) Give reasons for non-participation at each stage	9
		(c) Consider use of a flow diagram	9
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9, 10
		(b) Indicate number of participants with missing data for each variable of interest	9, 10
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	NA
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	*NA*
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	*13*
		Cross-sectional study—Report numbers of outcome events or summary measures	*NA*
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	13
		(*b*) Report category boundaries when continuous variables were categorized	13
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	14
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	15
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14, 15
Generalisability	21	Discuss the generalisability (external validity) of the study results	14, 15
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	2

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Trajectories in long-term conditions accumulation and mortality in older adults: A group-based trajectory modelling approach using the English Longitudinal Study of Ageing

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Trajectories in long-term conditions accumulation and mortality in older adults: A group-based trajectory modelling approach using the English Longitudinal Study of Ageing

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Competing interests

None declared.

Ethics approval

Ethical approval for the study was provided by the Faculty of Medicine Ethics Committee, University Hospital Southampton, (reference number 67953).

Data availability statement

ELSA data were available through the UK Data Archive and are widely available to access in this way; as such, our study data will not be made available for access.

Abstract

Objectives

To classify older adults into clusters based on accumulating long-term conditions (LTC) as trajectories, characterise clusters, and quantify their associations with all-cause mortality.

Design

We conducted a cross-sectional study using the English Longitudinal Study of Ageing (ELSA) over nine years (n=15,091 aged 50 years and older). Group-based trajectory modelling was used to classify people into clusters based on accumulating LTC over time. Derived clusters were used to quantify the associations between trajectory memberships, sociodemographic characteristics, and all-cause mortality by conducting regression models.

Results

Five distinct clusters of accumulating LTC trajectories were identified and characterised as: "no-LTC" (18.57%), "single-LTC" (31.21%), "evolving multimorbidity" (25.82%), "moderate multimorbidity" (17.12%), and "high multimorbidity" (7.27%). Increasing age was consistently associated with a larger number of LTC. Ethnic minorities (aOR = 2.04; 95%CI 1.40 to 3.00) were associated with the "high multimorbidity" cluster. Higher education and paid employment were associated with a lower likelihood of progression over time towards an increased number of LTC. All the clusters had higher all-cause mortality than the "no-LTC" cluster.

Conclusions

The development of multimorbidity in the number of conditions over time follows distinct trajectories. These are determined by non-modifiable (age, ethnicity) and modifiable factors (education and employment). Stratifying risk through clustering will enable practitioners to identify older adults with a higher likelihood of worsening LTC over time to tailor effective interventions to prevent mortality.

Keywords

Multimorbidity, trajectories, mortality, English Longitudinal Study on Ageing (ELSA), older adults.

Strengths and limitations

- The main strength of the current study is the use of a large and nationally representative dataset of people aged 50 years and older assessing longitudinal data to examine long-term conditions (LTC) trajectories.
- The measurement was limited to ten long-term conditions, based on what was available in the English Longitudinal Study of Ageing, which may not be exhaustive of all possible long-term conditions.

Introduction

Globally, the average life expectancy has risen from 66.8 years in 2000 to 73.4 years in 2019 (1). By 2050, the population over 60 and 80 years will reach 2.1 billion and 426 million, respectively (2,3). This rise in longevity raises the risk of developing multimorbidity, which is the co-occurrence of two or more chronic diseases (4). The worldwide prevalence of multimorbidity among older people is reported to be between 55-98% (5), and in the UK, this is expected to rise from 54% in 2015 to 68% in 2035 (2). Multimorbidity represents an ongoing challenge for healthcare systems because people with multimorbidity have worse care outcomes, including functional limitation and disability (6,7), higher service utilisation (5), mortality (8) and poorer quality of life (5). Management of multimorbidity places considerable economic and logistical burdens on services traditionally organised around single disease models (6). There are a range of risk factors for multimorbidity, although these may vary 'quantitively and qualitatively across life stages, ethnicities, sexes, socioeconomic groups and geographies' (9). The most significant risk factor in multimorbidity, in virtually all contexts, is older age (9,10). Other documented risk factors include low education, obesity, hypertension, depression, and low physical function, which were generally positively associated with multimorbidity (10).

While there is ample evidence of identified risk factors (7,9) and adverse care outcomes for multimorbidity cross-sectionally to help understand the prevalence and patterns of LTC, they provide little evidence on temporal elements, including patterns of LTC development over time (8,10,11). There is a paucity of longitudinal approaches examining patterns in the accumulation of diseases (12). Understanding the trajectory that an older adult will follow in the progression towards an increased number of LTC could help predict when intervention is needed and inform targeted and earlier preventive interventions. To address this gap in the literature, this study aimed to classify older adults with LTC into clusters based on the accumulation of conditions as trajectories over time, characterise these clusters, and quantify the association between derived clusters and all-cause mortality.

Methods

Data source and study population

The English Longitudinal Study of Aging (ELSA) is a longitudinal cohort of people aged 50 years or older living in England (13). The ELSA cohort profile has been described in detail elsewhere (14). In summary, it included 12,099 people at study entry in 2002 with follow-up every two years with self-report questionnaires on physical and mental health, well-being, finances, and attitudes around ageing over time. Four yearly additional nurse visits collected objective data such as anthropometric data (13,15). The ELSA is an open cohort, and refreshment samples were added depending on the proportional age requirement for ELSA, so the total number of people in this cohort was 15,091. Our baseline was wave 2 (2004/5) of the ELSA cohort, the first collecting time point in the study of long-term conditions with a nine-year follow-up to wave 6 (2012/3), the most recent wave with available data on all-cause mortality status.

Multimorbidity

Multimorbidity was defined as the presence of two or more of the following ten conditions: hypertension, diabetes, cancer, lung disease, cardiovascular disease, stroke, mental health disorder, arthritis, Parkinson's disease, and dementia. These are self-reported by patients, relatives or carers and verified by nurse visits (13). These ten conditions were available within the ELSA dataset based on our earlier work to define multimorbidity (16,17). After statistical consideration due to the small sample size and clinical discussion, we grouped some of the conditions as follows: people with depression were combined with mental health disorders, asthma was combined with lung disease, Alzheimer's within dementia, and finally, those with heart attack, angina, heart murmur, abnormal heart rhythm and congestive heart failure combined into those with cardiovascular disease.

All-cause mortality

All-cause mortality was reported by end-of-life interviews on waves 2, 3, 4 and 6 with relatives and friends after death.

Covariates

Sociodemographic variables included were age, sex, ethnicity (defined as white/non-white), education, employment, and marital status. The education variable was categorised into four groups: less than upper secondary level, upper secondary and vocational level, tertiary level, and others. Employment status was categorised into 'paid employment and 'unemployed'. Marital status was categorised into three groups: never married, married/having a partner, and separated/divorced/widowed. These covariates were based on the baseline. We used data provided in the nearest subsequent waves if they were missing at baseline.

