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Citation: Stafford M, Knight H, Hughes J, Alarilla A, Mondor L, Pefoyo Kone A, et al. (2022) Associations between multiple long-term conditions and mortality in diverse ethnic groups. PLoS ONE 17(4): e0266418. https://doi.org/ 10.1371/journal.pone.0266418

Editor: Kjell Torén, University of Gothenburg: Goteborgs Universitet, SWEDEN

Received: November 2, 2021

Accepted: March 20, 2022

Published: April 1, 2022

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Data Availability Statement: The study uses individual patient data that is collected as part of routine care. Individual patient data from electronic health records cannot be shared publicly because they are considered sensitive data in the UK by the Data Protection Act and patient confidentiality is protected through information governance restrictions. Application to use the data may be obtained from the Clinical Research Practice Datalink team on submission of a data application through the Research Governance Process https:// www.cprd.com/data-access. **RESEARCH ARTICLE**

Associations between multiple long-term conditions and mortality in diverse ethnic groups

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Abstract

Background

Multiple conditions are more prevalent in some minoritised ethnic groups and are associated with higher mortality rate but studies examining differential mortality once conditions are established is US-based. Our study tested whether the association between multiple conditions and mortality varies across ethnic groups in England.

Methods and findings

A random sample of primary care patients from Clinical Practice Research Datalink (CPRD) was followed from 1st January 2015 until 31st December 2019. Ethnicity, usually selfascribed, was obtained from primary care records if present or from hospital records. Longterm conditions were counted from a list of 32 that have previously been associated with greater primary care, hospital admissions, or mortality risk. Cox regression models were used to estimate mortality by count of conditions, ethnicity and their interaction, with adjustment for age and sex for 532,059 patients with complete data. During five years of follow-up, 5.9% of patients died. Each additional condition at baseline was associated with increased mortality. The direction of the interaction of number of conditions with ethnicity showed a statistically higher mortality rate associated with long-term conditions in Pakistani, Black African, Black Caribbean and Other Black ethnic groups. In ethnicity-stratified models, the mortality rate per additional condition at age 50 was 1.33 (95% Cl 1.31,1.35) for White ethnicity, 1.43 (95% Cl 1.26,1.61) for Black Caribbean ethnicity and 1.78 (95% Cl 1.41,2.24) for Other Black ethnicity.

Conclusions

The higher mortality rate associated with having multiple conditions is greater in minoritised compared with White ethnic groups. Research is now needed to identify factors that

Funding: The following authors received no specific funding for this work (MS, HK, JH, AA, SD). The following authors were supported by a grant (Agreement #694) from the Ontario Ministry of Health (https://www.ontario.ca/page/ministryhealth) to the Health System Performance Network (LM, APK, WW). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing interests: The authors have declared that no competing interests exist.

contribute to these inequalities. Within the health care setting, there may be opportunities to target clinical and self-management support for people with multiple conditions from minoritised ethnic groups.

Introduction

The number of people with multiple long-term conditions, or multimorbidity, is rising. Though there is no accepted international definition of multimorbidity [1], recent large-scale studies using electronic health records in the UK estimate 23–27% of people have two or more long-term conditions [2, 3]. Multimorbidity has been consistently associated with poorer outcomes for patients, with risk of death increasing with each additional condition [4, 5] and some studies suggesting that the association may be multiplicative [6], and more pronounced when conditions concern different body systems (complex multimorbidity) [7–11] though the association between higher risk of mortality and multimorbidity is weaker at older ages [12, 13]. Multimorbidity is also associated with higher use of health care [2] and reduced quality of life [14, 15]. Many health and care systems are designed to care for patients with single conditions, but there is growing recognition that if they are to improve outcomes for patients, health care systems must be adapted to address the challenge of multimorbidity [16, 17].

There is an established body of evidence that the prevalence of multimorbidity is socially patterned. Previous studies have demonstrated an association between the prevalence of multiple conditions and socioeconomic disadvantage in households [18] and local areas [2, 3, 19]. The prevalence of multiple conditions is also higher in some minoritised ethnic groups [20]. People from some minoritised ethnic groups are more likely to have experienced discrimination and multiple disadvantage over their life course, leading to an increased risk of experiencing material deprivation, living in deprived areas and an associated higher prevalence of downstream behavioural risk factors including smoking and obesity [20, 21]. Poorer experience of healthcare services has also been reported by some minoritised ethnic groups, and they are less likely than their counterparts in the majority population to report that they are able to manage their own health [22].

