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A syndemic approach to the study of Covid-19-related death: a cohort study using UK Biobank data

Daniela Fonseca de Freitas[1,2,3,†], **Kamaldeep Bhui**[1,4,5,†], **Christophe Clesse**[6,7], **Uzma Zahid**[1,8], **Roisin Mooney**[1], **Easter Joury**[9], **Richard D. Hayes**[2] and **Mizanur Khondoker**[10]

[1]CHiMES Collaborative, Department of Psychiatry, Medical Sciences Division, University of Oxford, Oxford, UK
[2]Department of Psychological Medicine, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK
[3]National Health Service England, London, UK
[4]Nuffield Department of Primary Care Health Sciences, Wadham College, University of Oxford. WPA Collaborating Centre, Oxford, UK
[5]East London and Oxford Health National Health Service Foundation Trusts, Oxford Health Biomedical Research Centre, Global Policy Institute, Queen Mary University of London, London, UK
[6]Centre for Psychiatry and Mental Health, Wolfson Institute of Population Health, Queen Mary University of London, London, UK
[7]School of Psychology, Whitelands College, University of Roehampton, London, UK
[8]Department of Psychology, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK
[9]Dental Public Health, Faculty of Medicine and Dentistry, Queen Mary University of London and Barts Health National Health Service Trust, London, UK
[10]Norwich Medical School, University of East Anglia, Norwich, UK
Address correspondence to Kamaldeep Bhui, E-mail: kam.bhui@psych.ox.ac.uk
†Daniela Fonseca de Freitas and Kamaldeep Bhui are joint first authors.

ABSTRACT

Background The Covid-19 pandemic showed higher infection, severity and death rates among those living in poorer socioeconomic conditions. We use syndemic theory to guide the analyses to investigate the impact of social adversity and multiple long-term conditions (MLTC) on Covid-19 mortality.

Methods The study sample comprised 154 725 UK Biobank participants. Structural equation modeling was used to investigate pathways between traumatic events, economic deprivation, unhealthy behaviors, MLTC, for Covid-19 mortality. Cox regression analysis was used to investigate MLTC and Covid-19 mortality. We also tested effect modification by traumatic events, economic deprivation and unhealthy behaviors.

Results Covid-19 mortality ($n = 186$) was directly explained by overall level of MLTC. Economic deprivation and unhealthy behaviors contributed to Covid-19 death indirectly via their negative impact on MLTC. The risk for Covid-19 mortality grew exponentially for every quintile of predicted scores of MLTC. The presence of traumatic events, economic deprivation or unhealthy behaviors did not modify the impact of MLTC on Covid-19 mortality.

Conclusions Results suggest a serially causal pathway between economic deprivation and unhealthy behaviors leading to MLTC, which increased the risk of Covid-19 mortality. Policies to tackle the social determinants of health and to mitigate the negative impact of multimorbidity are needed.

Keywords: Covid-19; epidemics; ethnic minority; healthcare disparities; mortality; multimorbidity; public health; syndemics

Introduction

Syndemic theory proposes that adverse social conditions and power inequities lead to poorer health outcomes.[2–5] Covid-19 pandemic demonstrated that health crises affect the most vulnerable more severely, showing worse outcomes for some high-risk groups, including those who were obese, had multiple long-term conditions (MLTC), were living in deprived areas and belonged to ethnic minorities.[6] The disproportional high Covid-19 mortality among deprived and racialized communities may be an example of a syndemic.[2,7]

Daniela Fonseca de Freitas, Postdoctoral Researcher
Kamaldeep Bhui, Professor
Christophe Clesse, Postdoctoral Researcher
Uzma Zahid, Postdoctoral Researcher
Roisin Mooney, Postdoctoral Researcher
Easter Joury, National Institute for Health and Care Research Clinical Lecturer and Specialist
Richard D. Hayes, Senior Lecturer
Mizanur Khondoker, Associate Professor

There is uncertainty about the pathways to higher mortality, whether economic deprivation has an indirect impact through long-term conditions, or whether the joint health risks of deprivation and social adversity act in a synergistic way to increase mortality. Differential pathways to mortality may require distinct policy and practice interventions, although synergies between risk factors mean greater benefits if interventions can target these risk factors and the synergistic mechanisms. We investigate pathways to Covid-19 mortality[1,4,8,9] taking account of traumatic events, economic deprivation, health behaviors and higher MLTC burden.