Statistical analysis

Descriptive statistics were used to summarise participants' characteristics. We used group-based trajectory modelling (GBTM) to classify older adults with LTC into clusters based on accumulating conditions as trajectories over time. GBTM is a finite mixture model applying maximum likelihood to identify a cluster of people following similar trajectories by the number of conditions over time (18). This model assumes the same error variance for all clusters and time points and treats missing data as 'missing at random' (19). The procedure for selecting the best model included two steps: identifying the ideal number of trajectory groups and determining polynomial orders to represent the shapes of the trajectories (18,20). Based on the observed distribution, we employed a censored normal model to specify LTC (21,22). We fitted the models iteratively, starting with one and increasing up to a maximum of six clusters that would be useful in a clinical setting (20). We selected the number of trajectory clusters based on the following criteria: the lowest Bayesian Information Criterion (BIC) value, Average Posterior Probability Assignment (APPA) >70%, Odds of a Correct Classification (OCC) >5, the percentage of participants in each trajectory groups >5% of the total sample (if less than 5% it is unlikely to be conceptually useful for clinical practice) (22–24). We first used cubic polynomials to characterise the shape of the clusters of LTC trajectories. However, after selecting the number of trajectories, we refitted the model to use lower-order terms when the higher-order terms were insignificant (20). We then assigned individuals to the trajectory group based on the maximum posterior probability (20). Multinomial logistic regression was then performed to test the association between socio-demographic factors and clusters of LTC trajectory, with the "no-LTC" cluster as the reference. Binary logistic regression was also performed to quantify the association between the clusters of LTC trajectory membership and all-cause mortality, adjusting for all the covariates mentioned above. A squared term

of age was included in the model to account for the non-linear relationship between age and mortality. The significance level was set at a p-value <0.05, and all analyses were performed using STATA M.P v17.0.

Patient and Public Involvement

This study was conducted as part of a wider mixed-methods programme of research exploring the potential of machine learning to address multimorbidity through the 'clustering' of patients based on similarities in clinical and social care needs. Patient and public involvement has been incorporated throughout the wider research programme from the initial inception, design, and dissemination of findings. The initial results and the final written draft of the study submitted in this manuscript were shared with our programme's patient and public representative.

Results

Participants' characteristics

There were 9,170 participants in wave 2 and we identified 15,091 individuals participating in at least one wave during the follow-up period (The flow of participants through the study is shown in **Figure 1**). Six participants were excluded, as they had no information on LTC. After excluding those (n = 123) with missing data on covariates, 14,962 people were included in the final analysis. The mean (SD) age of the cohort was 61.9 (11) years; most were females (53.5%), whites (96.5%), with educational attainment of upper secondary or vocational (43.1%), employed (56.8%), and married or had a partner (72%) (**Table 1**).

Table 1. Participants' characteristics overall and stratified by clusters of LTC trajectories.

	Total	No-LTC	Single-LTC	Evolving multimorbidity	Moderate multimorbidity	High multimorbidity
	14962 (100%)	2826 (18.9%)	4802 (32.1%)	3739 (25.0%)	2532 (16.9%)	1063 (7.1%)
Age, mean (SD)	61.9 (11)	56.0 (9.1)	60.0 (10.0)	62.9 (10.8)	67.1 (10.7)	69.8 (10.4)
Sex						
Male	6951 (46.5)	1402 (20.2)	2361 (34.0)	1675 (24.1)	1050 (15.1)	463 (6.7)
Female	8011 (53.5)	1424 (17.8)	2441 (30.5)	2064 (25.8)	1482 (18.5)	600 (7.5)
Ethnicity						
White	14440 (96.5)	2726 (18.9)	4629 (32.1)	3618 (25.1)	2451 (17.0)	1016 (7.0)
Non-white	522 (3.5)	100 (19.2)	173 (33.1)	121 (23.2)	81 (15.5)	47 (9.0)
Education						
Less than upper secondary	5107 (34.1)	629 (12.3)	1417 (27.8)	1326 (26.0)	1136 (22.2)	599 (11.7)
Upper secondary, vocational	6444 (43.1)	1399 (21.7)	2186 (33.9)	1609 (25.0)	941 (14.6)	309 (4.8)
Tertiary	2277 (15.2)	626 (27.5)	859 (37.7)	497 (21.8)	227 (10.0)	68 (3.0)
Others	1134 (7.6)	172 (15.2)	340 (30.0)	307 (27.1)	228 (20.1)	87 (7.7)
Employment						
Paid employment	8500 (56.8)	895 (10.5)	2278 (26.8)	2333 (27.5)	2033 (23.9)	961 (11.3)
Unemployed	6462 (43.2)	1931 (30.0)	2524 (39.1)	1406 (21.8)	499 (7.7)	102 (1.6)
Marital status						
Never married	789 (5.3)	148 (18.8)	268 (34.0)	189 (24.0)	131 (16.6)	53 (6.7)
Married/partner	10766 (72.0)	2282 (21.2)	3635 (33.8)	2674 (24.8)	1566 (14.6)	609 (5.7)
Separated/divorced/widowed	3407 (22.8)	396 (11.6)	899 (26.4)	876 (25.7)	835 (24.5)	401 (11.8)

Note: The percentages in the "total" column are presented vertically, whereas in the other five columns horizontally.

Clusters of LTC trajectory

We examined one to six clusters in the model to determine the optimal cluster number. Five clusters were selected based on the model fit indicators (**Supplementary Table 1**) and the interpretability of classified trajectories.

Participants displayed high posterior probabilities of belonging to their assigned clusters ranging from 0.88 to 0.97 across the five clusters. The "no-LTC" cluster (18.57%) was dominated by people (95.2%) without any record of the examined long-term condition during the follow-up, and the "single-LTC" cluster (31.21%) consisted of those who did not develop multimorbidity during the study period but may have had one long-term condition (**Figure 2**). The "evolving multimorbidity" cluster (25.82%) was characterised by people who progressed from less than two long-term conditions at baseline to two, three, or four by the end of follow-up. Two clusters had multimorbidity profiles which showed increasing numbers of long-term conditions ("moderate multimorbidity" (17.12%) and "high multimorbidity" (7.27%)). Those in these clusters started with multimorbidity and continued to have higher counts of long-term conditions in the following periods.

Clusters of LTC trajectory and socio-demographic characteristics

Increasing age was consistently associated with all LTC clusters, compared to the "no-LTC" cluster (**Table 1 & 2**). Females had higher odds (aOR = 1.13; 95%CI 1.01 to 1.27) of being in the "moderate multimorbidity" clusters than males. Being non-white increased the odds of belonging to the "high multimorbidity" cluster by 2.04 times (aOR = 2.04; 95%CI 1.40 to 3) compared to whites. Higher education and paid employment decreased the odds of belonging to any of the four clusters than those with less than upper secondary education and unemployment, respectively.

Table 2. The association between socio-demographic factors and clusters of LTC trajectories.