Whether minoritised ethnic groups experience disadvantage or discrimination over the course of their lives will differ between countries and over time, and as a result, evidence on mortality risk for minoritised ethnic groups varies. For example while excess deaths in Black populations in the US have remained high for many years [23], in the UK, the link between ethnic minority status and mortality risk varies by cause of death [24] and migration status [25]. Research in the UK on this topic has been hampered due to lack of ethnicity data on death certificates and historically poor recording of ethnicity in medical records, though the latter has improved markedly in recent years.

A previous study in the United States of America found that having multiple chronic conditions resulted in reduced life expectancy but the impact did not differ between African Americans and non-Hispanic White people [26]. Analysis of the Health and Retirement Study, on the other hand, found that Black and Hispanic Americans were more likely to have multisystem multimorbidity and more likely to die during follow-up compared with their White American counterparts [27]. We are not aware that this has been assessed in the UK context, though here studies have investigated ethnic differences in long-term survival for people with a single or index condition of interest. These point to the possibility of ethnic differences in survival across a range of conditions, for example lower two-year survival for Black women in England with breast cancer [28] and higher survival for people in London with unipolar depression from Black Caribbean, Black African, South Asian and Chinese ethnic backgrounds [29].

It is plausible that many of the factors contributing to high prevalence of multiple conditions may also contribute to poorer survival in minoritised ethnic groups once multiple conditions are established. Likewise, the potential for differences across ethnic groups in the association between long-term conditions and mortality may be greater where the organisation of health care and the recommended treatments and lifestyle changes are especially complex, as is the case with multiple conditions.

The aims of our study were to estimate the mortality risk of having multiple conditions, assess whether this risk is seen for complex multimorbidity, and examine whether the magnitude or direction of these risks varies across ethnic groups, compared with people of White ethnicity living in England.

Methods

Participants

Our sample was drawn from primary care records. Over 95% of the England population are registered with a general practice. A random sample of 600,000 adults (age 18 and over) was drawn from the Clinical Practice Research Datalink (CPRD Aurum [30]). This research database of pseudonymised routinely collected primary care records captures diagnoses, symptoms, prescriptions, referrals and tests and includes over 40 million patients (13 million currently registered as of June 2021). CPRD Aurum comprises GP practices using the EMIS Web software (one of four main general practice IT systems in operation) that have agreed to contribute data. Eligible adults were in a CPRD practice on 1st January 2014 (to ensure records were up to date at least one year before the study start), were alive and still registered at the study start on 1st January 2015, and were eligible for linkage to Hospital Episode Statistics (HES) and Office for National Statistics mortality data. Data linkage was carried out by a Trusted Third Party, namely NHS Digital, the organisation with responsibility for standardising, collecting and publishing data from across the health care system in England. They were followed until the study end (31st December 2019) or death if this was earlier and were censored if they left the CPRD practice or the practice stopped providing data to CPRD. The study was reviewed for ethical and methods content and approved by the CPRD team (eRAP protocol number 20_000239). Patients cannot be identified from CPRD so GPs are not required to seek individual patient consent. However, patients may opt out of having their patient information being shared for research purposes through the national data opt-out scheme.

Measures

Survival time was calculated from 1st January 2015 to death or censoring.

The number of long-term conditions was counted at study start. We used a list of 32 physical and mental health conditions (S1 Table) that have previously been associated with higher mortality risk, poorer functioning, and requiring primary care input [2.3]. They were taken from a list of 37 conditions that had been both previously validated based on CPRD [31] and included in published code lists [32, 33]. This was repeated to calculate number of conditions at the study end or censoring date, which may be fewer than at study start as we allowed for three conditions (anxiety/depression, asthma and cancers) to resolve.

Complex multimorbidity was defined as having three or more long-term conditions in three or more different body systems [34] (S1 Table).

