Multimorbidity pattern and risk of dementia in later life: an 11-year follow-up study using a large community cohort and linked electronic health records.

Authors:

Mizanur Khondoker*,[1], Alexander Macgregor[1], Max O Bachmann[1], Michael Hornberger[1], Chris Fox[1,2] and Lee Shepstone[1].

Authors' affiliations:

[1]Norwich Medical School, University of East Anglia, Norwich, England, UK.

[2] College of Medicine and Health, University of Exeter, Exeter, England, UK

*Corresponding author

Email: m.khondoker@uea.ac.uk

ABSTRACT

Background: Several long-term chronic illnesses are known to be associated with an increased risk of dementia independently, but little is known how combinations or clusters of potentially interacting chronic conditions may influence the risk of developing dementia.

Methods: 447,888 dementia free participants of the UK Biobank cohort at baseline (2006 – 2010) were followed-up until 31 May 2020 with a median follow-up duration of 11.3 years to identify incident cases of dementia. Latent Class Analysis (LCA) was used to identify multimorbidity patterns at baseline and covariate adjusted Cox regression was used to investigate their predictive effects on the risk of developing dementia. Potential effect moderations by C-reactive protein (CRP) and APOE genotype were assessed via statistical interaction.

Results: LCA identified four multimorbidity clusters representing *Mental health*, *Cardiometabolic*, *Inflammatory/autoimmune* and *Cancer* related pathophysiology respectively. Estimated hazard ratios (HR) suggests that multimorbidity clusters dominated by *Mental health* (HR=2.12, p<0.001, 95%CI: 1.88 to 2.39)*, and *Cardiometabolic* conditions (2.02, p<0.001, 1.87 to 2.19) have the highest risk of developing dementia. Risk level for the *Inflammatory/autoimmune* cluster was intermediate (1.56, p<0.001, 1.37 to 1.78) and that for the *Cancer* cluster was least pronounced (1.36, p<0.001, 1.17 to 1.57). Contrary to expectation, neither C-reactive protein (CRP) nor APOE genotype was found to moderate the effects of multimorbidity clusters on the risk of dementia.

Conclusions: Early identification of older adults at higher risk of accumulating multimorbidity of specific pathophysiology, and tailored interventions to prevent or delay the onset of such multimorbidity may help prevention of dementia.

Keywords: Multimorbidity, Dementia, Latent Class Analysis, Clustering, Hazard Ratio

KEY MESSAGES:

What is already known on this topic: Although individual chronic conditions have been established as risk factors for dementia, how clusters of potentially interacting chronic conditions may influence the risk of dementia is not well known.

What this study adds: Identified statistically robust and reproducible clusters of multiple long-term conditions and investigated their effects on the risk of developing dementia.

How this study might affect research, practice, or policy: Delaying onset of cardiometabolic, psychiatric and inflammatory patterns of multimorbidity may help prevention and management of dementia.

INTRODUCTION

The number of people living with dementia is increasing as the pace of ageing in the worldwide population accelerates, with numbers expected to rise from an estimated 50 million in 2020 to 152 million by 2050[1]. The estimated $818 billion annual worldwide cost (as of 2018) is only a part of the huge burden this poses on people living with dementia, their families, caregivers, and the society as a whole[2]. The estimated prevalence of dementia in the UK (in 2018) was 1.56% of the total population, projected to rise to 2.67% in 2050 [3]. The corresponding prevalence estimates and projections (for 2050) were similar in other European counties, e.g., 1.66% and 2.63% for Sweden, 1.83% and 3.31% for France, 2.12% and 4.13% for Italy, and 1.91% and 3.43% for Germany. There is no cure and focus has been on preventive strategies via early identification of risk factors[4].

The co-occurrence of two or more chronic diseases or medical conditions in one person is termed "multimorbidity"[5]. People with dementia aged over 65 years have, on average, 4.6 of the 10 most common chronic conditions apart from dementia [6], which often start before the onset of dementia and may play a causal role in its development. Previous studies have suggested diabetes, depression, osteoarthritis and hearing impairment as independent risk factors for dementia[7, 8]. Although co-occurring conditions may potentially interact with each other [5], little is known how combinations or clusters of potentially interacting chronic conditions may influence the risk of developing dementia. Better understanding of any potential impacts of multimorbidity patterns on dementia risk is important because this may reveal pathophysiological interactions between disease combinations that may explain underlying causal mechanisms of developing dementia. Knowledge of novel pathophysiological interactions may pave the way towards developing effective prevention strategies and curative medications. A systematic review on the associations between multimorbidity and Alzheimer's disease identified 11 studies most of which were based on small samples, sizes ranging from 40 to 679 [9]. Nine out of 11 studies indicated that multimorbidity was associated with at least one cognitive, functional, and psychiatric domain, but none looked at the direct impacts of patterns of multimorbidity on the development of dementia. Two of the recent cohort studies based on the UK Biobank reported associations of a wide range of individual chronic conditions and a numeric multimorbidity score or binary indicators on dementia [8, 10], but one did not investigate any potential effects of multimorbidity clusters on risk of dementia [8, 10], and the other explored clusters in a subset data within men and women separately [10]. A recent 12-year follow-up study of 2,478 Swedish participants identified specific patterns of multimorbidity to be associated with increased risk of dementia, but to the best of our knowledge, this is the largest study investigating the impact of multimorbidity patterns on incident dementia in the general population [11].

There is substantial variation in the way multimorbidity burden is quantified in the current literature. The commonly used numeric indices of multimorbidity such as the Charlson Index [12] or simple disease count (0, 1, 2, 3, 4+ diseases) has limited usefulness as they do not establish a direct link between specific diseases and the outcome[13]. To facilitate prevention strategies, it would potentially be more useful to know which combinations or patterns of diseases are most strongly associated with dementia.

We report the results from a retrospective longitudinal study investigating the association between multimorbidity patterns on incident dementia based on a large (n=447,888) community cohort (The UK Biobank [14], https://www.ukbiobank.ac.uk). Using algorithmic clustering of the selected conditions we investigated the predictive effects of multimorbidity clusters on the risk of developing dementia.

METHODS

Study design, participants and follow-up: This is a retrospective follow-up study of 447,888 participants aged 40–69 years at baseline (2006 –2010) from the UK Biobank cohort [14] with a median follow-up duration of 11.3 years.

Selection of chronic conditions: Informed by clinical knowledge and the current literature on multimorbidity research [5, 15-18], we selected a concise list of conditions that are considered chronic in nature; have clearly identifiable pathophysiology; are known to have substantial impact on patients in terms of need for long term treatment, reduced function, reduced quality of life, risk of future morbidity, incident dementia and mortality [19]. Consulting recommendations in multimorbidity literature such as the rationale given in a previous work [15] and systematic reviews [16, 18], and the diseases listed in the UK pay-for-performance quality and outcomes framework (QOF)), we have identified a list of 27 chronic conditions that are considered to be useful in ageing and dementia research.

Outcome: Incidence of all-cause dementia (ACD) represented as time-to-events. As is recommended for analysis of disease onset in cohort studies[20], age at dementia onset was defined as the analysis time.

Exposure: Multimorbidity clusters at baseline using a set of 27 pre-selected chronic conditions (Supplementary **Table ST1**).

Covariates: We have accounted for several putative risk factors including the APOE genotype, inflammatory marker (C-reactive protein), and a wide range of potential confounders including socio-demographic factors (age, gender, ethnicity, education, deprivation index), physical and behavioural characteristics (BMI, smoking status), social engagement activities, and geographical location (biobank assessment centres).

Statistical analysis: Latent Class Analysis (LCA)[21-23], widely used in the multimorbidity clustering literature [24-26], was implemented using the R package *poLCA* (https://CRAN.R-project.org/package=poLCA)[27] for clustering multimorbidity. The stability and reproducibility of the cluster solutions were assessed using Jensen–Shannon divergence (JSD) measure [28]. The association of multimorbidity clusters on the risk of developing dementia was tested using Cox regression models [29], implemented using Stata/MP 17.0 (StataCorp. 2021, College Station, TX: StataCorp LLC).

The full methods section is given in the supplementary **Appendix SA1.** We followed the reporting of observational studies in epidemiology (STROBE) guidelines in reporting the results.

Sensitivity analyses: We conducted a sensitivity analysis by excluding the youngest age group (aged <55 years at baseline) which accounted for most of the early-onset dementia cases. As participants diagnosed with cancer at baseline are likely to die before developing dementia, a second sensitivity analysis has been conducted using Fine and Gray's (1999)[30] competing-risks regression by considering cancer related deaths as competing events.

RESULTS

Participants: The final analysis was based on a sample of 447,888 participants. Details are given in the participant flow diagram (**Supplementary Figure SF1**).

Descriptive statistics: Median follow-up time from the date of recruitment (baseline) to the observation end date of the study (31 May 2020, determined by the availability of hospital admission records at the time of project data approval) for detection of incident dementia via the linked NHS hospital admission records and death register was 11.3 years with IQR 10.6 – 12.0

years. To allow temporal precedence of exposure to outcome, incident cases within one year from baseline were excluded. After exclusions, a total of 5,139 incident cases of all cause dementia were included in the final analysis. Descriptive statistics of the participant characteristics at baseline are given in **Table 1** and described in **Supplementary Appendix SA2.**

Table 1*: Descriptive statistics of participant characteristics at baseline (time of recruitment).*

Participant characteristics	All participants (n=447,888)	Participants with ≥ 2 chronic conditions (n=55,908)	Participants with ≤ 1 chronic condition (n=391,980)
Age (years)			
Median (IQR)	58.0 (50.0 –63.0)	62.0 (57.0 – 66.0)	57.0 (49.0 – 63.0)
Sex – n (%)			
Male	204,561 (45.7)	28,750 (51.4)	175,811 (44.8)
Female	243,327 (54.3)	27,158 (48.6)	216,169 (55.2)
Ethnicity – n (%)			
White	424,944 (94.9)	52,862 (94.5)	372,082 (94.9)
BAME	22,944 (5.1)	3,046 (5.6)	19,898 (5.1)
Education – n (%)			
Higher	168,133 (37.5)	15,975 (28.6)	152,158 (38.8)
Upper secondary	49,963 (11.2)	4,823 (8.6)	45,140 (11.5)
Lower secondary	119,366 (26.6)	13,358 (23.9)	106,008 (27.0)
Vocational	29,451 (6.6)	4,451 (8.0)	25,000 (6.4)
Other	80,975 (18.1)	17,301 (30.9)	63,674 (16.2)
Index of multiple deprivation (IMD) – n (%)			
Quintile 1	90,688 (20.2)	8,485 (15.2)	82,203 (21.0)
Quintile 2	90,249 (20.2)	9,581 (17.1)	80,668 (20.6)
Quintile 3	89,617 (20.0)	10,554 (18.9)	79,063 (20.2)
Quintile 4	89,184 (19.9)	11,976 (21.4)	77,208 (19.7)
Quintile 5	88,150 (19.7)	15,312 (27.4)	72,838 (18.6)
Body mass index (BMI)			
Mean (SD)	27.4 (4.8)	29.4 (5.5)	27.1 (4.6)
Smoking – n (%)			
No	245,994 (54.9)	25,413 (45.5)	220,581 (56.3)
Yes	201,894 (45.1)	30,495 (54.5)	171,399 (43.7)
Social engagement activities – n (%)			
No	37,795 (8.4)	5,140 (9.2)	32,655 (8.3)
Yes	410,093 (91.6)	50,768 (90.8)	359,325 (91.7)
APOEε4 genotype – n (%)			
Positive (e3e4 or e4e4)	98,475 (22.0)	12,118 (21.7)	86,357 (22.0)
Negative	224,420 (50.1)	27,501 (49.2)	196,919 (50.2)
Unknown	124,993 (27.9)	16,289 (29.1)	86,357 (27.7)
C-Reactive protein (CRP) – n (%)			
Normal (< 5 mg/L)	395,927 (88.4)	45,014 (80,5)	350,91 (89.5)
Elevated (≥ 5 mg/L)	51,961 (11.6)	10,894 (19.5)	51,961 (10.5)

Latent Class Analysis (LCA): A trace plot of Bayesian information criterion (BIC) and class separation quality (entropy) against the number of latent classes for the training sample is given in **Figure 1(A)**. The goodness-of-fit statistics (AIC and BIC), the percentage change in BIC from ($k-$

1)-class to k-class models, and the entropy values are given in the Supplementary **Table ST2.** Based on the BIC, class separation quality and clinical interpretability of clusters, the four-class solution was chosen as the most concise and optimal representation of the multimorbidity patterns of the study sample (details in **Supplementary Appendices SA1 and SA2**). The distribution of class membership of training sample into the four latent classes is shown in **Figure 1(B)**. The class allocation shares for the optimal four-class solution based on the training sample were 17, 21, 41 and 21% for classes 1 to 4 respectively. The corresponding class distributions for the test and total samples [**Figure 1(C)** and **Figure 1(D)**] were very similar to that of the training sample which we have discussed further within the "Assessment of stability and reproducibility" section

[*Figure1 around here*]

The distribution of the top five dominant conditions for each of the four latent classes obtained from the total (training + test) sample is shown in **Figure 2.** The strength of dominance of a condition within a cluster was measured in terms of *exclusivity* [31], defined as the proportion of participants with a condition c in the ith cluster (n_{ic}) to the total number of participants in the whole sample with that condition (n_c), which can be expressed algebraically as (n_{ic}/n_c).

As can be seen from the cluster compositions in **Figure 2**, the multimorbidity patterns of the algorithmically derived clusters were not always fully consistent with a particular pathophysiological pattern. In this regard, Cluster 3, labelled as cardiometabolic dominated cluster, has performed the best and has shown a clear correspondence with the pathophysiological pattern of cardiometabolic conditions (the exclusivity measures for hypercholesterolemia, heart/circulatory disease, stroke, diabetes, and hypertension were 95, 82, 74, 66 and 58% respectively). The other three clusters were labelled as - Inflammation dominated (Cluster 1), Mental health dominated (Cluster 2), and Cancer dominated (Cluster 4), based on the exclusivity of the top conditions. Similar patterns were observed for the training and test samples (Supplementary **Figures SF2 and SF3**).

[*Figure2 around here*]

Assessment of stability and reproducibility: Details of assessing robustness and reproducibility of the LCA solution are given in Supplementary **Appendices SA1 and SA2.** Briefly, the JSD matrix in **Figure 3(A)** shows that the class-membership distributions of the four-class LCA solutions between the training, test and the full samples are very similar as indicated by the very small JSD values for the three pairwise comparisons (smaller JSD means more similar). The JSD matrices in **Figures 3(B) to 3(D)** compare the distributions of the 27 chronic conditions within each cluster for the four-class LCA solutions between the training, test and full samples. The diagonal elements represent the comparisons between a cluster in one dataset (e.g., training sample) to the corresponding (matching) cluster in the other dataset (e.g., test sample), which were also found to be quite small. The similarity of results in terms of both class-membership distributions and within cluster distributions of the chronic conditions between independent (training and test) datasets provides convincing evidence of robustness and reproducibility of the LCA algorithm applied to this study.