	Adjusted OR (95%CI) (Reference: No-LTC)			
Socio-demographics	**Single-LTC**	**Evolving multimorbidity**	**Moderate multimorbidity**	**High multimorbidity**
Age	1.04 (1.03-1.04)	1.05 (1.05-1.06)	1.07 (1.06-1.08)	1.08 (1.07-1.09)
Sex				
Male	Reference	Reference	Reference	Reference
Female	1.00 (0.91-1.10)	1.11 (0.99-1.23)	1.13 (1.01-1.27)	0.95 (0.81-1.11)
Ethnicity				
White	Reference	Reference	Reference	Reference
Non-white	1.17 (0.91-1.50)	1.13 (0.85-1.49)	1.36 (1.00-1.86)	2.04 (1.40-3.00)
Education				
Less than upper secondary	Reference	Reference	Reference	Reference
Upper secondary, vocational	0.92 (0.81-1.03)	0.87 (0.77-0.99)	0.77 (0.67-0.88)	0.53 (0.45-0.64)
Tertiary	0.84 (0.72-0.97)	0.68 (0.58-0.80)	0.51 (0.42-0.62)	0.33 (0.25-0.45)
Others	1.01 (0.83-1.25)	1.04 (0.84-1.28)	0.99 (0.79-1.25)	0.76 (0.57-1.02)
Employment				
Unemployed	Reference	Reference	Reference	Reference
Paid employment	0.79 (0.70-0.89)	0.54 (0.4 8-0.62)	0.35 (0.31-0.40)	0.17 (0.13-0.21)
Marital status				
Never married	Reference	Reference	Reference	Reference
Married/partner	0.85 (0.69-1.04)	0.90 (0.72-1.14)	0.80 (0.62-1.03)	0.82 (0.58-1.15)
Separated/divorced/widowed	0.97 (0.77-1.23)	1.14 (0.88-1.48)	1.27 (0.96-1.68)	1.41 (0.98-2.04)

Abbreviation: LTC, Long-Term Conditions

Clusters of LTC trajectory and all-cause mortality

The "Single-LTC" (aOR = 1.81; 95% CI 1.21 to 2.73), the "evolving multimorbidity" (aOR = 2.26; 95% CI 1.51 to 3.38), the "moderate multimorbidity" (aOR = 2.62; 95% CI 1.75 to 3.94), and the "high multimorbidity" (aOR = 4.03; 95% CI 2.64 to 6315) clusters were significantly associated with higher all-cause mortality, compared with the people in the "no-LTC" cluster (**Table 3**).

Table 3. Association between clusters of LTC trajectory and all-cause mortality.

	Alive (14310, 95.6%)	Dead (652, 4.4%)	Unadjusted OR (95%CI)	Adjusted[1] OR (95%CI)	p-value[2]
Trajectory cluster					
No-LTC	2796 (98.9)	30 (1.1)	Reference	Reference	<0.0001
Single-LTC	4668 (97.2)	134 (2.8)	2.69 (1.81-4.01)	1.81 (1.21-2.73)	
Evolving multimorbidity	3566 (95.4)	174 (4.6)	4.59 (3.10-6.78)	2.26 (1.51-3.38)	
Moderate multimorbidity	2349 (92.8)	183 (7.2)	7.22 (4.89-10.7)	2.62 (1.75-3.94)	
High multimorbidity	931 (87.6)	132 (12.4)	13.6 (9.11-20.3)	4.03 (2.64-6.15)	

[1]Adjusted for age, sex, ethnicity, education, employment status, and marital status. Age was included in the model as a squared term.

[2] p-value for trend.

Abbreviation: LTC, long-term condition.

Discussion

This study examined clusters of LTC based on the accumulation of conditions as trajectories over time, their associations with sociodemographic factors, and all-cause mortality among older adults in England. We identified five distinct clusters that can be described as "no-LTC", "single-LTC", "evolving multimorbidity", "moderate multimorbidity", and "high multimorbidity". We observed that the accumulation of LTC over time progresses differently among older adults with distinction by ethnicity, educational level, and employment status. Specifically, ethnic minorities showed faster/steeper progression towards increased numbers of LTC, whereas higher education and paid employment had a protective effect on the increase in the accumulation of LTC.

An interesting finding was that clusters with different initial levels and rates of change in LTC indicating individual differences in the process of health deterioration. This is in line with previous studies that identified different rates of LTC (25). Those with persistently high levels of multimorbidity have also been similarly identified in other populations (26). However, consistent with the literature (25,26), we did not find any trajectories that indicated improvement in health over time (i.e., decreasing levels of LTC). This may be due to the difficulty of recovery from long-term conditions among older adults or due to the older population as it is anticipated that the mean number of conditions will increase as we follow them over time (waves).

The faster/steeper progression observed towards increased numbers of LTC in females is in line with previous literature, which found that the accumulation of long-term conditions was more severe for older females (27). An explanation can be that females tend to live longer than males, and as a result, they are more likely to develop chronic conditions associated with ageing, such as arthritis and dementia. The faster development of MLTC in ethnic minorities can be explained by evidence suggesting that access and engagement with healthcare are limited for some population groups, often on the basis of ethnicity. Specifically, a review from NHS Race and Health Observatory (28) suggests that there are 'clear barriers' for people from minority ethnic backgrounds to seek help for mental health problems, and another research has also found lower access to cancer screening in the UK (29). Socioeconomic risk factors are known to be associated with MLTC (30). Our findings support the role of higher educational attainment, a major socioeconomic risk factor, on MLTC prevention. Targeting education inequality is expected to lead further to the restriction of worsening MLTC. The effect of educational attainment on MLTC is thought to be explained by other risk factors that may mediate this association, such as body mass index and smoking.

Over their life course, individuals develop MLTC. It is necessary to challenge the common statement that MLTC is inevitable in an ageing society. To do this, the focus on MLTC should shift from sole management of high-risk older individuals to include integrated population-level prevention strategies throughout the life course to address the drivers of MLTC. Programs that bridge multiple clinical specialities and healthcare units should be developed to focus on single individuals, their specific clinical profiles, and their specific clinical trajectories (31). Knowledge of how long-term conditions cluster, and especially how the status of MLTC can change over subsequent years, helps not only in understanding the complexity and dynamic evolution of MLTC clusters but also in supporting clinicians who manage co-occurring long-term conditions and health policymakers who plan care resources use.

This is the first study to examine trajectories of MLTC with a view to stratifying within MLTC to identify those at greatest risk among older adults in England. The main strength of the current study is the use of a large dataset, assessing longitudinal data to examine MLTC trajectories and a dataset that is nationally representative of people aged 50 years and older, including a wide range of long-term conditions and sociodemographics. However, the results of this study should be interpreted with some caution. First, the measurement of MLTC was limited to ten long-term conditions that was all of what was available in ELSA, which may not be exhaustive of all possible long-term conditions. Findings could be different if more long-term conditions are considered. Second, although we examined the correlates of MLTC trajectories using the variables measured at the baseline (wave 2), we cannot conclude on the directionality of the associations. Another limitation is that because our study utilised a longitudinal design that examined age-related changes, there may be inherent confounding of age and period effects. These effects could not be disentangled in this study due to the nature of our data. Lastly, the probability of being in a cluster membership is based on model assignment, which can lead to misclassification bias.

In conclusion, LTC trajectories of older adults are characterised by dynamism but can still be tracked over time. Considering LTC clusters has potential to enable future researchers and practitioners to provide evidence in identifying older adults in England at a higher risk of worsening MLTC over time. Our findings contribute to existing evidence on the need to develop effective tailored interventions for at-risk individuals. Possible responses include targeting ethnic minorities for multimorbidity prevention. Additionally, higher levels of education can also lead to a further decrease in the number of long-term conditions. Policymakers should also commit to increasing MLTC awareness among at-risks groups and care providers.