Ethnic identity, usually self-ascribed, was obtained from SNOMED codes recorded by the GP or, where that was missing or incomplete (29.8%), from linked HES (Hospital Episode Statistics) records. Where multiple values of ethnicity have been recorded, we selected the modal value where this was unique, or the most recent value [35]. Categories from the England 2011 census were used in our analysis but we combined White British, White Irish and other White because these separate categories were not available in HES.

Socioeconomic deprivation was captured by 2015 Index of Multiple Deprivation (IMD) decile in the patient's area of residence based on lower-level super output area boundaries.

Statistical analysis

The analytical sample included those with complete data on sex, age (n = 0 excluded), ethnicity (n = 67524 excluded), or deprivation (n = 417 excluded). Excluded patients were younger, more likely to be men, over-represented in less deprived areas, and had fewer conditions (S2 Table).

The association between survival time and baseline number of long-term conditions was modelled using a multilevel Cox proportion hazards model with adjustment for baseline age (centred at age 50 to aid interpretation), sex and ethnicity. Number of conditions was included as a continuous variable after confirming its association with survival time was linear (S1 Fig). Interactions of age by ethnicity and age by number of conditions were included to improve model fit. Age was included as a continuous variable in all models due to small numbers of patients and deaths in some age group-ethnicity cells. We present hazard ratios estimated at age 50. A two-level model was used to allow for the clustering of patients within GP practices (model 1).

We assessed model 1 for violations of the proportional hazards assumption. The association between sex and mortality hazard was found to depend on follow-up time (p = 0.004), with a marginally higher hazard for men after 2.5 years of follow-up. The association between baseline age and mortality hazard also depended on follow-up time (p = 0.02), with a marginally higher hazard with advancing age after 2.5 years of follow-up. However, the differences across follow-up time were small. Furthermore, allowing for time-varying estimates for sex and age did not alter the estimates for the main variables of interest (namely, ethnicity and number of long-term conditions) so we elected to present the simpler model without time-varying estimates.

To examine whether the association between survival time and long-term conditions varied by ethnicity, we added ethnicity by number of conditions interaction terms (model 2). A likelihood ratio test was used to test the combined statistical significance of these interactions (model 2 vs model 1). Where this test was statistically significant at the 5% level, we also present mortality hazard ratios from ethnicity-stratified models. In these models, the reference group comprises people with no long-term conditions of the same ethnicity.

We examined two possible factors that could explain survival differences across ethnic groups, if any were observed (model 3). We added number of long-term conditions at end of follow-up. Patterns and rate of long-term condition acquisition vary across ethnic groups [20, 27, 36, 37]. We also added socioeconomic deprivation. There is a well-established relationship between ethnic minority identity and greater socioeconomic deprivation, driven by long-standing structural factors that disadvantage people from minoritised ethnic groups in multiple domains including housing, education and employment. We hypothesised that any ethnic differences in the association between survival time and baseline number of conditions would be smaller in models that included number of long-term conditions at end of follow-up and deprivation.

In sensitivity analysis, we repeated model 2 replacing baseline number of conditions with presence or absence of complex multimorbidity. Cancers, circulatory, endocrine and respiratory system conditions are leading causes of death [38]. We also repeated model 2 replacing baseline number of conditions with presence or absence of a condition in these body systems.

Results

During the 5-year follow-up period, 5.9% of patients died (Table 1). The majority of patients were of White ethnic background (85.4%) and these were older and over-represented in less deprived areas compared with all other ethnic groups (S2 Table). The unadjusted mean number of long-term conditions at baseline was highest in the White ethnic group (1.23) and

Table 1. Description of the analytical sample.

Total sample	N = 532059
Baseline age	N (%)
18-29y	83649 (15.7)
30-39у	91659 (17.2)
40-49y	94416 (17.7)
50-59у	91484 (17.2)
60-69y	73705 (13.9)
70-79у	55875 (10.5)
80+y	41271 (7.8)
Women (%)	276147 (51.9)
Ethnicity	
Bangladeshi	3711 (0.7)
Pakistani	9233 (1.7)
Indian	15142 (2.8)
Other Asian	9022 (1.7)
Chinese	4608 (0.9)
Black African	11517 (2.2)
Black Caribbean	7357 (1.4)
Other Black	3119 (0.6)
Mixed	7227 (1.4)
Other	6910 (1.3)
White	454213 (85.4)
ndex of Multiple Deprivation decile	
1 (least deprived)	57123 (10.7)
2	55021 (10.3)
3	55798 (10.5)
4	52976 (10.0)
5	51212 (9.6)
6	52729 (9.9)
7	55159 (10.4)
8	51716 (9.7)
9	53927 (10.1)
10	46398 (8.7)
Died during follow-up	31460 (5.9)
Complex multimorbidity present	59073 (11.1)
Baseline number of conditions; mean (sd)	1.16 (1.49)