[*Figure3 around here*]

Association between multimorbidity clusters and risk of dementia:

The adjusted hazard ratios (HR) and 95% confidence intervals for the unadjusted and adjusted Cox regression model investigating the association between LCA-based multimorbidity clusters and incidence of dementia are presented in **Table 2.** The log (-log) survival probability plots and plots of scaled Schoenfield residuals for assessing PH assumption are presented in the **Supplementary**

Figures SF4(A) to SF4(J). The plots did not indicate any obvious deviations from the PH assumption for the exposure and the other covariates.

Based on the adjusted model (**Table 2**), the mental health conditions dominated (schizophrenia, depression) cluster showed the highest risk (HR=2.12, 95%CI: 1.88 to 2.39) of developing dementia, followed by cardiometabolic conditions (heart or circulatory system diseases, hypercholesterolemia, stroke, diabetes, hypertension) (HR=2.02, 1.87 to 2.19), inflammatory conditions (rheumatoid arthritis and other inflammatory polyarthropathies, psoriasis) (HR=1.56, 1.37 to 1.78) and cancer dominated clusters (HR=1.36, 1.17 to 1.57) respectively.

Assessment of statistical interaction in the Cox regression analysis suggested that the association between multimorbidity cluster and risk of dementia did not differ by APOE genotype or CRP level (multimorbidity cluster × APOEε4: Wald chi-squared (8) = 6.1, p=0.636; multimorbidity cluster × CRP: Wald chi-squared (4) =4.1, p=0.396). As the interaction terms were not statistically significant, only the main effects of APOE genotype and CRP were retained in the final analysis model (Table 2).

Table 2: Cox Regression analysis with LCA-based multimorbidity clusters as the exposure: hazard ratios (HR) and 95% confidence intervals (CI) for unadjusted and covariate adjusted Cox regression model.

Variables	Unadjusted		Covariate adjusted	
	HR	95% CI	HR	95% CI
Multimorbidity clusters (ref: No multimorbidity)				
Inflammation dominated	1.56	(1.37, 1.78)	1.56	(1.37, 1.78)
Mental health dominated	2.07	(1.84, 2.33)	2.12	(1.88, 2.39)
Cardiometabolic dominated	2.25	(2.08, 2.43)	2.02	(1.87, 2.19)
Cancer dominated	1.23	(1.06, 1.42)	1.36	(1.17, 1.57)
Sex (ref: Male)				
Female	--	--	0.79	(0.74, 0.83)
Ethnicity (ref: White)				
BAME	--	--	1.11	(0.96, 1.28)
Education (ref: Higher)				
Upper secondary	--	--	1.23	(1.11, 1.37)
Lower secondary	--	--	1.08	(0.99, 1.17)
Vocational	--	--	1.17	(1.04, 1.31)
Other	--	--	1.28	(1.19, 1.38)
Index of multiple deprivation (IMD, ref: Quintile 1)				
Quintile 2	--	--	1.08	(0.99, 1.19)
Quintile 3	--	--	1.05	(0.96, 1.16)
Quintile 4	--	--	1.25	(1.13, 1.37)
Quintile 5	--	--	1.62	(1.48, 1.79)
Body mass index (BMI)				
BMI (kg/m^2)	--	--	1.00	(0.99, 1.00)
Smoking (ref: Never smoker)				
Current or past smoker	--	--	1.11	(1.05, 1.18)
Social engagement (ref: Yes)				
No	--	--	1.33	(1.21, 1.46)
APOEe4 (ref: Negative)				
Positive (e3e4 or e4e4)	--	--	2.76	(2.59, 2.94)
C-Reactive protein (CRP) - (ref: Normal <5 mg/L)				
Elevated (≥ 5 mg/L)	--	--	1.20	(1.10, 1.30)
Assessment centre (ref: Manchester)				
21 Centres (including the reference) [*]	Reported in the Supplementary **Table ST3**			

In terms of the effects of important covariates, people without sufficient engagement in social and leisure activities were more likely to develop dementia (HR=1.33, 95%CI: 1.21 to 1.46). As is well established in the literature, carriers of at least one copy of APOEε4 genotype were substantially more likely to develop dementia (HR=2.76, 95%CI: 2.59 to 2.94). Elevated level of inflammation measured via CRP (≥ 5 mg/L) compared to normal level (<5 mg/L) was associated with increased risk of dementia (HR=1.20, 95%CI: 1.10 to 1.30) which is a novel finding for the UK Biobank cohort.

The results from the sensitivity analysis excluding youngest age group (**Supplementary Table ST4**) appear very similar to that of the main analysis (**Table 2**). Also, the sensitivity analysis accounting for cancer related deaths as competing events (**Supplementary Table ST5**) did not change the effects for mental health, cardiometabolic or inflammatory clusters materially.

DISCUSSION

Summary of key findings: The LCA analyses revealed four clusters of multimorbidity patterns of which the *Inflammation/Autoimmune* cluster (with rheumatoid arthritis, other inflammatory polyarthropathies, and psoriasis as the dominant conditions) and its association with dementia was a novel finding in our study. The other three clusters, named according to the dominant pathophysiological patterns of the conditions, were: *Mental health* (dominant conditions: schizophrenia and depression), *Cardiometabolic* (dominant conditions: heart or circulatory system diseases, hypercholesterolemia, stroke, diabetes, hypertension), and *Cancer cluster* (dominant conditions: various types of cancer). Risk of developing dementia for the *Mental health (or psychiatric)* and *Cardiometabolic* conditions were about two-fold higher (2.1- and 2.0 -fold higher relative hazard respectively) than that of the reference group with no multimorbidity. The increased risk for the *Inflammatory/autoimmune* cluster (1.6-fold) was intermediate. The *Cancer* cluster also indicated a higher susceptibility to develop dementia, but the relative hazard for this cluster was least pronounced (1.4-fold). Carriers of APOEε4 genotype were associated with increased risk of dementia as expected. A novel finding for the UK Biobank cohort was the association of CRP: higher levels of CRP were associated with increased risk of dementia.

The research and the findings in context of literature: Prevalence of multimorbidity in people with dementia is a norm rather than exception but understanding the predictive role of multimorbidity patterns in developing dementia is an under-researched area. New studies have however started to emerge in this interesting field. A Swedish cohort study used fuzzy c-means clustering and found three multimorbidity patterns: *neuropsychiatric*, *cardiovascular*, and *sensory impairment/cancer* to be associated with incident dementia [11]. An important additional pattern found in the current study is the *inflammatory/autoimmune* cluster which is also associated with increased risk of dementia which was also not identified in the gender stratified cluster analysis[10]. Also, rather than cardiovascular conditions forming a standalone cluster as in [11], our study revealed a combined *cardiometabolic* cluster of cardiovascular and metabolic conditions which are well known to be pathophysiologically linked [32]. Other key differences between our findings and that reported in [11] are the *psychiatric* and *cancer* clusters which were revealed in our study as separate patterns rather than jointly clustering with the *neurological* and *sensory* conditions respectively as reported in [11].

Our findings support and add to the existing knowledge on possible biological and pathophysiological links between co-existing chronic conditions and dementia. Specifically, cardiometabolic patterns of multimorbidity posing an increased risk of dementia supports the potential heart-brain connection in ageing such as atherosclerosis and arteriosclerosis as a common underlying pathophysiological mechanism [33]. The association between inflammatory cluster and

dementia may potentially support the perceived hypothesis that increased risk of dementia in rheumatoid arthritis may be caused by inflammation leading to reduced blood flow to the brain[34]. Although APOE genotype or CRP did not moderate the effects of multimorbidity clusters on dementia, both factors were independently associated with risk of dementia. A potential alternative explanation for the role of CRP might be that CRP acts as a catalyst for accumulation of multimorbidity, and multimorbidity acts as an intermediate factor (or mediator) in influencing the risk of dementia (CRP→Multimorbidity→dementia). It's also notable that being an APOEε4 carrier increases the risk of dementia as much as any patterns of multimorbidity. Therefore, integration of genetics and multimorbidity patterns in clinical practice may be useful for making dementia risk clearer.

Strengths and potential limitations of the study: Key strengths of our study includes use of a much larger sample, larger number of incident dementia (5,139 compared to 506 in [11]), and a more objective LCA algorithm based on a more rigorous statistical basis [35]. Taking advantage of bigger cohort, our study provides a more definitive answer to the effect moderation questions suggesting that neither CRP nor APOE genotype moderates the effects of multimorbidity patterns on the risk of developing dementia.

There are several limitations of our study, most of which are inherited from the shortcomings of the UK Biobank cohort. First, the study relied on the linked NHS electronic hospital admission records and death register to identify the chronic conditions and dementia incidence, as the cohort is not fully linked to primary care data. Therefore, there is a possibility of missed diagnosis of chronic conditions as well as dementia cases. Second, the date of diagnosis in hospital admission record does not necessarily indicate the date of onset of a disease, so there may be inaccuracies in the recorded times of exposure (chronic conditions) and of incident dementia. Third, the UK Biobank cohort is not fully representative of the national population (e.g., men, ethnic minority, and socio-economically deprived groups are under-represented) which may have implications on the generalisability of the results. Cross-sectional nature of cluster evaluation and not taking account of possible effects of medications may potentially be the other limiting factors of the study. Furthermore, although the extent of missing data on individual covariates were low, analysis of available data meant removing approximately 10% of the eligible participants due to missing data in at least one of the covariates. We however do not anticipate any substantial undesirable effect of these exclusions as the characteristics of the excluded participants (reported in **Supplementary Table ST6**) were very similar to that of the analysis sample.

CONCLUSIONS

People living with cardiometabolic or mental health clusters of multimorbidity appear to be more than twice as likely to develop dementia as people without multimorbidity. Early detection of emerging pathophysiological patterns during accumulation of multimorbidity in older adults may play an important role in terms of prevention and management of dementia. Delaying onset of cardiometabolic, psychiatric and inflammatory patterns of multimorbidity may help preventing dementia. There is an urgent need to better integrate multimorbidity patterns in risk assessment of dementia in health check-ups. Further research is needed to better understand the longitudinal patterns in accumulation of multimorbidity, the role of inflammation in the accumulation process, and their impact on dementia and other health outcomes.

CONFLICT OF INTEREST

Authors declare no conflict of interest.

RESEARCH ETHICS APPROVAL

UK Biobank has approval from the Northwest Multi-centre Research Ethics Committee (MREC) as a Research Tissue Bank (RTB) approval. This approval means that researchers do not require separate ethical clearance and can operate under the RTB approval.

Supplementary materials: See additional file.

REFERENCES

1. Guerchet, M. and M. Prince, *Numbers of people with dementia worldwide: An update to the estimates in the World Alzheimer Report 2015.* Alzheimer's Disease International (https://www.alzint.org), 2020.
2. Wolters, F.J. and M.A. Ikram, *Epidemiology of Dementia: The Burden on Society, the Challenges for Research.* Methods Mol Biol, 2018. **1750**: p. 3-14.
3. Europe, A., *Dementia in Europe Yearbook 2019: Estimating the prevalence of dementia in Europe.* Alzheimer Europe, 2019. **2019**: p. 180.
4. Robinson, L., E. Tang, and J.-P. Taylor, *Dementia: timely diagnosis and early intervention.* Bmj, 2015. **350**.
5. Boyd, C.M. and M. Fortin, *Future of Multimorbidity Research: How Should Understanding of Multimorbidity Inform Health System Design?* Public Health Reviews, 2010. **32**(2): p. 451-474.
6. Guthrie, B., et al., *Adapting clinical guidelines to take account of multimorbidity.* BMJ : British Medical Journal, 2012. **345**: p. e6341.
7. Norton, S., et al., *Potential for primary prevention of Alzheimer's disease: an analysis of population-based data.* Lancet Neurol, 2014. **13**(8): p. 788-94.
8. Shang, X., et al., *Association of a wide range of chronic diseases and apolipoprotein E4 genotype with subsequent risk of dementia in community-dwelling adults: A retrospective cohort study.* EClinicalMedicine, 2022. **45**: p. 101335-101335.
9. Haaksma, M.L., et al., *Comorbidity and progression of late onset Alzheimer's disease: A systematic review.* PLoS One, 2017. **12**(5): p. e0177044.
10. Calvin, C.M., et al., *Association of Multimorbidity, Disease Clusters, and Modification by Genetic Factors With Risk of Dementia.* JAMA Network Open, 2022. **5**(9): p. e2232124-e2232124.
11. Grande, G., et al., *Multimorbidity burden and dementia risk in older adults: The role of inflammation and genetics.* Alzheimer's & Dementia, 2021. **17**(5): p. 768-776.

12. Charlson, M.E., et al., *A new method of classifying prognostic comorbidity in longitudinal studies: development and validation.* J Chronic Dis, 1987. **40**(5): p. 373-83.

13. Stirland, L.E., et al., *Measuring multimorbidity beyond counting diseases: systematic review of community and population studies and guide to index choice.* BMJ, 2020. **368**: p. m160.

14. Sudlow, C., et al., *UK Biobank: An Open Access Resource for Identifying the Causes of a Wide Range of Complex Diseases of Middle and Old Age.* PLOS Medicine, 2015. **12**(3): p. e1001779.

15. Barnett, K., et al., *Epidemiology of multimorbidity and implications for health care, research, and medical education: a cross-sectional study.* Lancet, 2012. **380**(9836): p. 37-43.

16. Diederichs, C., K. Berger, and D.B. Bartels, *The measurement of multiple chronic diseases--a systematic review on existing multimorbidity indices.* J Gerontol A Biol Sci Med Sci, 2011. **66**(3): p. 301-11.

17. France, E.F., et al., *Multimorbidity in primary care: a systematic review of prospective cohort studies.* The British journal of general practice : the journal of the Royal College of General Practitioners, 2012. **62**(597): p. e297-e307.

18. Ho, I.S.-S., et al., *Examining variation in the measurement of multimorbidity in research: a systematic review of 566 studies.* The Lancet Public Health, 2021. **6**(8): p. e587-e597.

19. Cassell, A., et al., *The epidemiology of multimorbidity in primary care: a retrospective cohort study.* British Journal of General Practice, 2018. **68**(669): p. e245-e251.

20. Thiébaut, A.C. and J. Bénichou, *Choice of time-scale in Cox's model analysis of epidemiologic cohort data: a simulation study.* Stat Med, 2004. **23**(24): p. 3803-20.

21. Lazarsfeld, P. and N. Henry, *Latent structure analysis New York.* NY Houghto-Mifflin Comptllly, 1968.

22. Goodman, L.A., *The analysis of systems of qualitative variables when some of the variables are unobservable. Part IA modified latent structure approach.* American Journal of Sociology, 1974. **79**(5): p. 1179-1259.

23. Goodman, L.A., *Exploratory latent structure analysis using both identifiable and unidentifiable models.* Biometrika, 1974. **61**(2): p. 215-231.

24. Hall, M., et al., *Multimorbidity and survival for patients with acute myocardial infarction in England and Wales: Latent class analysis of a nationwide population-based cohort.* PLoS Med, 2018. **15**(3): p. e1002501.

25. Larsen, F.B., et al., *A Latent Class Analysis of Multimorbidity and the Relationship to Socio-Demographic Factors and Health-Related Quality of Life. A National Population-Based Study of 162,283 Danish Adults.* PLoS One, 2017. **12**(1): p. e0169426.

26. Zhu, Y., et al., *Characteristics, service use and mortality of clusters of multimorbid patients in England: a population-based study.* BMC Med, 2020. **18**(1): p. 78.