Methods

Setting

In this retrospective cohort study, we used secondary data from the UK Biobank (UKBB), a dataset that benefits from linkages to other health-related records (e.g. hospital data, cancer registries, primary care and death-related data) and has been widely used in Covid-19 studies.[10–13] The UKBB comprises information from 502 412 participants living in the UK and aged 40–69 years at the time of recruitment.[13] The initial recruitment occurred between 2006 and 2010, with new waves of data collection being conducted later.

Ethical procedures were safeguarded by the establishment of the UK Biobank Ethics and Governance Council in 2006. In 2011, the UKBB received ethics approval from the North West Multi-Centre Research Ethics Committee with subsequent renewals every 5 years (references: 11/NW/0382; 16/NW/0274; 21/NW/0157).[13,14] This research was approved by the UKBB (application 57601). The UKBB ensured participants informed consent, in compliance with the Data Protection Act and the Human Tissue Act. Under the established ethics approvals,[14] researchers do not need to make project-based applications for ethics committees. Participants are free to withdraw from UKBB at any time. Data from participants who withdrew from UKBB were excluded from the analyses.

Outcome

Covid-19 mortality was measured between 01/01/2020 and 31/12/2021 via a UKBB data linkage to the Office of National Statistics death certificates. This was defined by Covid-19 registered as the cause or probable cause of death (ICD-10 codes U071 or U072).[11]

Exposures and covariates

Covariates and potential risk factors included sociodemographic information, traumatic events, health behaviors and MLTC. Age was dichotomized at 70 years of age on 1 January 2020. Ethnicity was coded as a binary variable—White British and ethnic minorities—due to the small number of people in each ethnic group who died with Covid-19 (see Table S1 in Supplementary material (SM)). Annual household income was measured at baseline and recoded into a binary indicator of low household income comprising incomes below £31 000. High Townsend deprivation at baseline was recoded into a binary variable comprising the two quintiles with the highest deprivation in all UKBB sample.

Information on traumatic events was collected in a follow-up assessment (in 2016) on a subset of the participants (n = 157 315). These events comprised of: (i) feeling hated by a family member as a child, (ii) not being loved as a child, (iii) physically abused by family as a child, i(v) sexually molested as a child, (v) not having someone to take to a doctor when needed as a child, (vi) victim of physically violent crime, (vii) victim of sexual assault, (viii) witnessing sudden violent death, (ix) belittlement by partner or ex-partner as an adult, (x) physical violence by partner or ex-partner as an adult, (xi) sexual interference by partner or ex-partner without consent as an adult, (xii) involved in combat or exposed to war-zone. Responses were coded into 'never true' or 'rarely true–very often true'; 'prefer not to answer' was considered missing data.

Health behaviors and lifestyle were assessed at baseline. Body mass index (BMI) was used to measure obesity (BMI $\geq$ 30). Alcohol intake was coded into 'never/special occasions' and 'more than 1–3 times per month'. Physical activity levels were coded as 'high/moderate' or 'low'. Poor appetite or overeating, trouble falling or staying asleep or sleeping too much, and ever addicted to any substance or behavior were categorized as 'no' or 'yes'.

Drawing from literature on multimorbidity[15] and Covid-19 death,[10,11,16–18] we considered 29 MLTC up to the start of the observation window (1 March 2020). Detailed information on the diagnoses of each condition is in SM (Table S2). This information was based on self-reported conditions at baseline and the date of the 'first occurrence' of ICD10 diagnoses derived from (i) primary care data, (ii) hospital inpatient data, (iii) death register records and (iv) self-reported medical conditions reported at any assessment. For cancer, we considered self-reported cancers and information from the cancer registers.

Statistical analyses

Syndemics & statistics

Tsai[9] proposed three ways to operationalize syndemic effects:

- 'Mutually causal epidemics' refer to situations where adverse conditions mutually reinforce each other, leading to worse health outcomes.