https://doi.org/10.1371/journal.pone.0266418.t001

lowest in the Chinese ethnic group (0.33). People of Chinese ethnicity also had the lowest mean number of long-term conditions and lowest prevalence of complex multimorbidity across all age groups (<u>S3 Table</u>).

The initial model (model 1) addressed the first objective, to assess whether number of longterm conditions is associated with mortality. This model is based on the assumption that the association between number of conditions and mortality is consistent across ethnic groups. Each additional long-term condition at baseline was associated with increased mortality. For example, the estimated hazard ratio (HR) for a man of White ethnicity at age 50 was 1.80 with two conditions and HR = 3.25 with four conditions, compared to their counterpart with no conditions (see <u>Table 2</u> for hazard ratios estimated at age 50 and <u>S4 Table</u> for full set of estimates). A statistically significant negatively signed interaction for number of conditions by baseline age shows that the relative difference in mortality for those with more versus no conditions was smaller at older ages. Ethnicity was associated with mortality and this association depended on age. At all ages, the mortality rate was significantly lower for those of Indian or Chinese ethnicity than for those of White ethnicity.

To address the second objective, interaction terms for ethnicity by number of conditions were added. Their addition improved model fit (likelihood ratio test 0.05). Positive estimates for each of these interaction terms showed a tendency for higher mortality associated with each additional condition in all minoritised ethnic groups compared with those of White ethnicity, with the exception of those from a Bangladeshi background (full set of estimates in S4 Table). Interaction terms attained statistical significance for Pakistani, Black African, Black Caribbean and Other Black ethnic groups. From ethnicity-stratified models, we obtained the mortality hazard ratio for each additional condition at age 50 (Table 3). The mortality hazard

	Hazard ratio	95% CI
		95% CI
Baseline number of conditions		
0	1	
1	1.34	(1.32,1.36)
2	1.80	(1.75,1.86)
3	2.42	(2.32,2.53)
4	3.25	(3.06,3.45)
Ethnicity		
Bangladeshi	0.86	(0.55,1.31)
Pakistani	1.08	(0.84,1.40)
Indian	0.62	(0.49,0.78)
Other Asian	0.74	(0.54,1.01)
Chinese	0.40	(0.22,0.76)
Black African	0.97	(0.77,1.23)
Black Caribbean	1.21	(0.94,1.56)
Other Black	1.31	(0.89,1.94)
Mixed	1.22	(0.95,1.58)
Other	0.78	(0.54,1.14)
White	1	

Table 2. Mortality hazard ratios for baseline number of conditions and ethnicity estimated at age 50 (assuming association between number of conditions and mortality is same for all ethnic groups)^a.

^aEstimates are from Cox regression model 1 including baseline number of conditions, ethnicity, baseline age, sex, and interactions for number of conditions by age and ethnicity by age based on n = 532059 observations.

https://doi.org/10.1371/journal.pone.0266418.t002

	Hazard ratio	95% CI	Number of observations in model
Bangladeshi	1.60	(1.24,2.07)	3711
Pakistani	1.40	(1.24,1.58)	9233
Indian	1.43	(1.28,1.61)	15142
Other Asian	1.64	(1.38,1.95)	9022
Chinese	1.57	(1.03,2.38)	4608
Black African	1.36	(1.14,1.62)	11517
Black Caribbean	1.43	(1.26,1.61)	7357
Other Black	1.78	(1.41,2.24)	3119
Mixed	1.68	(1.42,1.98)	7227
Other	1.31	(1.05,1.62)	6910
White	1.33	(1.31,1.35)	454213

Table 3. Mortality hazard ratio per additional condition from ethnicity-stratified models estimated at age 50 (examining whether ethnicity moderates the association between total number of LTCs and survival).