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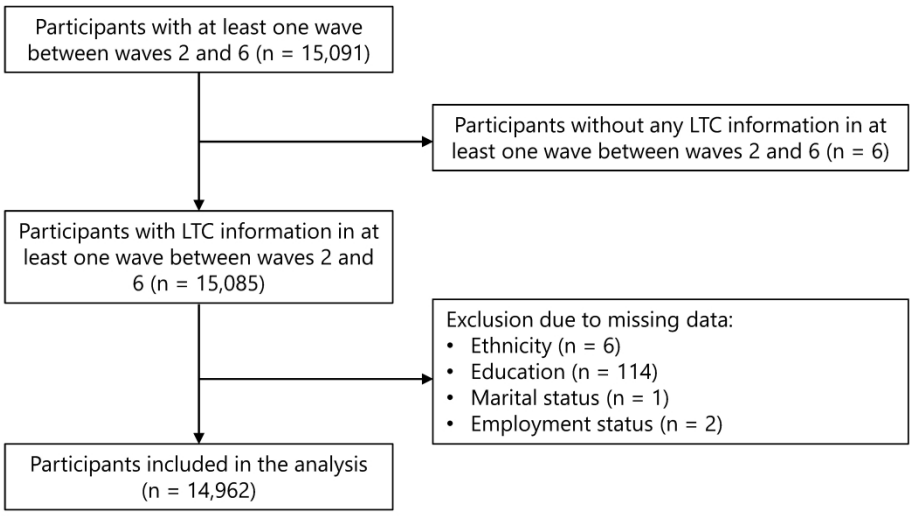
Figure legends

Figure 1. Flow chart of participants selection. MLTC, multiple long-term conditions.

Figure 2. Clusters of long-term condition (LTC) trajectories over time (wave 2 to 6) in the English Longitudinal Study of Aging study. The solid lines represent the estimated mean count of LTC profiles for the five clusters. The "no-LTC" cluster included people who did not have any of the examined LTC; the "single-LTC" cluster included those who did not develop MLTC but may have had one LTC; the ''evolving MLTC'' cluster included those who developed MLTC lately; the ''moderate MLTC'' cluster included those who started with the lower number of MLTC and developed further long-term conditions; the ''high MLTC'' cluster consisted of those who started with the higher number of MLTC and developed additional long-term conditions. Abbreviation: MLTC, Multiple long-term conditions.



Flow chart of participants selection. MLTC, multiple long-term conditions.

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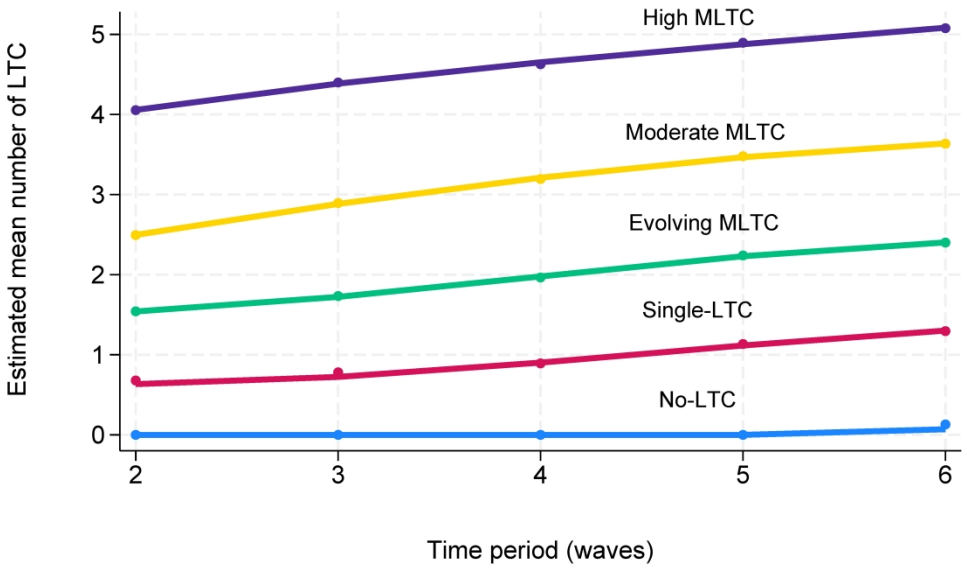

Clusters of long-term condition (LTC) trajectories over time (wave 2 to 6) in the English Longitudinal Study of Aging study. The solid lines represent the estimated mean count of LTC profiles for the five clusters. The "no-LTC" cluster included people who did not have any of the examined LTC; the "single-LTC" cluster included those who did not develop MLTC but may have had one LTC; the "evolving MLTC" cluster included those who developed MLTC lately; the "moderate MLTC" cluster included those who started with the lower number of MLTC and developed further long-term conditions; the "high MLTC" cluster consisted of those who started with the higher number of MLTC and developed additional long-term conditions. Abbreviation: MLTC, Multiple long-term conditions.

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Trajectories in long-term conditions accumulation and mortality in older adults: A group-based trajectory modelling approach using the English Longitudinal Study of Ageing

Christos V. Chalitsios[1], Cornelia Santoso[1], Yvonne Nartey[1], Nusrat Khan[1], Glenn Simpson[1], Nazrul Islam[1], Beth Stuart[2], Andrew Farmer[3], Hajira Dambha-Miller[1]

Supplements

Supplementary Table 1. Statistical parameters of the optimal number of clusters selection.

Number of groups	Group membership		Trajectory shapes	BIC (sample size=15085)	APPA	OCC
1	(1)	100	3	-85493.21	1	N/A
2	(1)	53.49	33	-73870.19	0.94	12.80
	(2)	46.51			0.94	17.71
3	(1)	21.77	333	-63524.35	0.97	105.25
	(2)	53.83			0.96	18.03
	(3)	24.40			0.95	67.92
4	(1)	19.24	3333	-59262.14	0.96	93.69
	(2)	36.07			0.93	24.44
	(3)	32			0.90	19.03
	(4)	12.69			0.96	172.34
5	(1)	19.35	33333	-56474.28	0.97	119.07
	(2)	30.77			0.90	18.95
	(3)	25.43			0.88	23.76
	(4)	17.15			0.90	44.02
	(5)	7.31			0.95	284.50
6	(1)	15.57	333333	-57000.83	0.96	109.69
	(2)	29.21			0.90	19.32
	(3)	23.82			0.87	20.91
	(4)	15.12			0.90	44.32
	(5)	6.27			0.95	259.29
	(6)	10.6			0.92	221.23

Note: Trajectory shapes (0=intercept, 1=linear, 2=quadratic, 3=cubic); BIC = Bayesian Information Criterion; APPA = average posterior probability assignment; OCC = odds of a correct classification according to maximum posterior probability group.

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	6
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6, 7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*6*
Bias	9	Describe any efforts to address potential sources of bias	6, 7
Study size	10	Explain how the study size was arrived at	NA
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	7
		(*c*) Explain how missing data were addressed	7
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	7
		(*e*) Describe any sensitivity analyses	7

Continued on next page

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9
		(b) Give reasons for non-participation at each stage	9
		(c) Consider use of a flow diagram	9
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9, 10
		(b) Indicate number of participants with missing data for each variable of interest	9, 10
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	NA
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	*NA*
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	*13*
		Cross-sectional study—Report numbers of outcome events or summary measures	*NA*
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	13
		(*b*) Report category boundaries when continuous variables were categorized	13
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	14
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	15
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14, 15
Generalisability	21	Discuss the generalisability (external validity) of the study results	14, 15
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	2

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Trajectories in long-term conditions accumulation and mortality in older adults: A group-based trajectory modelling approach using the English Longitudinal Study of Ageing

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Trajectories in long-term conditions accumulation and mortality in older adults: A group-based trajectory modelling approach using the English Longitudinal Study of Ageing

Christos V. Chalitsios[1], Cornelia Santoso[1], Yvonne Nartey[1], Nusrat Khan[1], Glenn Simpson[1], Nazrul Islam[1], Beth Stuart[2], Andrew Farmer[3], Hajira Dambha-Miller[1]

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Authors' contribution

HDM was responsible for the study's conception and design. All authors (CVC, CS, YN, NK, GS, NI, BS, AF, HDM) critically reviewed and edited the manuscript, and contributed to the interpretation of the data and results. Data management and statistical analyses were performed by CVC, CS and YN. The first draft of the manuscript was written by CVC, and all authors commented on and contributed to subsequent iterations of the manuscript. All authors read and approved the final manuscript before submission. HDM is the guarantor of the work.