- 'Synergistically interacting epidemics' refer to the exacerbation effects of having two or more health conditions by which the joint risks exceed the burden of one health risk alone.
- 'Serially causal epidemics' refer to situations where the excessive health burden derives from the accumulation of risks over time, where one adverse condition leads to another health risk.

Moderation analyses are a common way to test the exacerbation effects of interacting diseases, while path analyses are suitable to test models of causal epidemics.[9] Some researchers also estimated individual scores for syndemic effects.[1,9,19]

Modeling synergistic effects using structural equation modeling

We used structural equation modeling (SEM) to investigate the associations between traumatic events, economic deprivation, unhealthy behaviors, MLTC and Covid-19 death. As a data reduction method, we used exploratory factor analyses (EFAs) and confirmatory factor analyses (CFAs) to combine the large number of exposures into a smaller number of latent factors.[20–22] Detailed explanations of the EFAs and CFAs are presented in SM, Appendix B.

The latent factors corresponding to traumatic events, unhealthy behaviors, health condition (MLTC) and economic deprivation were incorporated into SEM models to predict Covid-19–related death. This analysis controlled for gender, age and ethnicity. The following criteria were used to assess satisfactory goodness-of-fit of the CFA models and SEM analysis: the comparative fit index (CFI) > 0.90, the Tucker–Lewis index (TLI) > 0.90, the root mean square error of approximation (RMSEA) < 0.05 and standardized root mean square residual (SRMR) < 0.05. Factor loadings were considered satisfactory if > 0.30.[1,23] We used maximum likelihood for estimation as a method to minimize potential bias caused by missing data.

Estimation of exacerbation effects predicting Covid-19

To test the potential dose–response relationship between Covid-19 death and MLTC, we analysed the association of each level of poorer health condition (MLTC, using quintiles of individual predicted scores identified in the CFA) with Covid-19 death.[1,9] This analysis was performed using Cox regression.

We examined exacerbation effects by assessing whether the effect of MLTC would be aggravated by the presence of adverse social conditions.[1,9] We tested effect modification between MLTC and (i) economic deprivation, (ii) trauma and (iii) unhealthy behaviors, in predicting Covid-19 death in a Cox regression. Based on the CFA models, we used the predicted individual scores of MLTC, traumatic events, economic deprivation and unhealthy behaviors. In the moderation analyses, these scores were dichotomized around the predicted sample mean.

In the Cox analyses, the individual observation periods were censored at the time of death or the end of the window on 31 December 2021. All analyses were conducted in R using the packages 'psych' (EFAs), and 'lavaan' (CFAs and SEM) and survival (Cox regression).[20,21,24]

Results

Sample

Our analyses included 154 725 participants in the UKBB cohort (Fig. S1 in SM). From the UKBB initial, we included: participants that not been lost during UKBB follow-up (as per UKBB monitoring and consent procedures), participants who completed the assessment of traumatic events, and participants who were alive at time of study start date (1 March 2020). In our sample, 57% were women, and the median age at 1 January 2020 was 69 years, with 42% of participants >70. Ethnic minorities comprised 9% of the cohort. During the study observation window, 1.1% of the participants from the sample died, with 0.12% ($n = 186$) having died from Covid-19. More information is presented in Table S1 in SM.

Data reduction

The results of the EFAs and CFAs used to identify natural clusters of traumatic events, unhealthy behaviors and health condition (MLTC) are presented in SM (Appendix A, Tables S3–S5). The CFA model with these three dimensions and the factor of economic deprivation (comprising low household income and high Townsend deprivation) presented a reasonable overall fit. After re-specification, the final model showed a satisfactory fit, with CFI and TLI close to the expected cut-off of > 0.90 and low RMSEA and SRMR values (see Model 1, Table S6 in SM). The four dimensions were all positively correlated, indicating a co-occurrence of traumatic events, economic deprivation, unhealthy habits and MLTC [$r_{[\text{economic deprivation} \sim \text{traumatic events}]} = 0.322$, $P < 0.001$; $r_{[\text{economic deprivation} \sim \text{MLTC}]} = 0.528$, $P < 0.001$; $r_{[\text{economic deprivation} \sim \text{unhealthy behaviors}]} = 0.252$, $P < 0.001$; $r_{[\text{MLTC} \sim \text{traumatic events}]} = 0.133$, $P < 0.001$; $r_{[\text{traumatic events} \sim \text{unhealthy behaviors}]} = 0.531$, $P < 0.001$; $r_{[\text{unhealthy behaviors} \sim \text{MLTC}]} = 0.291$, $P < 0.001$].