27. Linzer, D.A. and J.B. Lewis, *poLCA: An R Package for Polytomous Variable Latent Class Analysis.* Journal of Statistical Software, 2011. **42**(10): p. 1 - 29.

28. Lin, J., *Divergence measures based on the Shannon entropy.* IEEE Transactions on Information theory, 1991. **37**(1): p. 145-151.

29. Cox, D.R., *Regression models and life-tables.* Journal of the Royal Statistical Society: Series B (Methodological), 1972. **34**(2): p. 187-202.

30. Fine, J.P. and R.J. Gray, *A Proportional Hazards Model for the Subdistribution of a Competing Risk.* Journal of the American Statistical Association, 1999. **94**(446): p. 496-509.

31. Vetrano, D.L., et al., *Twelve-year clinical trajectories of multimorbidity in a population of older adults.* Nature Communications, 2020. **11**(1): p. 3223.

32. Qiao, Q., et al., *Metabolic syndrome and cardiovascular disease.* Ann Clin Biochem, 2007. **44**(Pt 3): p. 232-63.

33. Qiu, C. and L. Fratiglioni, *A major role for cardiovascular burden in age-related cognitive decline.* Nat Rev Cardiol, 2015. **12**(5): p. 267-77.

34. Sangha, P.S., et al., *The Link Between Rheumatoid Arthritis and Dementia: A Review.* Cureus, 2020. **12**(4): p. e7855.

35. Schreiber, J.B. and A.J. Pekarik, *Technical Note: Using Latent Class Analysis versus K-means or Hierarchical Clustering to Understand Museum Visitors.* Curator: The Museum Journal, 2014. **57**: p. 45-59.

FIGURE TITLE/ LEGENDS:

Figure 1: **(A):** *The trace plot of Bayesian Information Criterion (BIC) and entropy against the number of latent classes (or, clusters). The numbers within the circular and diamond shapes on the BIC and entropy trace lines represent the number of clusters in the corresponding latent class solution. The numbers beneath the BIC trace line represent the percent reduction in BIC (improvement in model fit) for the corresponding latent class solution compared to that with the previous (with one less number of classes) solution. The numbers above the entropy trace line represent the entropy values (class separation quality) for the corresponding latent class solution. The trace line for entropy starts from two clusters as entropy is not applicable for one-class models. Taken together the improvement in statistical fit index (BIC), the class separation quality (entropy) and the clinical interpretability of the clusters, the* **four-class solution** *has been chosen as a concise and optimal representation of the multimorbidity patterns of the study sample.* **(B), (C)** *and* **(D):** *Class membership distributions of the participants into the four latent classes for the training, test, and total samples respectively.*

Figure 2: *Multimorbidity patterns within the algorithmically derived clusters using LCA on the total sample. Distribution of the top 5 conditions in order of exclusivity (proportion of participants with the condition in the cluster relative to the total number of participants in the sample with that condition) are shown. The four clusters were labelled as* **Inflammation dominated** *(Cluster 1);* **Mental health dominated** *(Cluster 2),* **Cardiometabolic dominated** *(Cluster 3) and* **Cancer dominated** *(Cluster 4) based on the exclusivity criteria of the top conditions.*

Figure 3: **(A):** *Jensen–Shannon divergence (JSD) measures comparing the class membership distributions for the four-cluster latent class solutions between the training, test and full samples. The JSD measures for the three pairwise comparisons were very small (close to zero) suggesting that the class-membership distribution obtained from the training sample is almost identical to that of the test and the full sample.* **(B), (C)** *and* **(D):** *JSD matrix comparing the distributions of the chronic conditions within each cluster for the four-cluster latent class solutions between the training, test and full samples. As expected, the diagonal elements are close to zero suggesting that the distribution of chronic conditions within each cluster obtained from the training sample is very similar to that of the corresponding clusters obtained from the test and the full sample.*
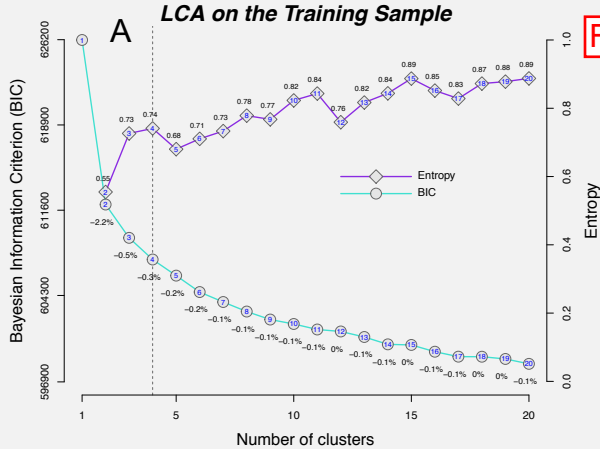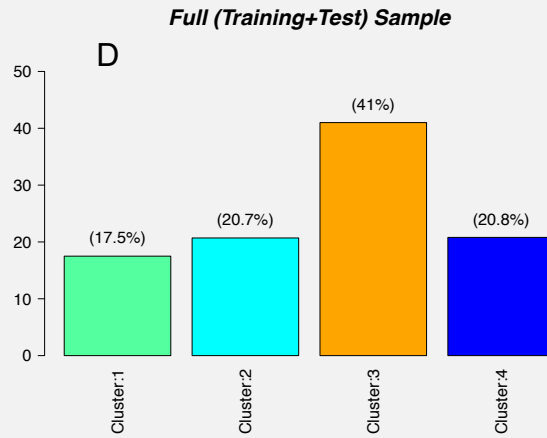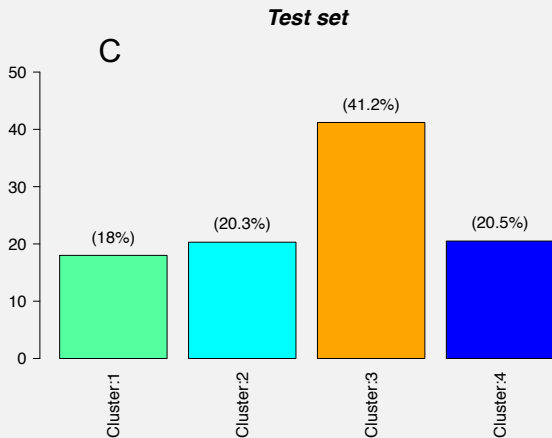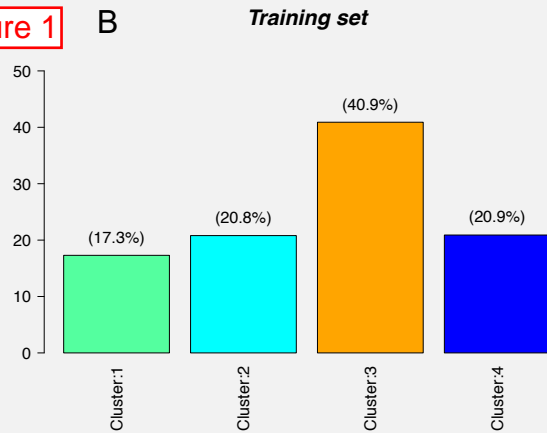

Figure 1

A — LCA on the Training Sample

B — Training set

C — Test set

D — Full (Training+Test) Sample

Total (training + test) sample
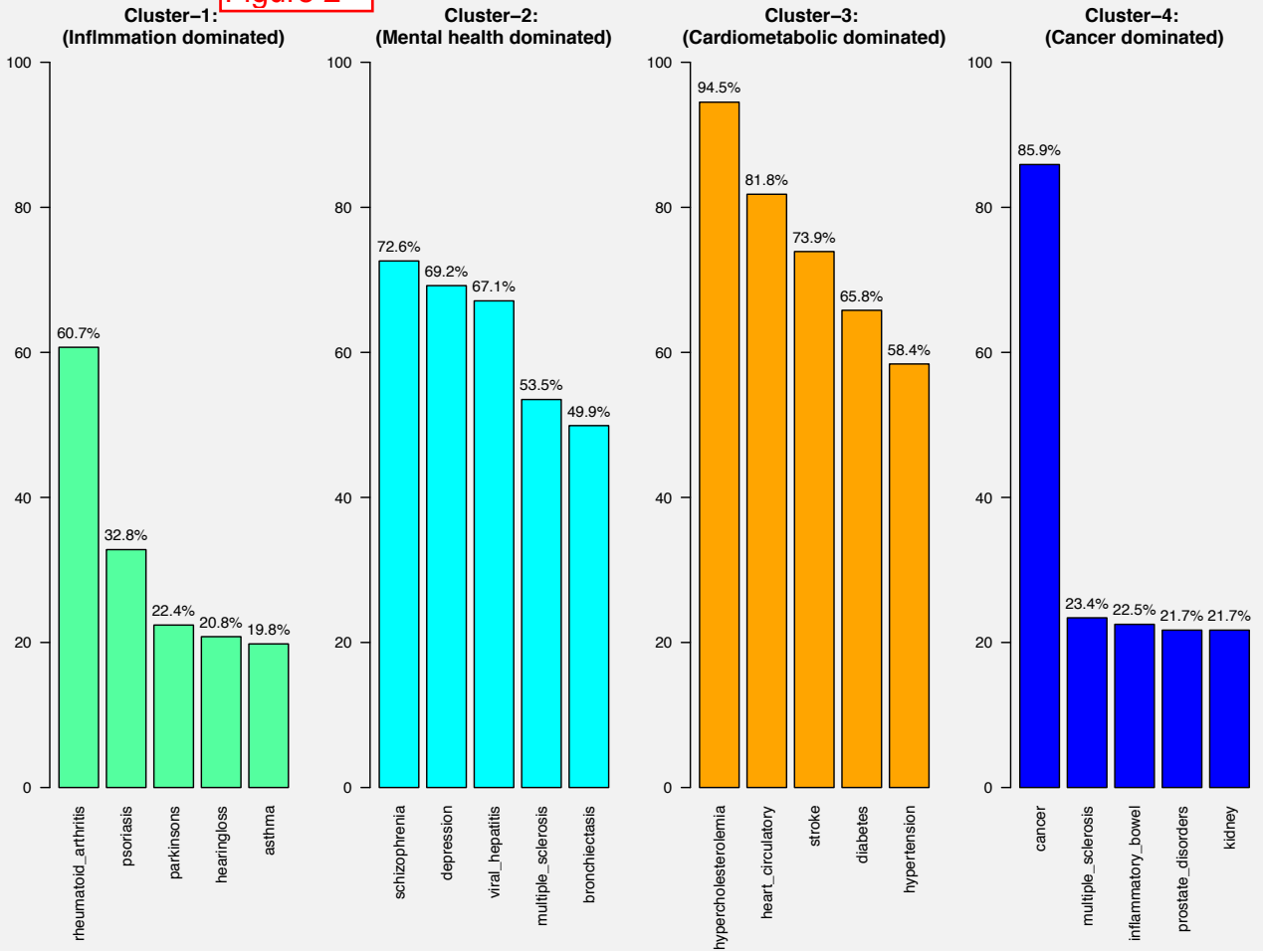
Figure 2

A — JSD (Comparing class membership distributions)

	Full (Training+Test) Sample	Training set	Test set
Full			
Training			
Test			

	Test	Training	Full
Full	4.0×10^{-6}	3.3×10^{-5}	(Full vs. Full)
Training	6.0×10^{-5}	(Train vs. Train)	3.3×10^{-5}
Test	(Test vs. Test)	6.0×10^{-5}	4.0×10^{-6}
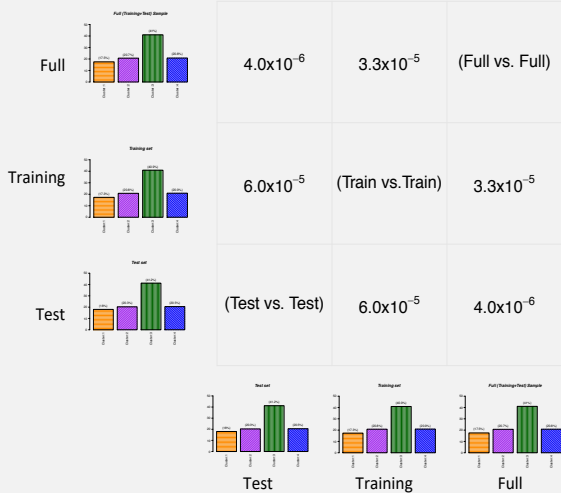
B — JSD (Training vs. test sample)

Training sample vs. Test sample

Training sample	Cluster:1	Cluster:2	Cluster:3	Cluster:4
Cluster:4	0.125	0.091	0.126	0.003
Cluster:3	0.137	0.174	0.008	0.153
Cluster:2	0.141	0.002	0.142	0.098
Cluster:1	0.026	0.112	0.129	0.114
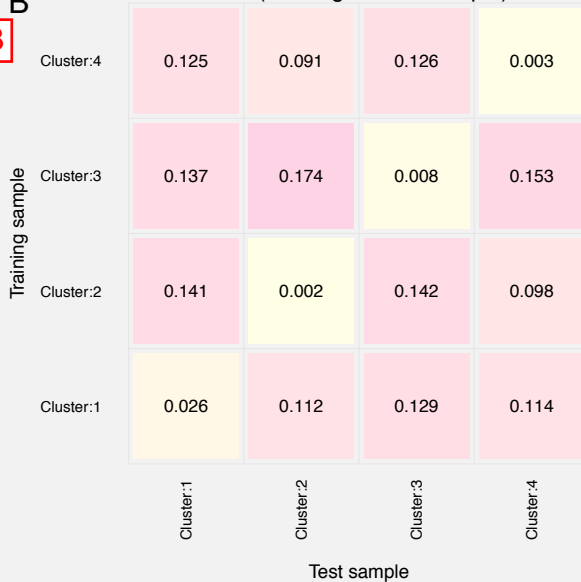
C — JSD (Training vs. full sample)

Training sample vs. Full sample

Training sample	Cluster:1	Cluster:2	Cluster:3	Cluster:4
Cluster:4	0.110	0.095	0.138	<0.001
Cluster:3	0.141	0.178	0.001	0.147
Cluster:2	0.120	<0.001	0.166	0.095
Cluster:1	<0.001	0.115	0.138	0.110

D — JSD (Test vs. full sample)

Test sample vs. Full sample

Test sample	Cluster:1	Cluster:2	Cluster:3	Cluster:4
Cluster:4	0.116	0.097	0.144	0.002
Cluster:3	0.129	0.142	0.004	0.127
Cluster:2	0.116	0.001	0.163	0.091
Cluster:1	0.022	0.14	0.139	0.127

Figure 3

Supplementary materials for:

Multimorbidity pattern and risk of dementia in later life: an 11-year follow-up study using a large community cohort and linked electronic health records.

Supplementary Appendices

Supplementary **Appendix SA1:**

METHODS

Study cohort: This study is based on the UK Biobank cohort [1], a large cohort with over 500,000 participants aged 40–69 years recruited during 2006 –2010, and an extensive range of phenotypic and genotypic details. Participants were recruited via 22 recruitment centres across England, Scotland and Wales covering rural and urban areas. Participants' data records are linked to National Health Service (NHS) hospital admission records, death and cancer registers, primary care records (for part of the cohort), and small area level data (index of multiple deprivation, IMD), thus providing further information on a wide range of health-related measures.