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Competing interests

None declared.

Ethics approval

Ethical approval for the study was provided by the Faculty of Medicine Ethics Committee, University Hospital Southampton, (reference number 67953).

Data availability statement

ELSA data were available through the UK Data Archive and are widely available to access in this way; as such, our study data will not be made available for access.

Abstract

Objectives

To classify older adults into clusters based on accumulating long-term conditions (LTC) as trajectories, characterise clusters, and quantify their associations with all-cause mortality.

Design

We conducted a longitudinal study using the English Longitudinal Study of Ageing (ELSA) over nine years (n=15,091 aged 50 years and older). Group-based trajectory modelling was used to classify people into clusters based on accumulating LTC over time. Derived clusters were used to quantify the associations between trajectory memberships, sociodemographic characteristics, and all-cause mortality by conducting regression models.

Results

Five distinct clusters of accumulating LTC trajectories were identified and characterised as: "no-LTC" (18.57%), "single-LTC" (31.21%), "evolving multimorbidity" (25.82%), "moderate multimorbidity" (17.12%), and "high multimorbidity" (7.27%). Increasing age was consistently associated with a larger number of LTC. Ethnic minorities (aOR = 2.04; 95%CI 1.40 to 3.00) were associated with the "high multimorbidity" cluster. Higher education and paid employment were associated with a lower likelihood of progression over time towards an increased number of LTC. All the clusters had higher all-cause mortality than the "no-LTC" cluster.

Conclusions

The development of multimorbidity in the number of conditions over time follows distinct trajectories. These are determined by non-modifiable (age, ethnicity) and modifiable factors (education and employment). Stratifying risk through clustering will enable practitioners to identify older adults with a higher likelihood of worsening LTC over time to tailor effective interventions to prevent mortality.

Keywords

Multimorbidity, trajectories, mortality, English Longitudinal Study on Ageing (ELSA), older adults.

Strengths and limitations

- The main strength of this study is the use of a large dataset, the English Longitudinal Study of Ageing (ELSA), assessing longitudinal data to examine MLTC trajectories.
- The ELSA dataset is nationally representative of people aged 50 years and older, including a broad range of long-term conditions and sociodemographics.
- The measurement was limited to ten long-term conditions, based on what was available in ELSA, which may not be exhaustive of all possible long-term conditions.
- The probability of being in a cluster membership is based on model assignment, which can lead to misclassification bias.

Introduction

Globally, the average life expectancy has risen from 66.8 years in 2000 to 73.4 years in 2019 (1). By 2050, the population over 60 and 80 years will reach 2.1 billion and 426 million, respectively (2,3). This rise in longevity raises the risk of developing multimorbidity, which is the co-occurrence of two or more chronic diseases (4). The worldwide prevalence of multimorbidity among older people is reported to be between 55-98% (5), and in the UK, this is expected to rise from 54% in 2015 to 68% in 2035 (2). Multimorbidity represents an ongoing challenge for healthcare systems because people with multimorbidity have worse care outcomes, including functional limitation and disability (6,7), higher service utilisation (5), mortality (8) and poorer quality of life (5). Management of multimorbidity places considerable economic and logistical burdens on services traditionally organised around single disease models (6). There are a range of risk factors for multimorbidity, although these may vary 'quantitively and qualitatively across life stages, ethnicities, sexes, socioeconomic groups and geographies' (9). The most significant risk factor in multimorbidity, in virtually all contexts, is older age (9,10). Other documented risk factors include low education, obesity, hypertension, depression, and low physical function, which were generally positively associated with multimorbidity (10).

While there is ample evidence of identified risk factors (7,9) and adverse care outcomes for multimorbidity cross-sectionally to help understand the prevalence and patterns of LTC, they provide little evidence on temporal elements, including patterns of LTC development over time (8,10,11). There is a paucity of longitudinal approaches examining patterns in the accumulation of diseases (12). Understanding the trajectory that an older adult will follow in the progression towards an increased number of LTC could help predict when intervention is needed and inform targeted and earlier preventive interventions. To address this gap in the literature, this study aimed to classify older adults with LTC into clusters based on the accumulation of conditions as trajectories over time, characterise these clusters, and quantify the association between derived clusters and all-cause mortality.

Methods

Data source and study population

The English Longitudinal Study of Aging (ELSA) is a longitudinal cohort of people aged 50 years or older living in England (13). The ELSA cohort profile has been described in detail elsewhere (14). In summary, it included 12,099 people at study entry in 2002 with follow-up every two years with self-report questionnaires on physical and mental health, well-being, finances, and attitudes around ageing over time. Four yearly additional nurse visits collected objective data such as anthropometric data (13,15). The ELSA is an open cohort, and refreshment samples were added depending on the proportional age requirement for ELSA, so the total number of people in this cohort was 15,091. Our baseline was wave 2 (2004/5) of the ELSA cohort, the first collecting time point in the study of long-term conditions with a nine-year follow-up to wave 6 (2012/3), the most recent wave with available data on all-cause mortality status.

Multimorbidity

Multimorbidity was defined as the presence of two or more of the following ten conditions: hypertension, diabetes, cancer, lung disease, cardiovascular disease, stroke, mental health disorder, arthritis, Parkinson's disease, and dementia. These are self-reported by patients, relatives or carers and verified by nurse visits (13). These ten conditions were available within the ELSA dataset based on our earlier work to define multimorbidity (16,17). After statistical consideration due to the small sample size and clinical discussion, we grouped some of the conditions as follows: people with depression were combined with mental health disorders, asthma was combined with lung disease, Alzheimer's within dementia, and finally, those with heart attack, angina, heart murmur, abnormal heart rhythm and congestive heart failure combined into those with cardiovascular disease.

All-cause mortality

All-cause mortality was reported by end-of-life interviews on waves 2, 3, 4 and 6 with relatives and friends after death.

Covariates

Sociodemographic variables included were age, sex, ethnicity (defined as white/non-white), education, employment, and marital status. The education variable was categorised into four groups: less than upper secondary level, upper secondary and vocational level, tertiary level, and others. Employment status was categorised into 'paid employment and 'unemployed'. Marital status was categorised into three groups: never married, married/having a partner, and separated/divorced/widowed. These covariates were based on the baseline. We used data provided in the nearest subsequent waves if they were missing at baseline.