Following previous work,[1] we estimated a syndemic load factor, a third-order latent factor. The Goodness-of-Fit (GoF) of the model with syndemic load factor was good, and the standardized factor weights (λ) were of moderate to high strength. The goodness-of-fit indices of the models with the

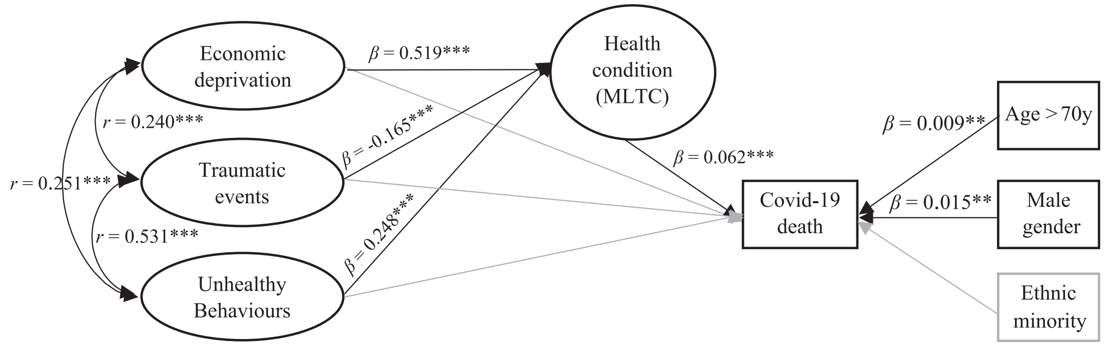

Fig. 1 Structural equations model predicting Covid-19–related death. Gray lines denote non-significant relationships (regression coefficients are not depicted). Dark lines represent significant relationships. $^{***}P < 0.001$, $^{**}P < 0.01$

syndemic load factor and without it were similar (Model 1 versus 2, Table S6 in SM). This suggests that having one third-order factor does not fit the data better than having the four correlated second-order factors.

Predicting Covid-19 mortality

The SEM model with the syndemic load factor predicting Covid-19 death revealed that syndemic load was significantly related to Covid-19 death while adjusting for age, gender and ethnicity (Model 3, Table S6 in SM). The fit of this model to the data was fair.

We tested if Covid-19 death would be directly predicted by trauma, deprivation, unhealthy behaviors and MLTC (Model 4, Table S6 in SM). We observed that only MLTC was a significant predictor of Covid-19 death. Deprivation, trauma and unhealthy behaviors were not significant predictors of Covid-19 death, when adjusting for MLTC. The model presented a fair fit to the data.

Estimation of accumulation of risks via mediation pathway

Given the syndemic effect of serial causation (i.e. a full mediation effect, where the direct effect is nullified when accounting for the mediation factor),[9] we tested if economic deprivation, traumatic events and health behaviors would be indirectly related to Covid-19 death via their association with MLTC. The model revealed that all three dimensions indirectly affected Covid-19 death via their impact on MLTC, but there were no direct effects. Economic deprivation and unhealthy behaviors predicted more MTLC burden, which contributed to higher Covid-19 mortality. Unexpectedly, traumatic events, which in previous models were positively correlated to health condition (MLTC), negatively predicted MTLC, albeit the magnitude of the associations was low. The model's overall fit was fair (see Table 1 for estimates and Fig. 1 for a graphic representation).

Exacerbation of impact or synergies between health conditions

Cox regression results predicting Covid-19 death using the quintiles of predicted individual scores for the MLTC showed that the risk of higher MLTC burden was associated with an exponential increase in risk of Covid-19 death. Compared to the healthier quintile, a person in the second healthiest quintile had almost four times the risk for Covid-19 death, and those in the least healthy quintile had 28 times increased risk (see Table 2 for all HRs and Fig. S3, in SM, for graphical representation).