Participants: All participants aged 40 to 69 years at the time of recruitment except those who (i) withdrew consent and ceased to be participants of the cohort, (ii) had pre-existing dementia or developed dementia within one year from the date of recruitment, and (iii) had missing data in either the exposure, outcome, or any of the covariates chosen to be accounted for in the multivariable analysis, were included.

Follow-up: Participants were followed up for incident dementias of all forms until the observation end date (31 May 2020), death or date of loss to follow-up via the linked NHS electronic hospital admission records and death register, with a median follow-up duration of 11.3 years.

Outcome: We used incidence of all-cause dementia (ACD) as the outcome of interest. A participant was defined as an incident ACD case if their NHS hospital admission records or death register had any of the dementia ICD-10 (International Statistical Classification of Diseases and Related Health Problems 10th Revision) diagnosis codes (F00, F01, F02, F03, G30, G31) during the follow-up period. The incidence outcomes were represented as time-to-events (time-to-ACD) for statistical analyse, with time to event defined as age at dementia onset with time of recruitment (baseline) marked as the study entry. The date of first occurrence of ACD in hospital admission record or in death register was defined as the date of onset.

Exposure: Multimorbidity clusters at baseline were the main exposure of interest. Distinct groups of participants (multimorbidity clusters) based on similar patterns of observed co-occurrence of the selected conditions were identified using Latent Class Analysis (LCA)[2-4]. The clustering was based on a set of 27 pre-selected chronic conditions (Supplementary **Table ST1)**. For LCA clusters, participants were allocated to mutually exclusive clusters based on posterior probabilities of cluster membership. More detailed description of the clustering method is given in the Statistical methods section (below).

Covariates: Potential confounders include socio-demographic factors (age, gender, ethnicity, education, deprivation index), physical and behavioural characteristics (BMI, smoking status), social engagement activities, genetic and inflammatory markers (APOE genotype, C-reactive

protein), and geographical location (biobank assessment centres). In addition to being based on a much bigger cohort, our analysis accounted for a more extensive range of risk/confounding factors compared to the similar Swedish study[5]. Apart from the common set of covariates (age, sex, education, BMI) and effect modifiers (CRP and APOE genotype) included both studies, our analysis additionally accounted for ethnicity, index of multiple deprivation (IMD), smoking, social engagement, and geographical location of the participants.

Statistical methods

Algorithmic clustering of multimorbidity patterns: We have used LCA to find multimorbidity clusters using the R package $poLCA$ [6]. LCA is a statistical model-based clustering approach that finds distinct sub-groups of individuals based on similar patterns of multivariate categorical data, here, the sequence of binary (1=Yes, 0=No) indicators of the selected chronic conditions. Unlike many of the distance (or similarity) based exploratory clustering methods, LCA is a model-based probabilistic clustering algorithm in which participants are classified into mutually exclusive and exhaustive classes based on similar patterns of multimorbidity profiles. The method has been widely used in the multimorbidity clustering literature [7-9], as the probabilistic nature of the LCA algorithm based on statistically rigorous maximum likelihood estimation is considered to enhance objectivity, reproducibility, and stability of the clustering solutions. The multimorbid part of the sample, i.e., participants with at least two or more chronic conditions at baseline was used to derive distinct patterns of multimorbidity (clusters) using the LCA algorithm. The binary indicators of the 27 chronic conditions (Supplementary **Table: ST1**) were used as the manifest variables. LCA was run with varying number of classes ranging from a single class to 20 classes. As the likelihood function for latent class model is multimodal, we run LCA with multiple random sets of starting values to maximise the chance of reaching the global optimum. As recommended in the literature, the optimal number of latent classes was decided using a combination of criteria including statistical goodness-of-fit indices (the Bayesian Information Criteria (BIC)) a measure of class separation quality (Entropy) and clinical interpretability of the latent class solution [10, 11]. We used a normalised form of entropy [12], defined as Entropy $(E_k) = 1 - \{\sum_i \sum_k -p_{ik} \ln(p_{ik})\}/\{n \ln(K)\}$ where p_{ik} denotes the posterior probability of individual i in class k. The entropy measure defined above ranges from 0 to 1, where values closer to 1 indicate better separation of classes.

Assessment of stability and reproducibility of the LCA cluster solution: The sample was randomly divided into an independent training set (80% of the multimorbid participants) and a test set (20% of the multimorbid participants). LCA was first applied to the training sample to obtain the optimal latent class solution, which was then replicated in the test set as well as in the full (training and test sets combined) sample for assessment of stability and reproducibility of the cluster solution. The optimal cluster solution learned from the training sample was compared to the corresponding cluster solution obtained from the test sample as well as from the full (training + test) sample. Similarity of cluster solutions between the training and test samples was assessed using a modified (bounded and symmetric) version of the Kullback-Leibler divergence statistic, termed Jensen–Shannon divergence (JSD) measure [13]. JSD measures the similarity between two probability distributions - the smaller the JSD measure, the closer is the similarity between cluster solutions derived from different datasets. We compared the similarity of latent class solutions between the training and test samples at two levels: (i) distribution of cluster membership, and (ii) distribution of the chronic conditions

within each cluster. The former (i.e., comparison of cluster membership distribution) involved assessing the similarity of proportional allocation of the members of the training sample to the latent classes to that of the test sample. The later involved comparing the distribution of the chronic conditions within each cluster of the training sample to that of the test sample.

Association between multimorbidity clusters and risk of dementia: We investigated the effects of multimorbidity clusters accounting for relevant covariates on the risk of developing dementia using Cox regression models [14]. Participants without multimorbidity (zero or one condition at baseline) were considered as the comparison (reference) group. The outcome (incidence of ACD) was represented as time-to-events. Participants not developing dementia during the observation period were considered censored at the end of the study observation (31 May 2020). Participants who were lost to follow-up or died before developing dementia were considered censored at the time of loss to follow-up or death. The Cox regression models included potential confounders as listed in the covariate section and investigated potential effect moderation by APOE genotype and C-reactive protein (CRP) via statistical interaction. In addition to being based on a much bigger cohort, our analysis accounted for a more extensive range of risk/confounding factors compared to[5]. Apart from the common set of covariates (age, sex, education, BMI) and effect modifiers (CRP and APOE genotype) included both studies, our analysis additionally accounted for ethnicity, index of multiple deprivation (IMD), smoking, social engagement, and geographical location of the participants.

The proportional hazards (PH) assumption of the Cox regression analysis was assessed graphically using log (-log) survival probability plots (for the exposure and categorical covariates) and plots of scaled Schoenfield residual [15] (for continuous covariates). As the cluster membership allocation in LCA involves uncertainty (i.e., participants are not typically allocated to clusters with 100% probability), a weighted Cox regression analysis was performed to account for classification uncertainty [16].

Ethical approval: We analysed anonymised data from the UK Biobank, which followed relevant regulatory and ethical procedures.UK Biobank has approval from the North West Multi-centre Research Ethics Committee (MREC) as a Research Tissue Bank (RTB) approval. This approval means that researchers do not require separate ethical clearance and can operate under the RTB approval.

Supplementary **Appendix SA2:**

ADDITIONAL RESULTS

Descriptive Statistics [Table 1, main paper**]:** The median age of the participants in the study sample was 58 years at baseline. The sample consisted of 243,327 (54.3%) females compared to 204,561 (45.7%) males. Participants were predominantly (94.9%) from the White ethnic background in comparison to that from the Black, Asian and minority ethnic (BAME) communities (5.1%). In terms of education, the largest proportion (37.5%) completed higher education (a college or university degree), followed by lower secondary (26.6%), other qualifications (18.1%), higher secondary (11.2%) and vocational qualifications (6.6%). The average BMI of the sample (27.4 kg/m^2) was higher than that is considered ideal (18.5 to 24.9 kg/m^2). There were slightly less current or ex-smokers (44.7%) than non-smokers (56.3%) and 8.1% of the sample reported to be involved in social engagement activities such as frequent family visit and/or leisure activities. The CRP level was categorised normal (< 5

mg/L) and elevated (≥ 5 mg/L). The majority (88.4%) of the participants had normal CRP level and the remaining (11.6%) had elevated CRP. Based on the genotype data 22% of the sample participants were found to be carriers (ε3ε4 or ε4ε4) of Apolipoprotein E (APOE) ε4 allele, the main genetic determinant of Alzheimer's disease risk.

Results from Latent Class Analysis (LCA): The BIC trace plot [**Figure 1(A)**, main paper] shows that the goodness-of-fit of the model improves as the number classes increases, but the magnitude of improvement is very small for models with number of classes (k) above four. Specifically, BIC drops 3.3% from 1-class to 2-class, 0.5% from 2-class to 3-class, and 0.3% from 3-class to 4-class models. The magnitude of improvement in goodness-of-fit continues to decay as k is increased further and appears negligible (ranges between 0% and 0.2%) for $k >$ 4. The entropy value also initially increases up until $k = 4$, reaching 74% for the 4-class model, and then starts to decline. Although some of the models with larger number of classes ($k > 8$) achieved better entropy values than the four-class model, they appeared less interesting in terms pathophysiological interpretability of the cluster structure. Taken together all these criteria (statistical goodness-of-fit, class separation quality and clinical interpretability of clusters), the four-class solution has been chosen as the most concise and optimal representation of the multimorbidity patterns of the study sample.

Results of the assessment of stability and reproducibility of LCA clusters:

The JSD matrix in **Figure 3(A)** compares the similarity of class-membership distributions (Figures 1(B) to 1(D)) of the four-class LCA solutions between the training, test and the full samples. The JSD measures for the three pairwise comparisons were found to be very small, specifically, 6.0×10^{-5}, 4.0×10^{-6} and 3.3×10^{-5} for the training vs. test, training vs. full and test vs. full samples respectively. As the JSD measures for the comparisons are very close to zero, this suggests that the class-membership distribution obtained from the training sample is almost identical to that of the test and the full sample. The JSD matrices in **Figures 3(B) to 3(D)** compare the distributions of the 27 chronic conditions within each cluster for the four-class LCA solutions between the training, test and full samples. The diagonal elements represent the comparisons between a cluster in one dataset (e.g., training sample) to the corresponding (matching) cluster in the other dataset (e.g., test sample). The vectors of diagonal elements for the three pairwise comparisons were found to be (0.026, 0.002, 0.008, 0.003) for the training vs. test; (<0.001, <0.001, 0.001, <0.001) for the training vs. full and (0.022, 0.001, 0.004, 0.002) for the test vs. full sample comparisons respectively. The four numbers within each diagonal line correspond to clusters 1 to 4 (i.e., the inflammation, mental health, cardiometabolic and cancer dominated clusters respectively). In general, the diagonal elements of the JSD matrix for each comparison appear quite small which suggests that the distribution of chronic conditions within each cluster obtained from the training sample is very similar to that of the corresponding clusters obtained from the test and the full sample. The similarity of clustering results in terms of both class-membership distributions and within cluster distributions of the chronic conditions between independent (training and test) datasets provides convincing evidence of robustness and reproducibility of the LCA algorithm applied to this study.

Supplementary Tables

Supplementary **Table ST1:** List of selected chronic conditions for multimorbidity clustering.

Short name	Name of disease/condition	Pathophysiology based clinical group	ICD-10 codes
Epilepsy	Epilepsy	Sensory-neurological	G40
Glaucoma	Glaucoma	Sensory-neurological	H40, H42
Hearing loss	Hearing loss	Sensory-neurological	H90, H91
Migraine	Migraine	Sensory-neurological	G43
Multiple sclerosis	Multiple sclerosis	Sensory-neurological	G35
Parkinson's	Parkinson's disease	Sensory-neurological	G20, G21, G22
Asthma	Asthma	Respiratory	J45
Bronchiectasis	Bronchiectasis	Respiratory	J47
COPD	Chronic obstructive pulmonary disease	Respiratory	J40, J41, J42, J43, J44
Anxiety	Anxiety and other neurotic stress related and somatoform disorders	Psychiatric	F40, F41, F42, F43, F44, F45, F48
Depression	Depression	Psychiatric	F33
Schizophrenia	Schizophrenia	Psychiatric	F20, F25, F28, F29
Diverticulosis	Diverticulosis	Inflammatory/auto-immune	K57
IBD	Inflammatory bowel disease	Inflammatory/auto-immune	K50, K51, K52, K58
Psoriasis	Psoriasis, dermatitis and eczema	Inflammatory/auto-immune	L20, L21, L22, L23, L24, L25, L26, L27, L28, L29, L30, L40
Rheumatoid arthritis	Rheumatoid arthritis and other inflammatory polyarthropathies	Inflammatory/auto-immune	M05-M19, M30-M36
Viral hepatitis	Viral hepatitis	Inflammatory/auto-immune	B18, B19
Diabetes	Diabetes	Cardiovascular-metabolic	E10, E11, E12, E13
Heart	Heart or Circulatory system disease	Cardiovascular-metabolic	I20, I21, I25, I48, I50, I51, I67, I73
Hypercholesterolaemia	Hypercholesterolaemia	Cardiovascular-metabolic	E78.0
Hypertension	Hypertension	Cardiovascular-metabolic	I10, I11, I13, I12, I15
Stroke	Stroke	Cardiovascular-metabolic	I63, I64, H34, I60, I61, G45
Cancer	Cancer	Cancer and other (Cancer/Kidney/Liver/Prostate/Thyroid)	C00-C03, C05-C26, C30, C32-C34, C37-C58, C60-C86, C88, C90-C97, D07, D25
Kidney	Chronic kidney disease	Cancer and other (Cancer/Kidney/Liver/Prostate/Thyroid)	N13, N18, N19, N26, N28, N29, Q61
Liver	Chronic liver disease	Cancer and other (Cancer/Kidney/Liver/Prostate/Thyroid)	K70-K77
Prostate	Prostate disorders	Cancer and other (Cancer/Kidney/Liver/Prostate/Thyroid)	N40, N41, N42
Thyroid	Thyroid disorders	Cancer and other (Cancer/Kidney/Liver/Prostate/Thyroid)	E00- E07

Supplementary **Table ST2:** Akaike information criterion (AIC**)**, Bayesian information criterion (BIC), sample size adjusted BIC (SABIC), and class separation quality (entropy) from the latent class analyses (LCA) on training sample (n= 44,898).

Number of latent classes (k)	AIC	BIC	SABIC	% Change in BIC from (k-1)-class to k-class LCA	% Change in SABIC	Entropy
1	625939	626174	626089	NA	NA	NA
2	611607	612086	611911	-2.2	-2.3	0.55
3	608511	609234	608970	-0.5	-0.5	0.73
4	606411	607378	607025	-0.3	-0.3	0.74
5	604788	605999	605557	-0.2	-0.2	0.68
6	603137	604592	604061	-0.2	-0.2	0.71
7	602040	603739	603120	-0.1	-0.2	0.73
8	600981	602923	602215	-0.1	-0.2	0.78
9	600051	602238	601440	-0.1	-0.1	0.77
10	599427	601858	600971	-0.1	-0.1	0.82
11	598711	601385	600410	-0.1	-0.1	0.84
12	598298	601216	600152	0.0	0.0	0.76
13	597581	600744	599590	-0.1	-0.1	0.82
14	596708	600114	598872	-0.1	-0.1	0.84
15	596413	600064	598732	0.0	0.0	0.89
16	595590	599484	598063	-0.1	-0.1	0.85
17	594922	599060	597551	-0.1	-0.1	0.83
18	594673	599055	597457	0.0	0.0	0.87
19	594238	598864	597176	0.0	0.0	0.88
20	593574	598444	596668	-0.1	-0.1	0.89

Supplementary Table ST3: Hazard ratios (HR), 95% confidence intervals and p-values for the categories of assessment centre in the fully adjusted Cox regression model. These results are from the same model and complementary to those reported in Table 2 (main manuscript).