Statistical analysis

Descriptive statistics were used to summarise participants' characteristics. We used group-based trajectory modelling (GBTM) to classify older adults with LTC into clusters based on accumulating conditions as trajectories over time. GBTM is a finite mixture model applying maximum likelihood to identify a cluster of people following similar trajectories by the number of conditions over time (18). This model assumes the same error variance for all clusters and time points and treats missing data as 'missing at random' (19). The procedure for selecting the best model included two steps: identifying the ideal number of trajectory groups and determining polynomial orders to represent the shapes of the trajectories (18,20). Based on the observed distribution, we employed a censored normal model to specify LTC (21,22). We fitted the models iteratively, starting with one and increasing up to a maximum of six clusters that would be useful in a clinical setting (20). We selected the number of trajectory clusters based on the following criteria: the lowest Bayesian Information Criterion (BIC) value, Average Posterior Probability Assignment (APPA) >70%, Odds of a Correct Classification (OCC) >5, the percentage of participants in each trajectory groups >5% of the total sample (if less than 5% it is unlikely to be conceptually useful for clinical practice) (22–24). We first used cubic polynomials to characterise the shape of the clusters of LTC trajectories. However, after selecting the number of trajectories, we refitted the model to use lower-order terms when the higher-order terms were insignificant (20). We then assigned individuals to the trajectory group based on the maximum posterior probability (20). Multinomial logistic regression was then performed to test the association between socio-demographic factors and clusters of LTC trajectory, with the "no-LTC" cluster as the reference. Binary logistic regression was also performed to quantify the association between the clusters of LTC trajectory membership and all-cause mortality, adjusting for all the covariates mentioned above. A squared term of age was included in the model to account for the non-linear relationship between age and mortality. The significance level was set at a p-value <0.05, and all analyses were performed using STATA M.P v17.0.

Patient and Public Involvement

This study was conducted as part of a wider mixed-methods programme of research exploring the potential of machine learning to address multimorbidity through the 'clustering' of patients based on similarities in clinical and social care needs. Patient and public involvement has been incorporated throughout the wider research programme from the initial inception, design, and dissemination of findings. The initial results and the final written draft of the study submitted in this manuscript were shared with our programme's patient and public representative.

Results

Participants' characteristics

There were 9,170 participants in wave 2 and we identified 15,091 individuals participating in at least one wave during the follow-up period (The flow of participants through the study is shown in **Figure 1**). Six participants were excluded, as they had no information on LTC. After excluding those (n = 123) with missing data on covariates, 14,962 people were included in the final analysis. The current analysis included 2688 (18.0%), 529 (3.5%), 4270 (28.5%), 4582 (30.6%) and 2893 (19.3%) people from wave 2, 3 4, 5 and 6, respectively. The mean (SD) age of the cohort was 61.9 (11) years; most were females (53.5%), whites (96.5%), with educational attainment of upper secondary or vocational (43.1%), employed (56.8%), and married or had a partner (72%) (**Table 1**).

Table 1. Participants' characteristics overall and stratified by clusters of LTC trajectories

	Total	No-LTC	Single-LTC	Evolving multimorbidity	Moderate multimorbidity	High multimorbidity
	14962 (100%)	2826 (18.9%)	4802 (32.1%)	3739 (25.0%)	2332 (16.9%)	1063 (7.1%)
Age, mean (SD)	61.9 (11)	56.0 (9.1)	60.0 (10.0)	62.9 (10.8)	64.1 (10.7)	69.8 (10.4)
Sex						
Male	6951 (46.5)	1402 (20.2)	2361 (34.0)	1675 (24.1)	1050 (15.1)	463 (6.7)
Female	8011 (53.5)	1424 (17.8)	2441 (30.5)	2064 (25.8)	1482 (18.5)	600 (7.5)
Ethnicity						
White	14440 (96.5)	2726 (18.9)	4629 (32.1)	3618 (25.1)	2451 (17.0)	1016 (7.0)
Non-white	522 (3.5)	100 (19.2)	173 (33.1)	121 (23.2)	81 (15.5)	47 (9.0)
Education						
Less than upper secondary	5107 (34.1)	629 (12.3)	1417 (27.8)	1326 (26.0)	1136 (22.2)	599 (11.7)
Upper secondary, vocational	6444 (43.1)	1399 (21.7)	2186 (33.9)	1609 (25.0)	941 (14.6)	309 (4.8)
Tertiary	2277 (15.2)	626 (27.5)	859 (37.7)	497 (21.8)	227 (10.0)	68 (3.0)
Others	1134 (7.6)	172 (15.2)	340 (30.0)	307 (27.1)	228 (20.1)	87 (7.7)
Employment						
Paid employment	8500 (56.8)	895 (10.5)	2278 (26.8)	2333 (27.5)	2033 (23.9)	961 (11.3)
Unemployed	6462 (43.2)	1931 (30.0)	2524 (39.1)	1406 (21.8)	299 (4.7)	102 (1.6)
Marital status						
Never married	789 (5.3)	148 (18.8)	268 (34.0)	189 (24.0)	131 (16.6)	53 (6.7)
Married/partner	10766 (72.0)	2282 (21.2)	3635 (33.8)	2674 (24.8)	1566 (14.6)	609 (5.7)
Separated/divorced/widowed	3407 (22.8)	396 (11.6)	899 (26.4)	876 (25.7)	765 (22.5)	401 (11.8)

Note: The percentages in the "total" column are presented vertically, whereas in the other five columns horizontally.

Clusters of LTC trajectory

We examined one to six clusters in the model to determine the optimal cluster number. Five clusters were selected using the model fit indicators (**Supplementary Table 1**) and the interpretability of classified trajectories. (25).

Participants displayed high posterior probabilities of belonging to their assigned clusters ranging from 0.88 to 0.97 across the five clusters. The "no-LTC" cluster (18.57%) was dominated by people (95.2%) without any record of the examined long-term condition during the follow-up, and the "single-LTC" cluster (31.21%) consisted of those who did not develop multimorbidity during the study period but may have had one long-term condition (**Figure 2**). The "evolving multimorbidity" cluster (25.82%) was characterised by people who progressed from less than two long-term conditions at baseline to two, three, or four by the end of follow-up. Two clusters had multimorbidity profiles which showed increasing numbers of long-term conditions ("moderate multimorbidity" (17.12%) and "high multimorbidity" (7.27%)). Those in these clusters started with multimorbidity and continued to have higher counts of long-term conditions in the following periods.

Clusters of LTC trajectory and socio-demographic characteristics

Increasing age was consistently associated with all LTC clusters, compared to the "no-LTC" cluster (**Table 1 & 2**). Females had higher odds (aOR = 1.13; 95%CI 1.01 to 1.27) of being in the "moderate multimorbidity" clusters than males. Being non-white increased the odds of belonging to the "high multimorbidity" cluster by 2.04 times (aOR = 2.04; 95%CI 1.40 to 3) compared to whites. Higher education and paid employment decreased the odds of belonging to any of the four clusters than those with less than upper secondary education and unemployment, respectively.

Table 2. The association between socio-demographic factors and clusters of LTC trajectories.