Hazard ratios are from separate Cox regression models for each ethnic group including baseline number of conditions, baseline age, sex, and interaction for number of conditions by age estimated at age 50.

https://doi.org/10.1371/journal.pone.0266418.t003

ratio per additional condition was 1.33 (95% CI 1.31, 1.35) for White ethnicity, 1.43 (95% CI 1.26,1.61) for Black Caribbean ethnicity and 1.78 (95% CI 1.41,2.24) for Other Black ethnicity.

Model 3 explored the contribution of deprivation and number of conditions at end of follow-up as possible explanations for ethnic differences in the association between long-term conditions and mortality. Increasing deprivation was associated with higher mortality (HR 1.74 95% CI (1.66,1.83) in the most compared with the least deprived tenth of areas in England; <u>S4 Table</u>). The number of conditions present at the end of follow-up varied little across the ethnic groups (<u>S4 Table</u>) and was not associated with mortality independently of all other covariates (HR 1.00 95% CI (0.99,1.01) for each additional condition). Inclusion of these two variables did not materially alter the estimates for ethnicity by number of baseline conditions interactions. In other words, there was no evidence that area deprivation and onset of new conditions are part of the underlying explanation for ethnic differences in the link between multiple conditions and mortality. We note that there was evidence that the main effect association between ethnicity and mortality was suppressed when deprivation was ignored. Lower mortality rates for most minoritised ethnic groups compared to the White ethnic group were even lower once deprivation was included in the regression model.

Complex multimorbidity was associated with higher mortality risk and the magnitude of this association also varied across ethnic groups and age (Tables 4 and <u>\$5</u>). Interaction terms show the mortality rate associated with complex multimorbidity was statistically significantly higher for people of Pakistani, Chinese, Black African or Other Black ethnicity compared with people of White ethnicity.

The presence of one or more circulatory conditions was associated with higher mortality, and the magnitude of this association was significantly greater in people of Pakistani and Other Black backgrounds (S6 Table). The presence of one or more endocrine conditions was associated with higher mortality, and the magnitude of this association was significantly greater in people of Pakistani, Indian, Black African and Other Black backgrounds. The presence of one or more respiratory conditions was also associated with higher mortality, though this association was significantly weaker in those from Black African or Black Caribbean ethnic groups compared with those of White ethnicity. There were insufficient numbers of people with cancers to examine their association with mortality.

	Hazard ratio	95% CI	Number of observations in model
Bangladeshi	2.01	(0.60,6.74)	3711
Pakistani	2.44	(1.39,4.27)	9233
Indian	3.32	(2.05,5.38)	15142
Other Asian	4.90	(2.39,10.05)	9022
Chinese	8.85	(2.07,37.73)	4608
Black African	2.46	(1.19,5.10)	11517
Black Caribbean	2.42	(1.38,4.23)	7357
Other Black	4.81	(1.75,13.20)	3119
Mixed ethnicity	4.53	(2.22,9.22)	7227
Other ethnicity	1.27	(0.40,4.00)	6910
White	2.35	(2.20,2.51)	454213

Table 4. Mortality associated with complex multimorbidity from ethnicity-stratified models.

Hazard ratios are from separate Cox regression models including complex multimorbidity at baseline, baseline age, sex, and interaction for complex multimorbidity by age estimated at age 50. Complex multimorbidity (3 or more conditions in 3 or more body systems) is compared with absence of complex multimorbidity (fewer than 3 conditions or in fewer than 3 body systems).

https://doi.org/10.1371/journal.pone.0266418.t004

Discussion

Contribution of our study

Our analysis of data from over half a million patients in primary care confirms that having multiple long-term conditions is associated with higher mortality. This association is seen for each additional condition and for combinations of three or more conditions in three different body systems. The raised mortality rate associated with having multiple conditions is greater in minoritised ethnic groups compared with White people. Our study identified people with multiple conditions from Black African, Black Caribbean, Other Black, Pakistani or Chinese backgrounds as having poorer survival compared with their White counterparts either for total number of conditions or for complex multimorbidity.