Variable	Covariate adjusted Hazard Ratio (SE)	p-value	95% CI
UK Biobank assessment centre (Ref: Manchester)			
Oxford	0.94 (0.09)	0.502	(0.77, 1.14)
Cardiff	0.46 (0.05)	<0.001	(0.36, 0.57)
Glasgow	0.22 (0.03)	<0.001	(0.17, 0.28)
Edinburgh	0.18 (0.03)	<0.001	(0.13, 0.25)
Stoke	0.85(0.08)	0.067	(0.71, 1.01)
Reading	0.78 (0.07)	0.009	(0.65, 0.94)
Bury	0.89 (0.07)	0.178	(0.76, 1.05)
Newcastle	0.81 (0.07)	0.009	(0.69, 0.95)
Leeds	0.90 (0.07)	0.190	(0.77, 1.05)
Bristol	0.81 (0.07)	0.016	(0.69, 0.96)
Barts	1.01 (0.11)	0.949	(0.81, 1.25)
Nottingham	1.02 (0.08)	0.825	(0.87, 1.20)
Sheffield	0.82 (0.07)	0.033	(0.70, 0.98)
Liverpool	0.98 (0.08)	0.792	(0.83, 1.15)
Middlesborough	0.92 (0.09)	0.372	(0.77, 1.11)
Hounslow	0.86 (0.08)	0.109	(0.73, 1.03)
Croydon	0.90 (0.08)	0.265	(0.75, 1.08)
Birmingham	0.75 (0.07)	0.004	(0.62, 0.91)
Swansea	0.14 (0.08)	<0.001	(0.05, 0.40)
Wrexham	0.31 (0.22)	<0.096	(0.08, 1.24)

Supplementary Table ST4: Sensitivity analysis excluding the youngest age group (aged <55 years): Unadjusted and covariate adjusted Cox Regression analysis after excluding the youngest age group: hazard ratios (HR) and 95% confidence intervals from Cox regression analysis.

| Exposure variable	Unadjusted		Adjusted	
	HR	95% CI	HR	95% CI
LCA Clusters (ref: No multimorbidity)				
Inflammation dominated	1.51	(1.32, 1.73)	1.52	(1.33, 1.74)
Mental health dominated	1.90	(1.67, 2.15)	1.96	(1.73, 2.23)
Cardiometabolic dominated	2.18	(2.02, 2.36)	1.98	(1.83, 2.15)
Cancer dominated	1.18	(1.01, 1.37)	1.30	(1.12, 1.51)

Supplementary Table ST5: *Competing-risks regression of dementia incidence by accounting for cancer related deaths as competing events: sub-distribution hazard ratios (SHR) and 95% confidence intervals (CI) for unadjusted and covariate adjusted Fine and Gray Competing-risks regression.*

Variables	Unadjusted		Covariate adjusted	
	SHR	95% CI	SHR	95% CI
Multimorbidity clusters (ref: No multimorbidity)				
Inflammation dominated	1.57	(1.38, 1.79)	1.57	(1.37, 1.79)
Mental health dominated	2.08	(1.85, 2.35)	2.14	(1.89, 2.41)
Cardiometabolic dominated	2.23	(2.06, 2.41)	2.01	(1.86, 2.18)
Cancer dominated	1.07	(0.93, 1.24)	1.19	(1.02, 1.37)
Sex (ref: Male)				
Female	--	--	0.79	(0.74, 0.83)
Ethnicity (ref: White)				
BAME	--	--	1.10	(0.96, 1.28)
Education (ref: Higher)				
Upper secondary	--	--	1.23	(1.11, 1.37)
Lower secondary	--	--	1.07	(0.99, 1.17)
Vocational	--	--	1.17	(1.04, 1.31)
Other	--	--	1.29	(1.19, 1.39)
Index of multiple deprivation (IMD, ref: Quintile 1)				
Quintile 2	--	--	1.08	(0.98, 1.19)
Quintile 3	--	--	1.05	(0.96, 1.16)
Quintile 4	--	--	1.24	(1.13, 1.37)
Quintile 5	--	--	1.62	(1.47, 1.78)
Body mass index (BMI)				
BMI (kg/m^2)	--	--	1.00	(0.99, 1.00)
Smoking (ref: Never smoker)				
Current or past smoker	--	--	1.11	(1.05, 1.18)
Social engagement (ref: Yes)				
No	--	--	1.32	(1.21, 1.45)
APOEε4 (ref: Negative)				
Positive (e3e4 or e4e4)	--	--	2.75	(2.59, 2.93)
C-Reactive protein (CRP) - (ref: Normal <5 mg/L)				
Elevated ($\geq$ 5 mg/L)	--	--	1.18	(1.09, 1.28)
Assessment centre (ref: Manchester)				
21 Centres (including the reference)	The coefficients for assessment centres not reported here as they are very similar to that of the main analysis (ST3).			

Supplementary Table ST6: Summary of participants characteristics for the analysis sample and the excluded sample due to missing data.
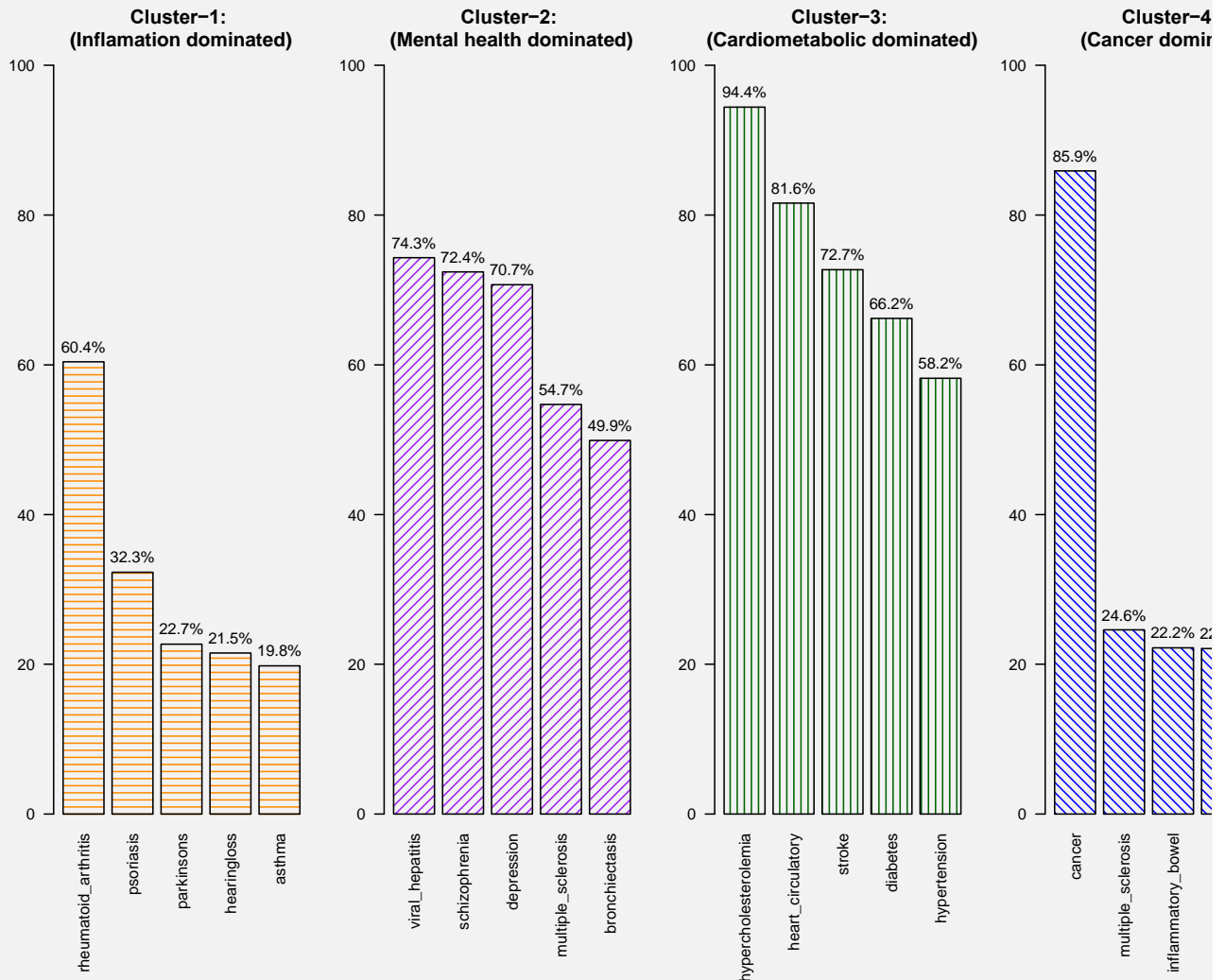
Dataset	Age at baseline (years)	Sex	Ethnicity	Multimorbidity count	Index of multiple deprivation (IMD)
	Mean (SD)	% Female	% White	(Min, Mean, Max)	Mean (SD)
Analysis sample (n=447888)	56.6 (8.1)	54.3	94.9	(0, 0.52, 13)	17.2 (14.0)
Excluded sample (n=54114)	56.3 (8.2)	55.2	92.1	(0, 0.58, 11)	18.9 (15.0)

Supplementary Figures
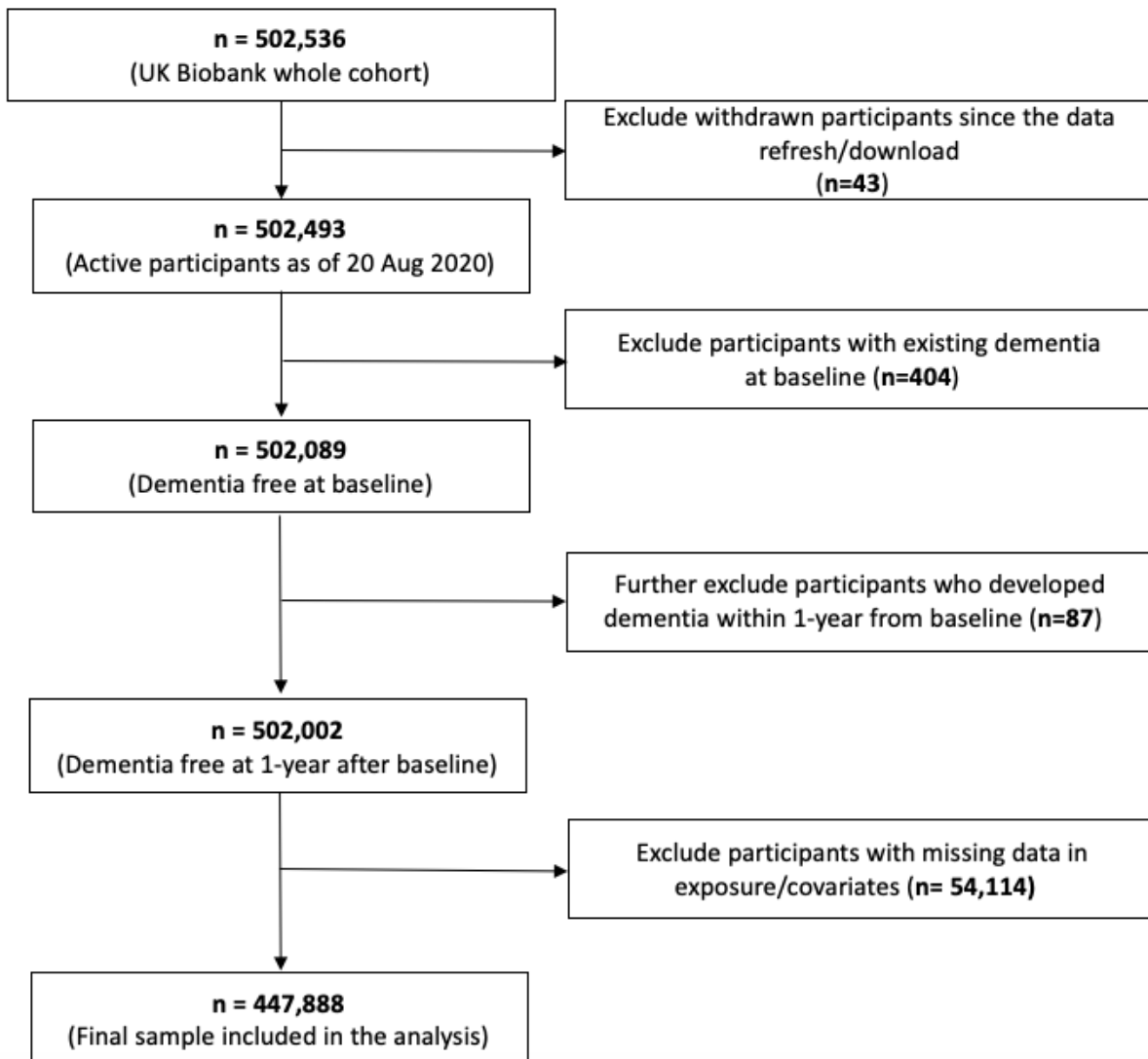
Supplementary Figure SF1: *Participants flow diagram.*