	Adjusted OR (95%CI) (Reference: No-LTC)			
Socio-demographics	**Single-LTC**	**Evolving multimorbidity**	**Moderate multimorbidity**	**High multimorbidity**
Age	1.04 (1.03-1.04)	1.05 (1.05-1.06)	1.07 (1.06-1.08)	1.08 (1.07-1.09)
Sex				
Male	Reference	Reference	Reference	Reference
Female	1.00 (0.91-1.10)	1.11 (0.99-1.23)	1.13 (1.01-1.27)	0.95 (0.81-1.11)
Ethnicity				
White	Reference	Reference	Reference	Reference
Non-white	1.17 (0.91-1.50)	1.13 (0.85-1.49)	1.36 (1.00-1.86)	2.04 (1.40-3.00)
Education				
Less than upper secondary	Reference	Reference	Reference	Reference
Upper secondary, vocational	0.92 (0.81-1.03)	0.87 (0.77-0.99)	0.77 (0.67-0.88)	0.53 (0.45-0.64)
Tertiary	0.84 (0.72-0.97)	0.68 (0.58-0.80)	0.51 (0.42-0.62)	0.33 (0.25-0.45)
Others	1.01 (0.83-1.25)	1.04 (0.84-1.28)	0.99 (0.79-1.25)	0.76 (0.57-1.02)
Employment				
Unemployed	Reference	Reference	Reference	Reference
Paid employment	0.79 (0.70-0.89)	0.54 (0.4 8-0.62)	0.35 (0.31-0.40)	0.17 (0.13-0.21)
Marital status				
Never married	Reference	Reference	Reference	Reference
Married/partner	0.85 (0.69-1.04)	0.90 (0.72-1.14)	0.80 (0.62-1.03)	0.82 (0.58-1.15)
Separated/divorced/widowed	0.97 (0.77-1.23)	1.14 (0.88-1.48)	1.27 (0.96-1.68)	1.41 (0.98-2.04)

Abbreviation: LTC, Long-Term Conditions

Clusters of LTC trajectory and all-cause mortality

The "Single-LTC" (aOR = 1.81; 95% CI 1.21 to 2.73), the "evolving multimorbidity" (aOR = 2.26; 95% CI 1.51 to 3.38), the "moderate multimorbidity" (aOR = 2.62; 95% CI 1.75 to 3.94), and the "high multimorbidity" (aOR = 4.03; 95% CI 2.64 to 6315) clusters showed an association between increasing rates of all-cause mortality relative to the severity and complexity of multimorbidity (**Table 3**).

Table 3. Association between clusters of LTC trajectory and all-cause mortality.

	Alive (14310, 95.6%)	Dead (652, 4.4%)	Unadjusted OR (95%CI)	Adjusted[1] OR (95%CI)	p-value[2]
Trajectory cluster					
No-LTC	2796 (98.9)	30 (1.1)	Reference	Reference	<0.0001
Single-LTC	4668 (97.2)	134 (2.8)	2.69 (1.81-4.01)	1.81 (1.21-2.73)	
Evolving multimorbidity	3566 (95.4)	174 (4.6)	4.59 (3.10-6.78)	2.26 (1.51-3.38)	
Moderate multimorbidity	2349 (92.8)	183 (7.2)	7.22 (4.89-10.7)	2.62 (1.75-3.94)	
High multimorbidity	931 (87.6)	132 (12.4)	13.6 (9.11-20.3)	4.03 (2.64-6.15)	

[1]Adjusted for age, sex, ethnicity, education, employment status, and marital status. Age was included in the model as a squared term.

[2] p-value for trend.

Abbreviation: LTC, long-term condition.

Discussion

This study examined clusters of LTC based on the accumulation of conditions as trajectories over time, their associations with sociodemographic factors, and all-cause mortality among older adults in England. We identified five distinct clusters that can be described as "no-LTC", "single-LTC", "evolving multimorbidity", "moderate multimorbidity", and "high multimorbidity". We observed that the accumulation of LTC over time progresses differently among older adults with distinction by ethnicity, educational level, and employment status. Specifically, ethnic minorities showed faster/steeper progression towards increased numbers of LTC, whereas higher education and paid employment had a protective effect on the increase in the accumulation of LTC.

Similar to an earlier study, we also found clusters that started with multimorbidity and continued to have higher counts of LTC in the following periods, demonstrating individual variations in the progression of health decline (25). Other existing work has also shown variations in rates of LTC (26). No trajectories were identified demonstrating that health had improved over time (indicated by falling numbers of LTC), a finding that aligns with the existing literature (25-27). This finding may indicate there is limited recovery from LTC in older adults or the result of an older population cohort where the mean number of conditions will likely increase over time (waves) (25).

The faster and steeper progression observed towards increased numbers of LTC in females aligns with previous research, which found that older females accumulated morbidities at a faster rate than most other cohorts (28). An explanation could be that females tend to live longer than males, and as a result, they are more likely to develop chronic conditions associated with ageing, such as arthritis and dementia. The faster development of MLTC in ethnic minorities can be explained by evidence suggesting that access and engagement with healthcare are limited for some population groups, often on the basis of ethnicity. Specifically, a review from NHS Race and Health Observatory (29) suggests that there are clear barriers for people from minority ethnic backgrounds to seek help for mental health problems, and another research has also found lower access to cancer screening in the UK (30). Socioeconomic risk factors are known to be associated with MLTC (31). Our findings support the role of higher educational attainment, a major socioeconomic risk factor, on MLTC prevention. Targeting education inequality is expected to lead further to the restriction of worsening MLTC. The effect of educational attainment on MLTC is thought to be explained by other risk factors that may mediate this association, such as body mass index and smoking (32).

Over their life course, individuals develop MLTC. It is necessary to challenge the common statement that MLTC is inevitable in an ageing society. To do this, the focus on MLTC should shift from sole management of high-risk older individuals to include integrated population-level prevention strategies throughout the life course to address the drivers of MLTC. As Vetrano et al., observe, knowledge of how long-term conditions cluster and how the health trajectories of individuals with multimorbidity change over time, can increase understanding of the complexity and dynamic evolution of multimorbidity clusters, as well as supporting clinicians who manage co-occurring long-term conditions and health policymakers who plan care resources use (33).

This is the first study to examine trajectories of MLTC with a view to stratifying within MLTC to identify those at greatest risk among older adults in England. The main strength of the current study is the use of a large dataset, assessing longitudinal data to examine MLTC trajectories and a dataset that is nationally representative of people aged 50 years and older, including a wide range of long-term conditions and sociodemographics. However, this study has several limitations. Firstly, the measurement of MLTC used was limited to the ten LTC available in the ELSA database, which only encompasses a relatively limited number of possible LTC. Therefore, the results may have been different if more conditions were included in our analysis. Second, although we examined the correlates of MLTC trajectories using the variables measured at the baseline (wave 2), we cannot conclude on the directionality of the associations. Similar to other studies with a longitudinal design that have investigated age-related changes in multimorbidity over time, there is likely to be a confounding of age and period effects (25). Lastly, the probability of being in a cluster membership is based on model assignment, which can lead to misclassification bias.

To conclude, our work concurs with Vetrano et al's observation that health trajectories of older adults with multimorbidity are typically characterised by dynamism and complexity but can still be tracked over time (33). Our findings contribute to existing evidence on the need to develop effective tailored interventions for at-risk individuals. Possible responses include targeting ethnic minorities for multimorbidity prevention. Additionally, higher levels of education can also lead to a further decrease in the number of long-term conditions. Policymakers should also commit to increasing MLTC awareness among at-risks groups and care providers.