The moderation analyses showed that the impact of MLTC on Covid-19 death was not modified by the presence of economic deprivation, traumatic events or unhealthy behaviors (see Table 3 for all HRs).

Discussion

Main findings

This study employed a syndemic approach to the study of Covid-19 mortality. The findings have implications for policy and practice. We observed a serial causal effect,[9] whereby economic deprivation and unhealthy behaviors led to MLTC (at the onset of the Covid-19 pandemic) and, consequently Covid-19-related death. The impact of economic deprivation on Covid-19 death seems to be fully mediated by higher MLTC burden.

The results support syndemic theory, whereby in conditions of inequality caused by poverty, stress or structural violence, synergistic effects concur to potentiate the concentration of diseases leading to worse health outcomes.[4,25] Our study did not show social adversity leading to higher mortality independently of MLTC. Consequently, tackling social inequalities is unlikely to reduce mortality, whereas tackling social determinants of MLTC is more likely to pre-

Table 1 Structural equations model: health conditions predicted by economic deprivation, traumatic events and unhealthy behaviors. Health condition predicting Covid-19 death, adjusted for demographics

SEM model goodness-of-fit indices	
CFI: 0.747 TLI: 0.723 RSMEA: 0.034 SRMR: 0.036	AIC: 1018738.252 BIC: 1019931.775 χ^2 (573) = 102057.629, P = <0.001

Standardized coefficients in the SEM model
Covid-19 death predicted by (regression coefficients):

Health condition (MLTC) latent variable: β = 0.062, $P < 0.001$
Economic deprivation latent variable: β = 0.013, P = 0.159
Traumatic events latent variable: β = −0.004, P = 0.486
Unhealthy behaviors latent variable: β = −0.002, P = 0.749
Age > 70: β = 0.009, P = 0.009
Gender Male: β = 0.015, $P < 0.001$
Ethnic minority: β = 0.001, P = 0.655

Health condition (MLTC) latent variable predicted by (regression coefficients):
Economic deprivation latent variable: β = 0.519, $P < 0.001$
Traumatic events latent variable: β = −0.165, $P < 0.001$
Unhealthy behaviors latent variable: β = 0.248, $P < 0.001$

Indirect effect predicting Covid-19-related death:
Economic deprivation → health condition (MLTC) → Covid-19: β = 0.032, $P < 0.001$
Traumatic events → health condition (MLTC) → Covid-19: β = −0.010, $P < 0.001$
Unhealthy behaviors → health condition (MLTC) → Covid-19: β = 0.015, $P < 0.001$

Correlations between latent factors:
Economic deprivation ∼ traumatic events: r = 0.240, $P < 0.001$
Economic deprivation ∼ unhealthy behaviors: r = 0.251, $P < 0.001$
Traumatic events ∼ unhealthy behaviors: r = 0.531, $P < 0.001$

Economic deprivation factor standardized loadings (all $P \leq 0.001$):
λ low household income: 0.391
λ high Townsend deprivation: 0.233

Traumatic events factor standardized loadings (all $P \leq 0.001$):
λ abuse/neglect: 0.638
  λ hated child: 0.668
  λ abused child: 0.522
  λ non-loved child: 0.431
  λ not taken to doctor: 0.247
    error non-loved child ∼ error not taken to doctor: 0.240
λ sexual violence: 0.527
  λ sexual assault: 0.845
  λ sexually molested as a child: 0.624
λ intimate partner violence: 0.665
  λ belittled by partner: 0.665
  λ physical violence by partner: 0.650
  λ sexual violence by partner: 0.517
λ crime/war violence: 0.317
  λ witnessed violent death: 0.462
  λ exposed to war-zone: 0.317
  λ victim of violent crime: 0.314

Unhealthy behaviors factor standardized loadings (all $P \leq 0.001$):
λ poor eating: 0.610
λ poor sleep: 0.454
λ substance addiction: 0.217