Training sample

Supplementary Figure SF2: *Multimorbidity patterns within the algorithmically derived clusters using LCA on the training sample. Distribution of the top 5 conditions in order of exclusivity (proportion of participants with the condition in the cluster relative to the total number of participants in the sample with that condition) are shown. The four clusters were labelled as* **Inflammation dominated** *(Cluster 1);* **Mental health dominated** *(Cluster 2),* **Cardiometabolic dominated** *(Cluster 3) and* **Cancer dominated** *(Cluster 4) based on the exclusivity of the top conditions.*
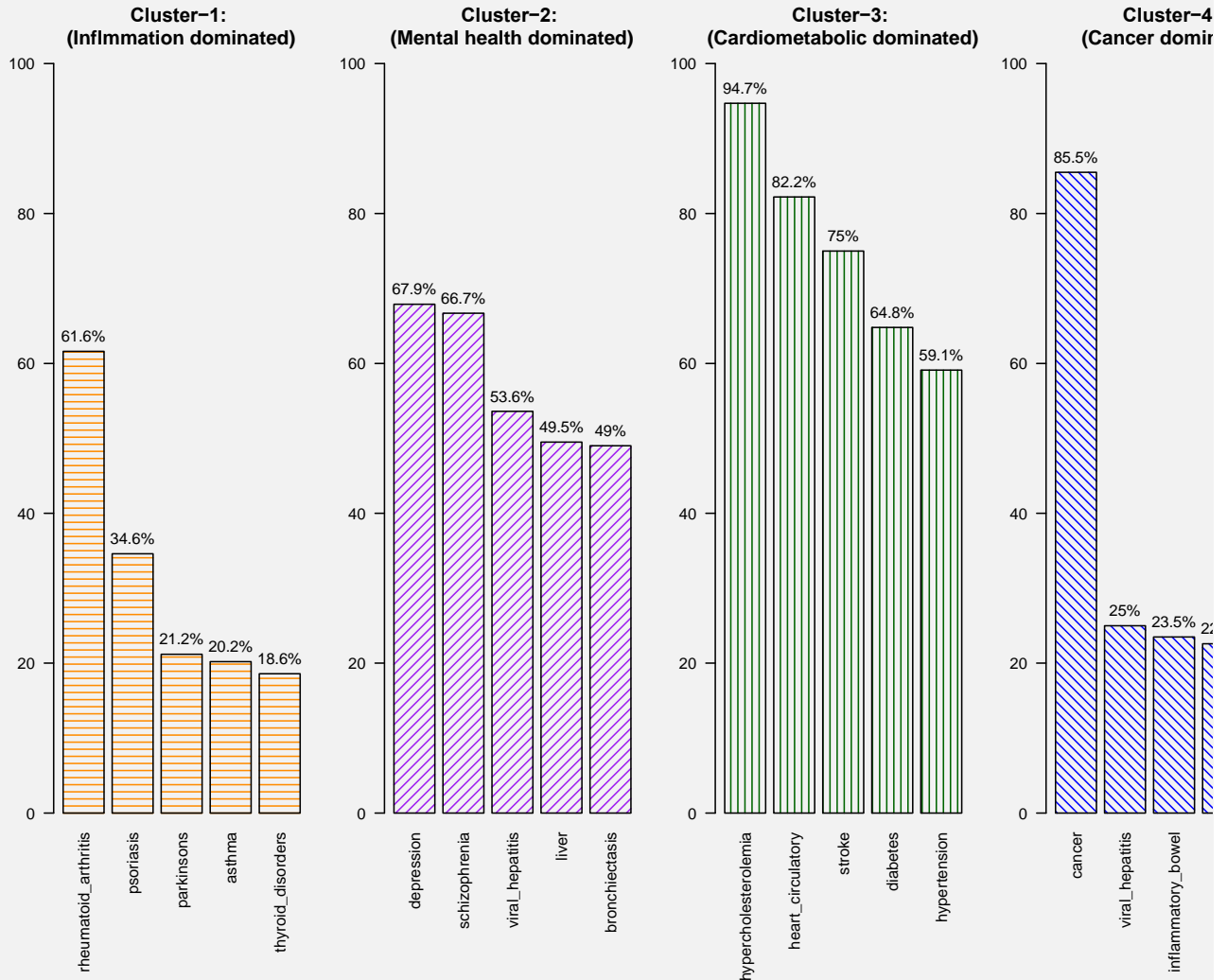
Supplementary Figure SF3: *Multimorbidity patterns within the algorithmically derived clusters using LCA on the test sample. Distribution of the top 5 conditions in order of exclusivity (proportion of participants with the condition in the cluster relative to the total number of participants in the sample with that condition) are shown. The four clusters were labelled as* **Inflammation dominated** *(Cluster 1);* **Mental health dominated** *(Cluster 2),* **Cardiometabolic dominated** *(Cluster 3) and* **Cancer dominated** *(Cluster 4) based on the exclusivity of the top conditions.*