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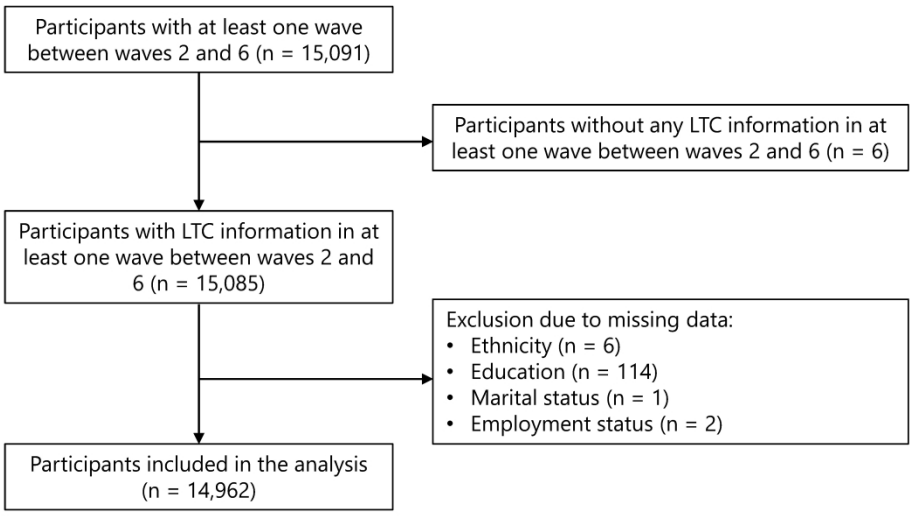
Figure legends

Figure 1. Flow chart of participants selection. MLTC, multiple long-term conditions.

Figure 2. Clusters of long-term condition (LTC) trajectories over time (wave 2 to 6) in the English Longitudinal Study of Aging study. The solid lines represent the estimated mean count of LTC profiles for the five clusters. The "no-LTC" cluster included people who did not have any of the examined LTC; the "single-LTC" cluster included those who did not develop MLTC but may have had one LTC; the ''evolving MLTC'' cluster included those who developed MLTC lately; the ''moderate MLTC'' cluster included those who started with the lower number of MLTC and developed further long-term conditions; the ''high MLTC''

cluster consisted of those who started with the higher number of MLTC and developed additional long-term conditions. Abbreviation: MLTC, Multiple long-term conditions.



Flow chart of participants selection. MLTC, multiple long-term conditions.

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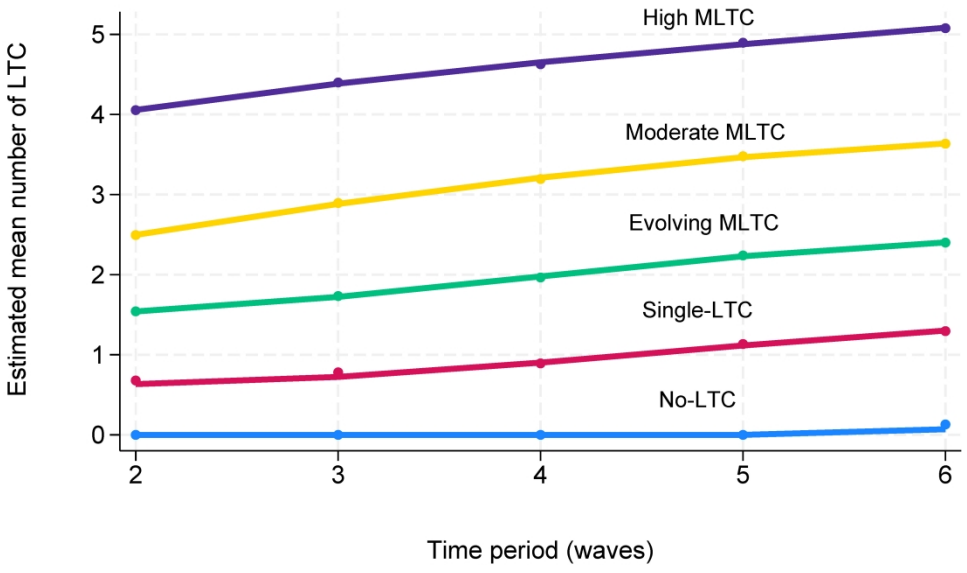

Clusters of long-term condition (LTC) trajectories over time (wave 2 to 6) in the English Longitudinal Study of Aging study. The solid lines represent the estimated mean count of LTC profiles for the five clusters. The "no-LTC" cluster included people who did not have any of the examined LTC; the "single-LTC" cluster included those who did not develop MLTC but may have had one LTC; the "evolving MLTC" cluster included those who developed MLTC lately; the "moderate MLTC" cluster included those who started with the lower number of MLTC and developed further long-term conditions; the "high MLTC" cluster consisted of those who started with the higher number of MLTC and developed additional long-term conditions. Abbreviation: MLTC, Multiple long-term conditions.

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Trajectories in long-term conditions accumulation and mortality in older adults: A group-based trajectory modelling approach using the English Longitudinal Study of Ageing

Christos V. Chalitsios[1], Cornelia Santoso[1], Yvonne Nartey[1], Nusrat Khan[1], Glenn Simpson[1], Nazrul Islam[1], Beth Stuart[2], Andrew Farmer[3], Hajira Dambha-Miller[1]

Supplements

Supplementary Table 1. Statistical parameters of the optimal number of clusters selection.

Number of groups	Group membership		Trajectory shapes	BIC (sample size=15085)	APPA	OCC
1	(1)	100	3	-85493.21	1	N/A
2	(1)	53.49	33	-73870.19	0.94	12.80
	(2)	46.51			0.94	17.71
3	(1)	21.77	333	-63524.35	0.97	105.25
	(2)	53.83			0.96	18.03
	(3)	24.40			0.95	67.92
4	(1)	19.24	3333	-59262.14	0.96	93.69
	(2)	36.07			0.93	24.44
	(3)	32			0.90	19.03
	(4)	12.69			0.96	172.34
5	(1)	19.35	33333	-56474.28	0.97	119.07
	(2)	30.77			0.90	18.95
	(3)	25.43			0.88	23.76
	(4)	17.15			0.90	44.02
	(5)	7.31			0.95	284.50
6	(1)	15.57	333333	-57000.83	0.96	109.69
	(2)	29.21			0.90	19.32
	(3)	23.82			0.87	20.91
	(4)	15.12			0.90	44.32
	(5)	6.27			0.95	259.29
	(6)	10.6			0.92	221.23

Note: Trajectory shapes (0=intercept, 1=linear, 2=quadratic, 3=cubic); BIC = Bayesian Information Criterion; APPA = average posterior probability assignment; OCC = odds of a correct classification according to maximum posterior probability group.

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	6
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6, 7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*6*
Bias	9	Describe any efforts to address potential sources of bias	6, 7
Study size	10	Explain how the study size was arrived at	NA
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	7
		(*c*) Explain how missing data were addressed	7
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	7
		(*e*) Describe any sensitivity analyses	7

Continued on next page

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9
		(b) Give reasons for non-participation at each stage	9
		(c) Consider use of a flow diagram	9
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9, 10
		(b) Indicate number of participants with missing data for each variable of interest	9, 10
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	NA
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	*NA*
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	*13*
		Cross-sectional study—Report numbers of outcome events or summary measures	*NA*
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	13
		(*b*) Report category boundaries when continuous variables were categorized	13
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	14
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	15
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14, 15
Generalisability	21	Discuss the generalisability (external validity) of the study results	14, 15
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	2

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.