Health condition (MLTC) factor standardized loadings (all $P \leq 0.001$):
λ respiratory disorders: 0.436
  λ COPD: 0.549
  λ bronchiectasis: 0.271
  λ asthma: 0.285
λ metabolic related disorders: 0.662
  λ hypertension: 0.560
  λ diabetes: 0.405
  λ CHD: 0.401
  λ CKD: 0.323
  λ obesity: 0.350
λ bowel related disorders: 0.725
  λ dyspepsia: 0.471
  λ diverticular: 0.347
  λ IBD/IBS: 0.299
λ musculoskeletal disorders: 0.530
  λ rheumatoid arthritis: 0.258
  λ osteoporosis: 0.258
λ liver related disorders: 0.222
λ stroke: 0.204

Notes: AIC—Akaike information criterion, BIC—Bayesian information criterion, ***$P < 0.001$, COPD—chronic obstructive pulmonary disease, CHD—coronary heart disease, CKD—chronic kidney disease, IBD/IBS—inflammatory bowel disease/irritable bowel syndrome.

Table 2 Cox regression with predicted health condition scores

Health condition (MLTC)	*Crude HR [95% CI]*	*Adjusted HR [95% CI][a]*
Healthiest quintile	Reference	Reference
Second healthiest quintile	4.01 [1.31–14.20]	3.82 [1.08–13.56]
Middle health quintile	8.68 [2.62–28.68]	7.48 [2.56–24.80]
Second least healthy quintile	11.72 [3.60–38.09]	9.77 [3.00–31.83]
Least healthy quintile	37.06 [11.77–116.68]	28.05 [8.87–88.72]

[a]Adjusted for age, gender and ethnicity.

Table 3 Moderation (effect modification) analyses between health conditions and economic deprivation, traumatic events and health behavior predicting Covid-19–related death in a Cox regression

	Crude HR [95% CI]	*Adjusted HR [95% CI][a]*
Health condition (MLTC)[a] economic deprivation	0.91 [0.40–2.08]	1.00 [0.44–2.30]
Health condition (MLTC)[a] traumatic events	1.36 [0.64–2.87]	1.34 [0.63–2.84]
Health condition (MLTC)[a] unhealthy behaviors	1.48 [0.67–3.25]	1.34 [0.61–2.97]

[a]Adjusted for age, gender and ethnicity and main effects of each variable.

vent mortality. Previous studies reported economic deprivation to be a risk for Covid-19 mortality.[12] There are various ways in which socioeconomic adversity is related to Covid-19 mortality, including: exposure (e.g. difficulties in working from home), transmission (e.g. difficulties in isolate if living in smaller homes), vulnerability (e.g. higher multimorbidity affecting recovery—in accord with our findings) and susceptibility (e.g. weaken immune responses due to chronic stresses).[25]

Traumatic events were positively correlated to deprivation, unhealthy behaviors and MLTC, but trauma was not directly related to Covid-19 after adjusting for those factors. This aligns with previous research linking adverse childhood experiences, economic deprivation and multimorbidity in adulthood.[26,27]

The synergistic effect of the co-existence of MLTC led to an exponential increase in the risk for Covid-19 mortality.[4] People in the quintile with more MLTC had 28 times more risk of dying from Covid-19 than those in the healthiest quintile. While earlier studies demonstrated a connection between Covid-19 death and the prevalence of MLTC,[11] our methodology seems to replicate the synergistic effects of the concentration of health conditions.[1]

The impact of MLTC on Covid-19 mortality was not aggravated by conditions of deprivation, trauma or the unhealthy behaviors considered. This may be influenced by the absence of updated information on health behaviors and economic status at the study's start. However, considering that health behaviors and economic status may be less amenable to major changes in older age, we assume the impact of this limitation to be minimal. In conjunction with findings from the SEM mediation model, there is strong evidence to suggest that the impact of economic deprivation on the relationship between health and Covid-19 was not one of effect modification but one of causation and cumulative adversity.