Supplementary Figure SF4: Assessing PH assumption by the exposure and covariates.
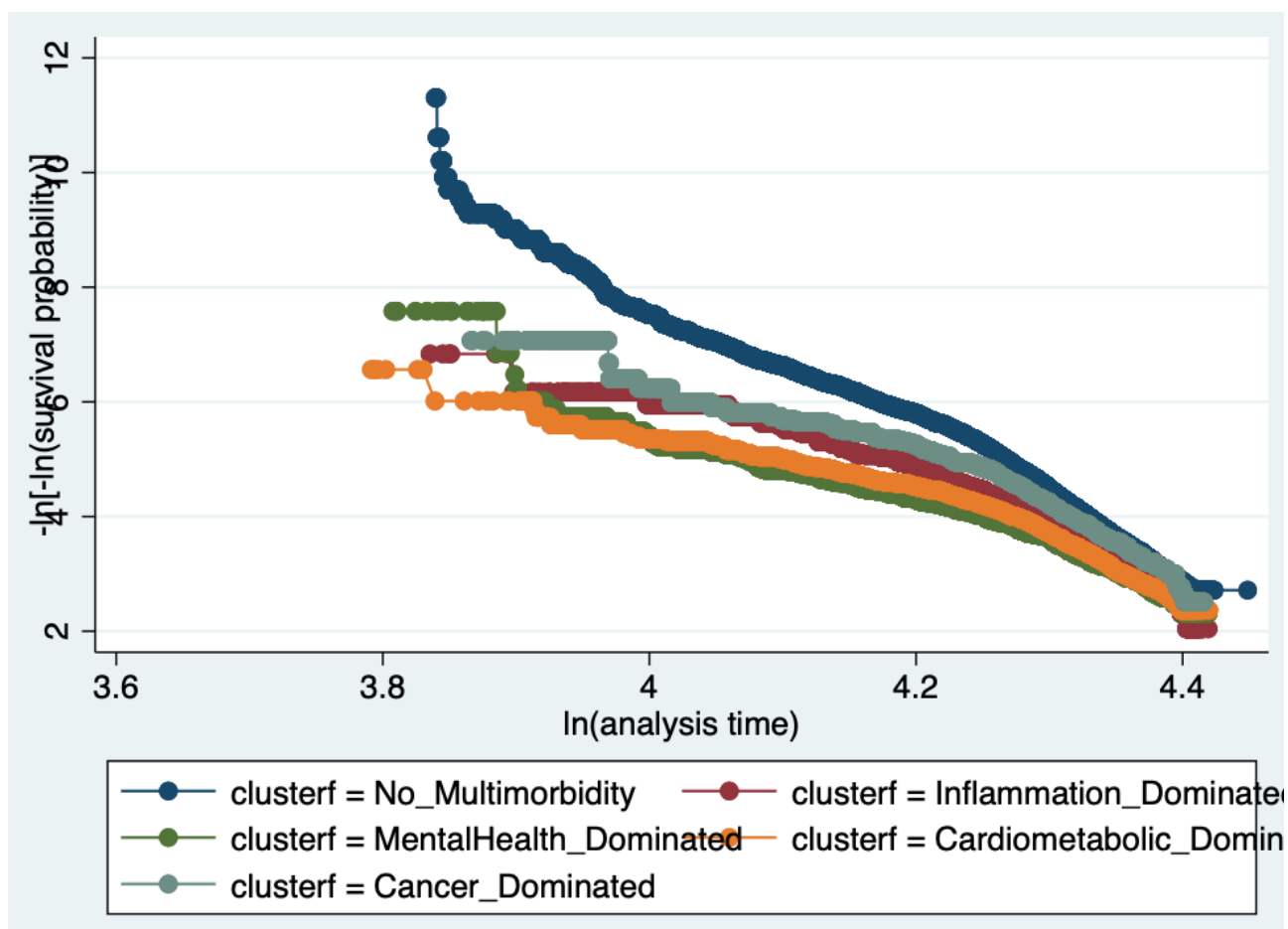
Figure SF4 (A): Log (-log) Survival probability plots by the exposure (LCA clusters) – adjusted for covariates.
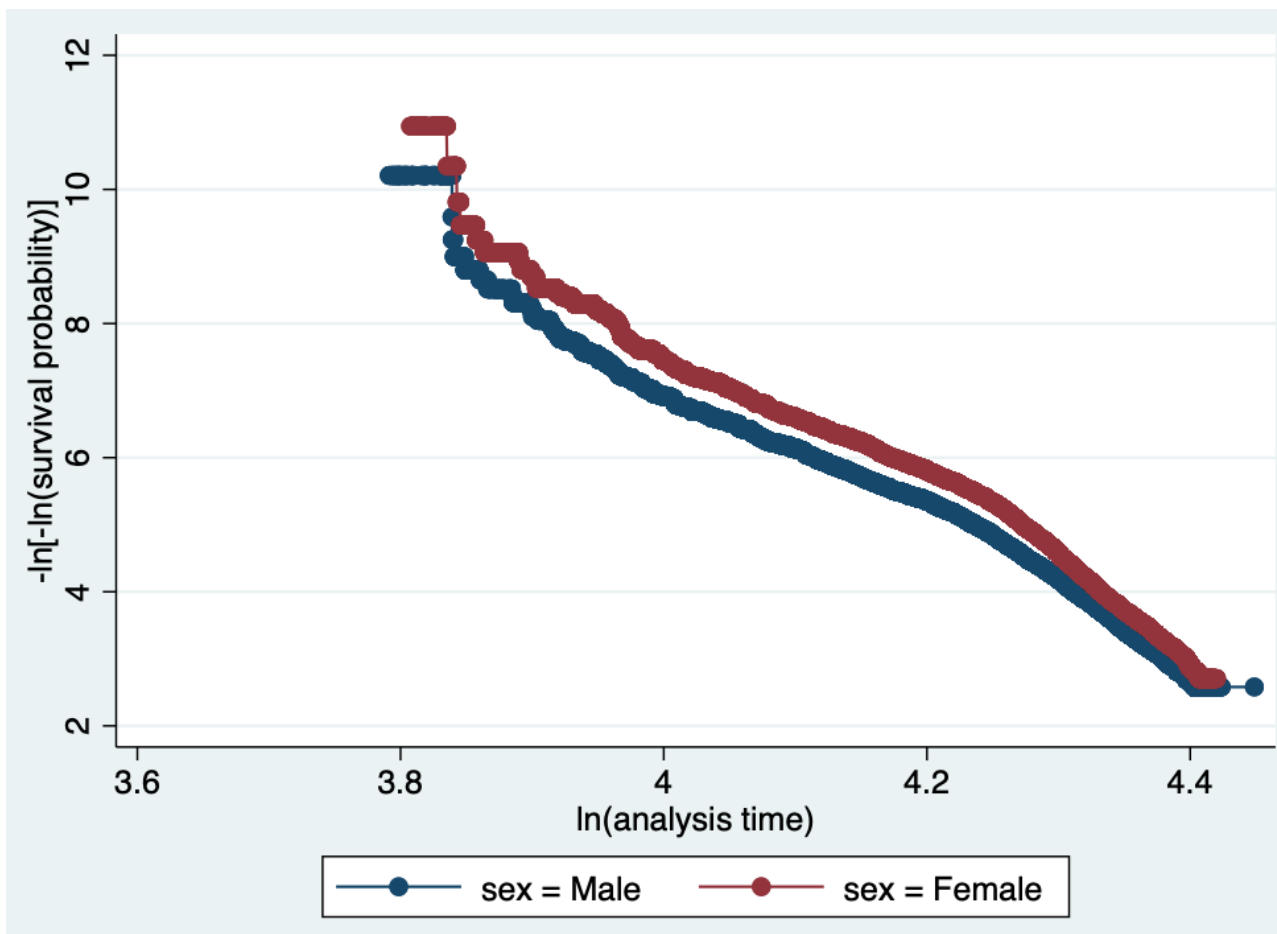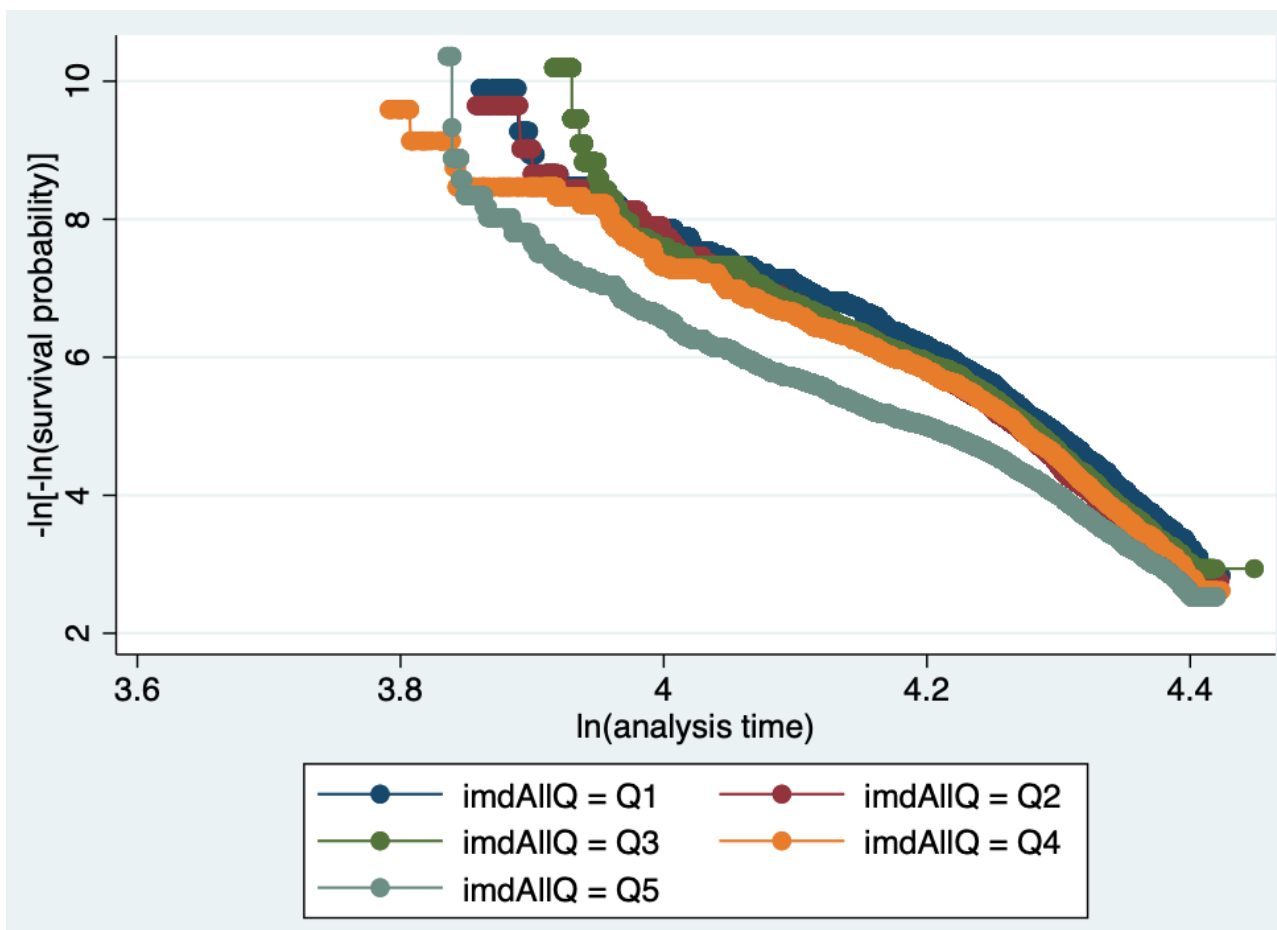
Figure SF4 (B): Log (-log) Survival probability plots by sex categories – adjusted for covariates.
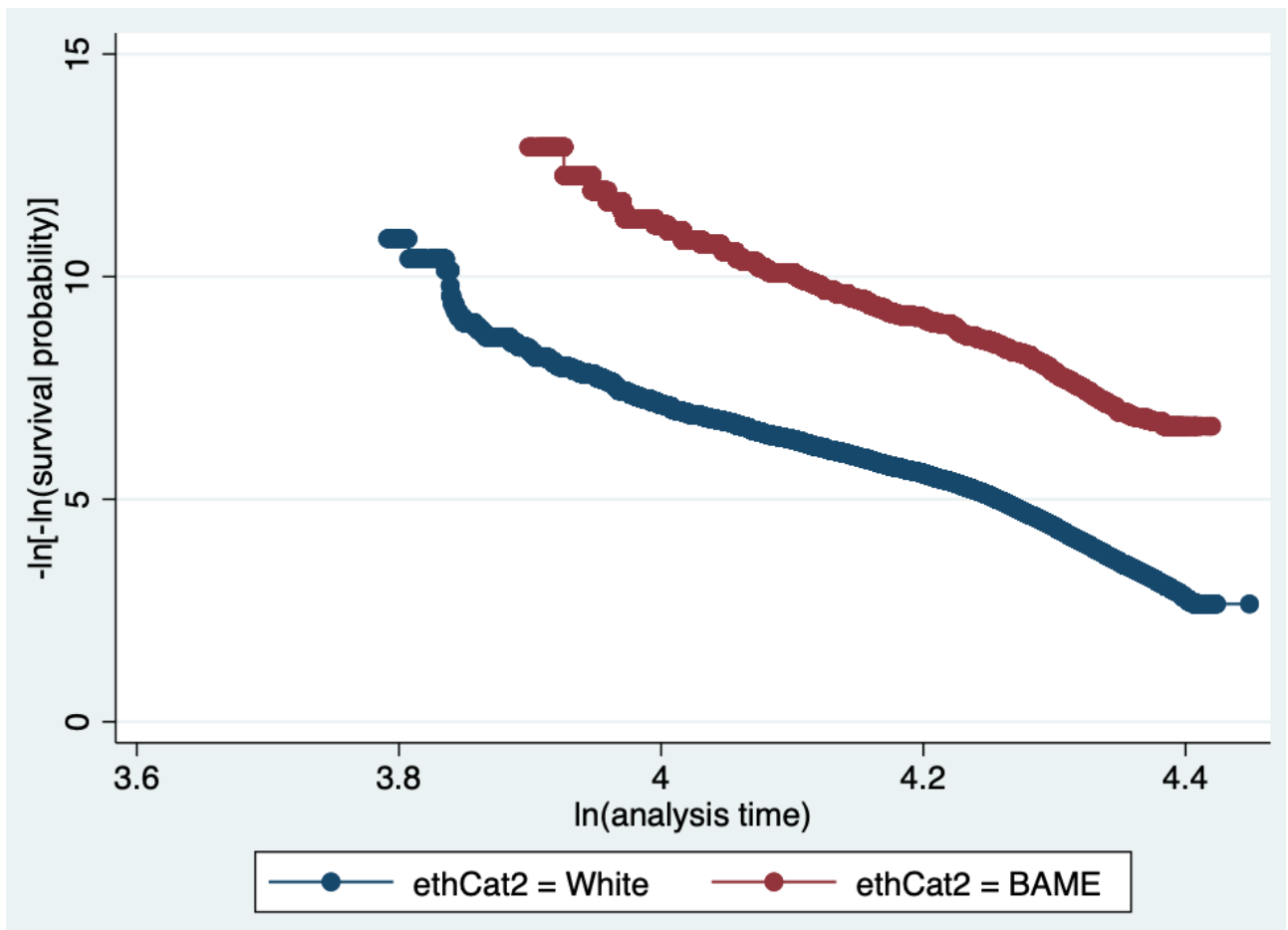
Figure SF4 (C): Log (-log) Survival probability plots by ethnicity categories – adjusted for covariates.
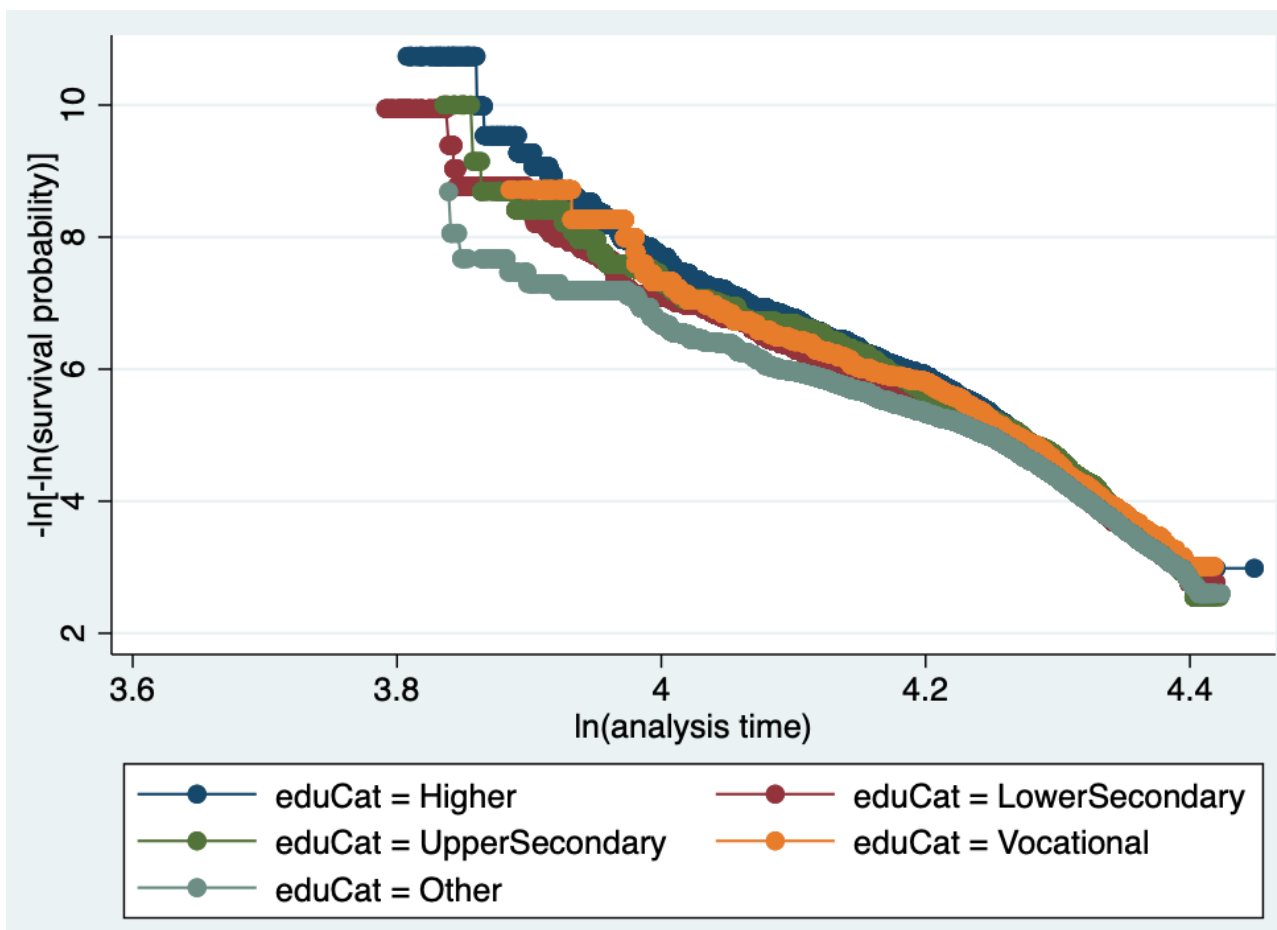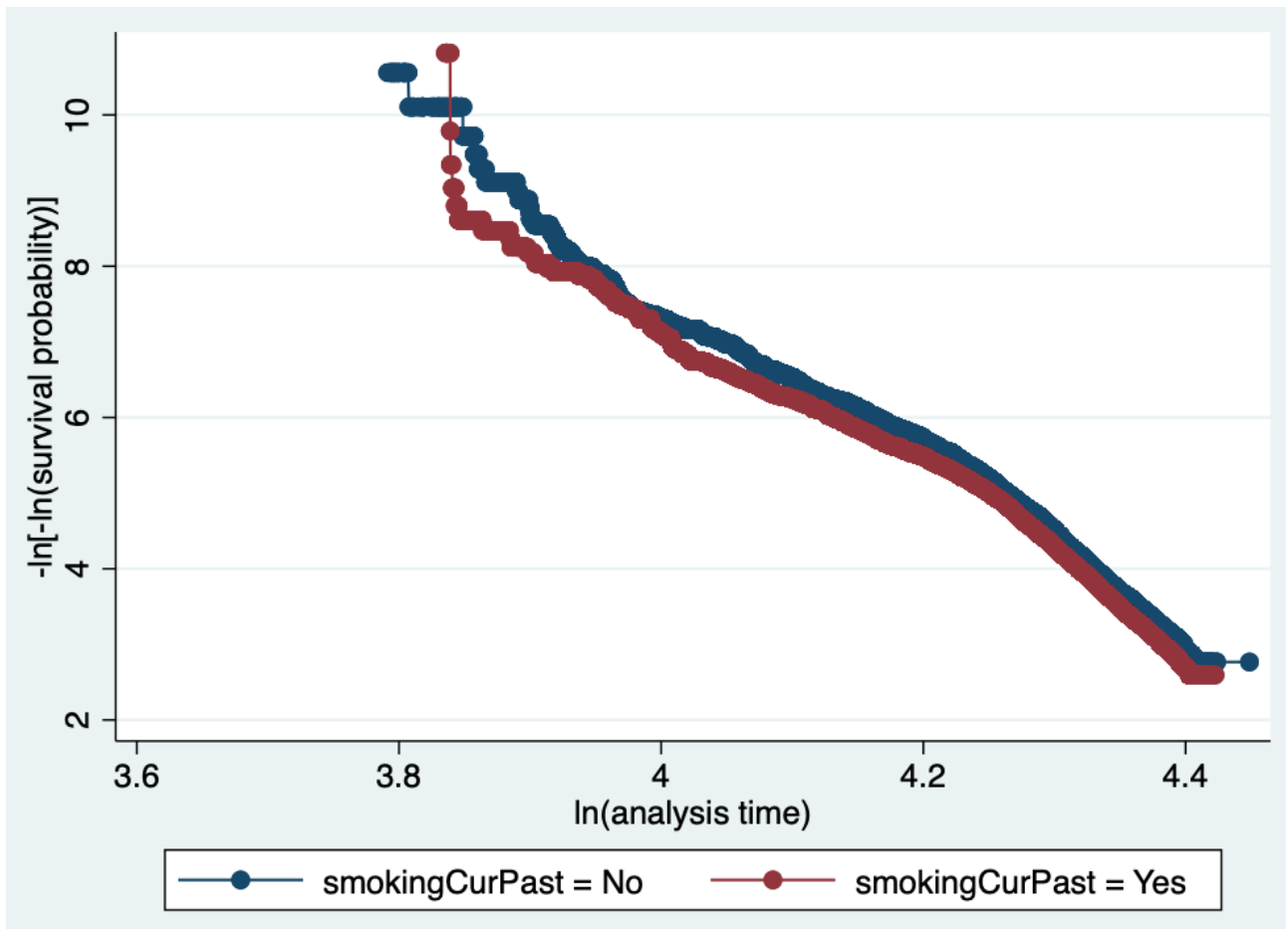
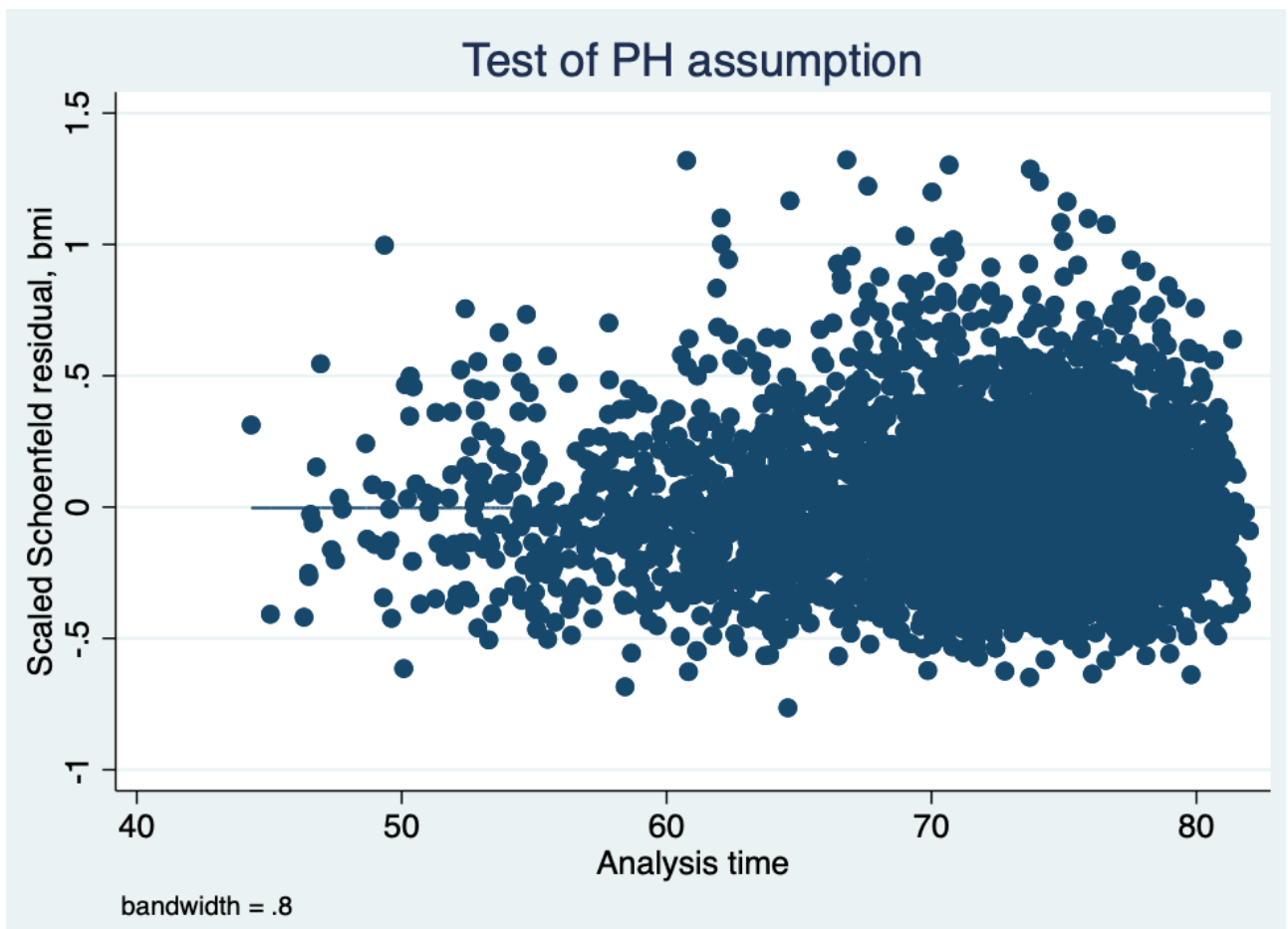**Figure SF4 (D):** Log (-log) Survival probability plots by education categories – adjusted for covariates.

Figure SF4 (E): Log (-log) Survival probability plots by IMD categories – adjusted for covariates.

Figure SF4 (F): Log (-log) Survival probability plots by smoking categories – adjusted for covariates.

Figure SF4 (G): Plot of scaled Schoenfeld residual against time for BMI (from the fully adjusted model)
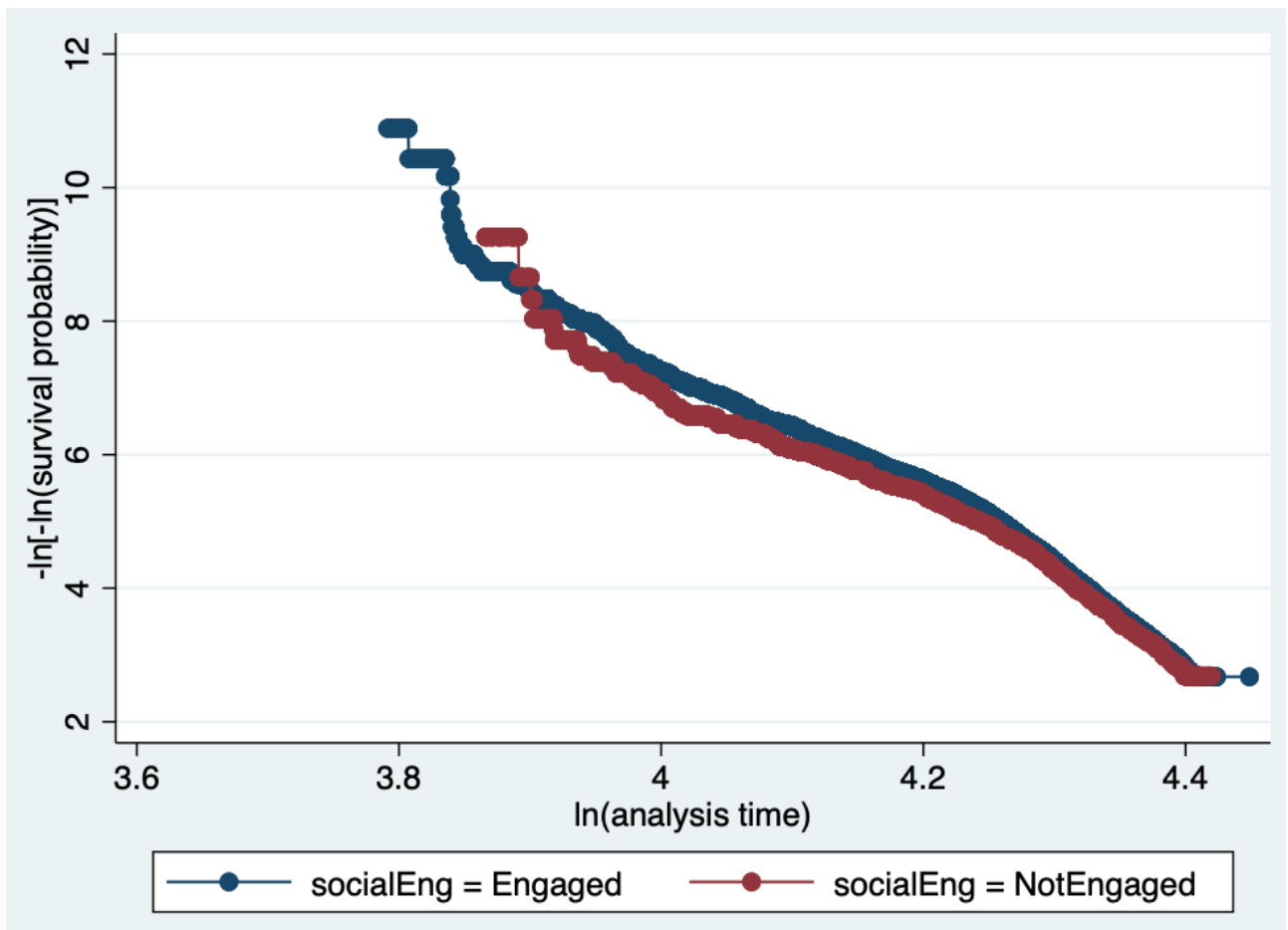
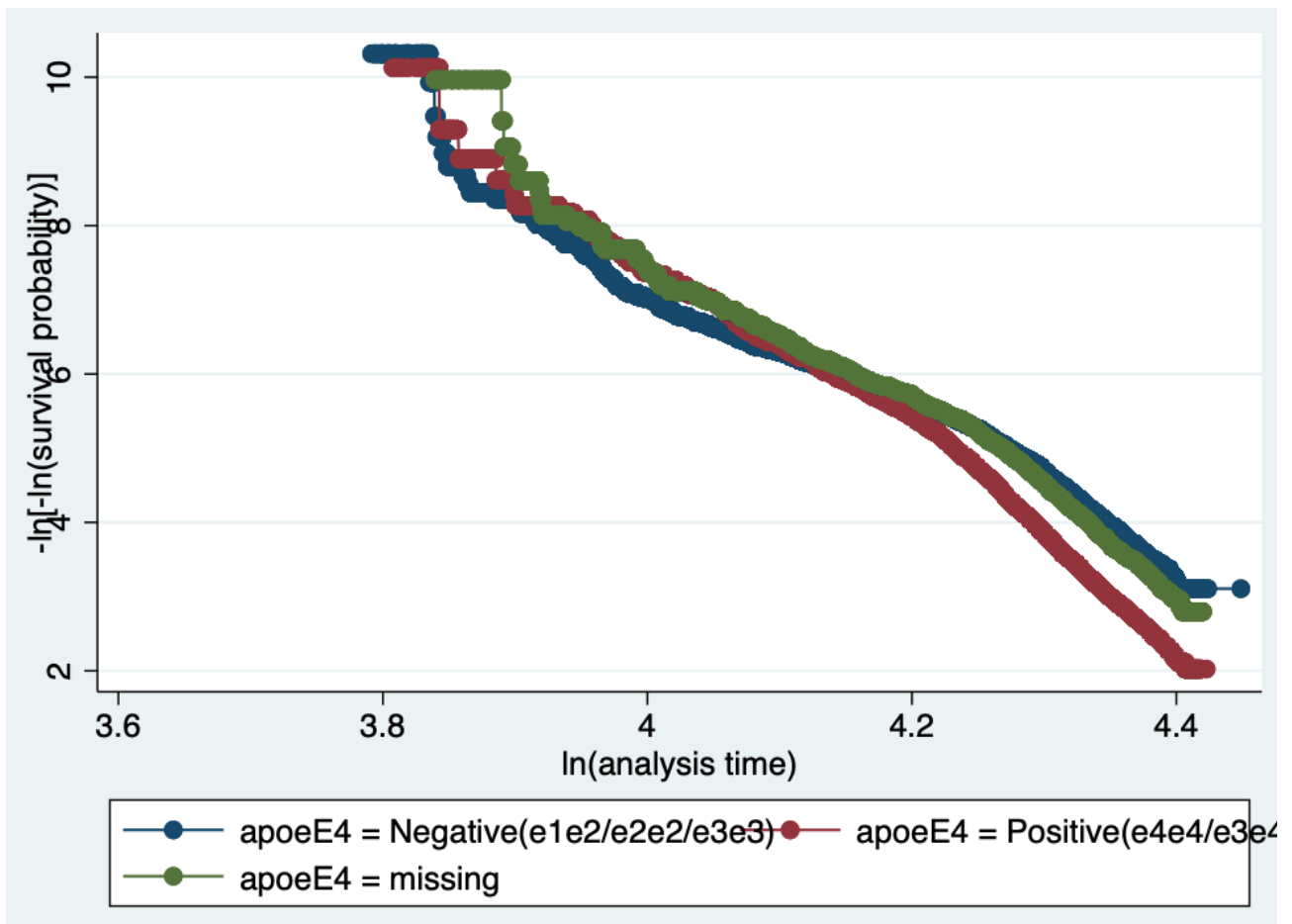**Figure SF4 (H):** Log (-log) Survival probability plots by social engagement activity categories – adjusted for covariates.

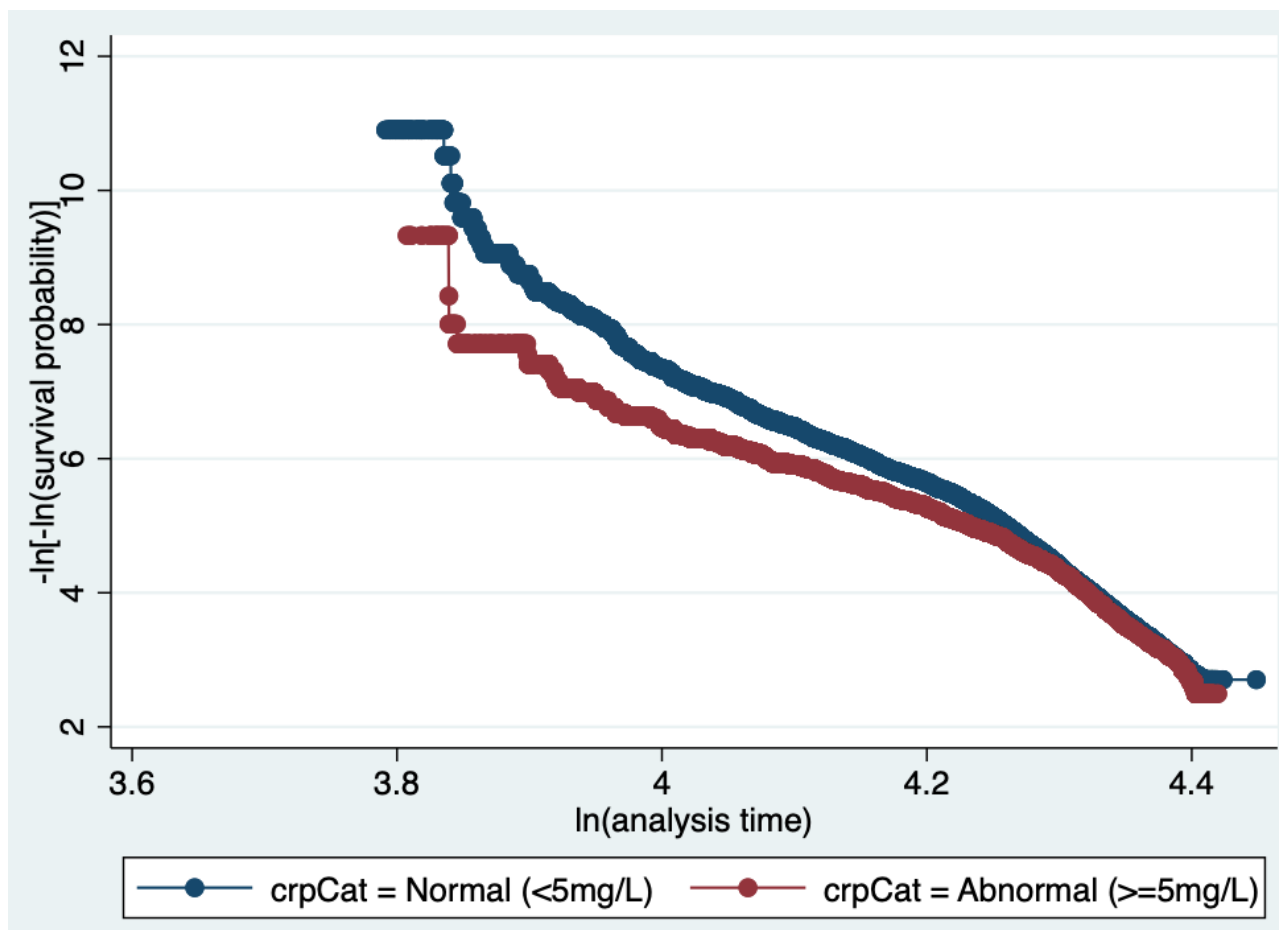**Figure SF4 (I):** Log (-log) Survival probability plots by APOE genotype categories – adjusted for covariates.

Figure SF4 (J): Log (-log) Survival probability plots by CRP categories – adjusted for covariates.

References

1. Sudlow, C., et al., *UK Biobank: An Open Access Resource for Identifying the Causes of a Wide Range of Complex Diseases of Middle and Old Age.* PLOS Medicine, 2015. **12**(3): p. e1001779.
2. Lazarsfeld, P. and N. Henry, *Latent structure analysis New York.* NY Houghto-Mifflin Comptllly, 1968.
3. Goodman, L.A., *The analysis of systems of qualitative variables when some of the variables are unobservable. Part IA modified latent structure approach.* American Journal of Sociology, 1974. **79**(5): p. 1179-1259.

4.   Goodman, L.A., *Exploratory latent structure analysis using both identifiable and unidentifiable models.* Biometrika, 1974. **61**(2): p. 215-231.

5.   Grande, G., et al., *Multimorbidity burden and dementia risk in older adults: The role of inflammation and genetics.* Alzheimer's & Dementia, 2021. **17**(5): p. 768-776.

6.   Linzer, D.A. and J.B. Lewis, *poLCA: An R Package for Polytomous Variable Latent Class Analysis.* Journal of Statistical Software, 2011. **42**(10): p. 1 - 29.

7.   Hall, M., et al., *Multimorbidity and survival for patients with acute myocardial infarction in England and Wales: Latent class analysis of a nationwide population-based cohort.* PLoS Med, 2018. **15**(3): p. e1002501.

8.   Larsen, F.B., et al., *A Latent Class Analysis of Multimorbidity and the Relationship to Socio-Demographic Factors and Health-Related Quality of Life. A National Population-Based Study of 162,283 Danish Adults.* PLoS One, 2017. **12**(1): p. e0169426.

9.   Zhu, Y., et al., *Characteristics, service use and mortality of clusters of multimorbid patients in England: a population-based study.* BMC Med, 2020. **18**(1): p. 78.

10.   Nylund, K.L., T. Asparouhov, and B.O. Muthén, *Deciding on the number of classes in latent class analysis and growth mixture modeling: A Monte Carlo simulation study.* Structural equation modeling: A multidisciplinary Journal, 2007. **14**(4): p. 535-569.

11.   Weller, B.E., N.K. Bowen, and S.J. Faubert, *Latent Class Analysis: A Guide to Best Practice.* Journal of Black Psychology, 2020. **46**(4): p. 287-311.

12.   Ramaswamy, V., et al., *An empirical pooling approach for estimating marketing mix elasticities with PIMS data.* Marketing science, 1993. **12**(1): p. 103-124.

13.   Lin, J., *Divergence measures based on the Shannon entropy.* IEEE Transactions on Information theory, 1991. **37**(1): p. 145-151.

14.   Cox, D.R., *Regression models and life‐tables.* Journal of the Royal Statistical Society: Series B (Methodological), 1972. **34**(2): p. 187-202.

15.   Grambsch, P.M. and T.M. Therneau, *Proportional hazards tests and diagnostics based on weighted residuals.* Biometrika, 1994. **81**(3): p. 515-526.

16.   Bakk, Z., F.B. Tekle, and J.K. Vermunt, *Estimating the association between latent class membership and external variables using bias-adjusted three-step approaches.* Sociological methodology, 2013. **43**(1): p. 272-311.

-----x----