What was already known and what this study adds

Studies demonstrated that Covid-19 mortality was higher in marginalized communities, namely, people of ethnic minorities and those living in more deprived areas.[6] Long-term conditions were observed to be risk factors for Covid-19 mortality.[11,12,17] Literature showed that economic adversity and negative life events are related to multimorbidity.[26,28,29] However, no empirical studies investigated the synergistic effects of these risk factors for Covid-19 mortality.[25,27]

Based on the literature search and expert consultation, we believe this is the first study to investigate Covid-19 mortality, considering health behaviors, multimorbidity, trauma and socio-demographics, employing a syndemic framework and related methods. The findings show socioeconomic adversity increases vulnerability to Covid-19 mortality due to its effects on the development of multimorbidity. This suggests that Covid-19 mortality in marginalized and ethnic minority groups was more related to multimorbidity and the greater risks of these due to socioeconomic conditions, rather than vulnerability to Covid-19 mortality through other pathways related to ethnicity and socioeconomic factors.

Limitations

Our study found no association between ethnicity and Covid-19 death, which differs from previous studies using UKBB or other community samples[10,11] and could be related to the reduced sample size of ethnic minority participants in our study.[10] We did not adjust for factors related to exposure to Covid-19 virus, namely the type of occupation or the number of people in households.[30–32] There is the potential non-identification of health conditions in some fractions of the sample due to limitations in data availability (e.g. primary care data was available until 2017, and for 45% of the initial UKBB cohort) and non-assessment of treatments that could indicate a health condition. However, any under-detection of health conditions should not affect the direction of the observed relationships. Furthermore, although the UKBB assessment centers' locations aimed to ensure socioeconomic, ethnic and urban/rural diversity, there is an overrepresentation of affluent and White British individuals in the dataset. Consequently, there are limitations to the generalizability of the prevalence statistics. However, the observed association estimates should be generalizable to older adults in the UK.

Implications

Economic adversity is a risk factor for worse health outcomes, including multimorbidity and mortality due to non-communicable illnesses (e.g. cancer and cardiovascular disease).[28,29] This study shows that economic adversity is also a risk factor for communicable illnesses that people have little control over exposure. Health policies should address the impact of socioeconomic factors and inequality on the outcomes of communicable illnesses that people cannot control. People who experience trauma might have increased vulnerability and susceptibility to illness. The provision of integrated care for those who experienced trauma may be needed to minimize its negative impact on physical health.

This study shows that a syndemic approach should be taken in preparation for another onset of a communicable illness. Policies must address the factors related to exposure and transmissibility of viruses and protect people who may show higher vulnerability and susceptibility due to social adversity, such as trauma and economic deprivation.[33] Adopting a syndemic approach implies addressing the social power imbalances and inequities related to economic factors and social disadvantage. To achieve equity in health, policies should consider individuals' mental, physical and social needs while addressing the wider economic inequality.[4]

Conclusion

The syndemic framework is a suitable and meaningful approach to the study of Covid-19 mortality. Economic deprivation, traumatic events and unhealthy behaviors are correlated to MLTC, which in turn contributes to higher vulnerability to Covid-19 illness. Policies need to acknowledge that socioeconomic factors are the fundamental cause of excessive illness. Interventions to prevent the onset of multimorbidity and modify its impact on health outcomes are needed.

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Authors' contributions

KB conceived the original idea based on long-standing work on ethnic inequalities in severe mental illness and the role of syndemics of psychosis to explain these. The data acquisition was done by KB as part of the Synergi Collaborative Centre's work. DFdF led the methodology and conducted the analyses with support from CC and guidance from MK. DFdF wrote the original draft of the manuscript, which was then refined by KB. All authors contributed to the review and revision of the manuscript. All authors approved the final version of the manuscript.

Supplementary data

Supplementary data are available at the *Journal of Public Health* online.

Competing interest

In the past 5 years, for works not related to this manuscript, DFdF received funds from the NIHR Maudsley Biomedical Research Centre, the UK Department of Health and Social Care, Janssen Research & Development LLC, and H. Lundbeck A/S. In the past 5 years, for works not related to this manuscript, RDH received funding from Janssen Research & Development LLC, H. Lundbeck A/S.

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Data availability

UK Biobank data are available for further studies. Please see http://www.ukbiobank.ac.uk/using-the-resource/.

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