Socioeconomic deprivation is strongly associated with mortality risk. People from most minoritised ethnic groups experienced higher levels of deprivation and omitting deprivation from models suppressed some of their mortality advantage. However, deprivation did not contribute to explaining the ethnic differences in the impact of long-term conditions on mortality. As clinicians and policy makers attempt to address the impact of the rising prevalence of multimorbidity, our findings suggest that there is an urgent need to focus on the needs of patients from minoritised ethnic groups as well as those in socioeconomically deprived areas.

Possible mechanisms

There are some plausible mechanisms which may explain the associations found in our study. Socioeconomic deprivation shows a clear patterning across ethnic groups and could contribute to poorer survival once multiple conditions are established. The role of socioeconomic deprivation was partially tested in this study, using an area-based measure. It remains a possibility that employment status, financial difficulties and other social and economic stressors may contribute to how effectively people from difference ethnic groups can manage their long-term conditions.

Differences in survival across ethnic groups may also be due to differences in the combination of conditions that are present. There is evidence that some combinations are more lethal than others. Complex cardiometabolic multimorbidity has been associated with high mortality risk [11]. Analysis of Danish register data showed that pairs including cancer, cardiovascular, lung, mental health or a neurological condition had highest mortality risk [7]. On the other hand, it has been hypothesised that multimorbidity including a condition that increases the opportunity for care from a physician may result in comorbid diseases being detected and managed, with a corresponding weaker impact on survival [8]. Investigation of condition clusters was beyond the scope of this study, but our analysis showed that the poorer survival for most minoritised ethnic groups was also seen when we focused only on conditions in the circulatory or endocrine systems. This was not seen for conditions in the respiratory system. The small number of people with cancer in most minoritised ethnic groups meant that we could not examine cancers separately but also suggests that cancers are not principal drivers of the ethnic inequalities observed.

Although the National Health Service provides care that is free at the point of need, differences in access to care and satisfaction with care across ethnic groups may also contribute to survival differences. It is plausible that earlier diagnosis in people of White ethnicity may lead to their better survival with the condition compared with other ethnicities, though evidence on ethnic differences in timing of diagnosis is currently inconclusive [39, 40]. Poorer access, experience and outcomes of health care interventions have been reported in some settings among minoritised ethnic groups [41]. Adherence to recommended treatment regimens, which can be complex in the case of multiple conditions, may also contribute to differences in survival with across ethnic groups. Accounts from people with lived experience of multiple conditions provide insight on the role of health professionals and health services to help people comply with recommendations and self-manage their conditions [42]. Furthermore, for specific conditions such as diabetes, studies have demonstrated persistent disparities in appropriate management, treatment and outcomes in primary care [43, 44]. Electronic health records can be further exploited in future work to understand patterns of health care for specific conditions across ethnic groups. For example, analysis of the Myocardial Ischaemia National Audit Project found the multimorbidity cluster with the poorest survival was less likely to be receiving pharmacological therapies though did not assess ethnic inequalities [45].

Differential mortality among those lost to follow-up might also explain the findings. It has been proposed that the selective return of less healthy first-generation migrants to their country of birth could contribute. Data to test this was not available to us but previous analysis in the UK [46] and elsewhere [47] suggests that this selection bias is too small to be a key explanation for lower mortality in ethnic minority or migrant groups.

The two previous studies exploring modification of the association between multiple conditions and mortality by ethnicity provided contrasting evidence. Both were based on cohort studies in the US but differed in their measurement of multiple conditions and analytical approach. Our findings align with the study focused on multisystem multimorbidity [27] but further replication is needed, along with international comparative studies to explore the role of societal context.

Strengths and limitations

A strength of our study is the large sample size which enabled us to disaggregate into eleven ethnic groups. However, there may be differences within groups, notably the White ethnic group as this combined White British, White Irish and other White people. We were unable to investigate possible disparities for minoritised White ethnic groups. In addition, those from other White backgrounds tend to be more socioeconomically disadvantaged compared to the White British group [48] so our study may underestimate differences between the White British majority and non-White minoritised ethnic groups. Usable ethnicity data was complete for

almost 90% of the sample, providing considerable scope for analysis to understand ethnic inequalities in health and care. This is an improvement over the last two decades and initiatives to improve ethnicity data quality should raise this even further. Nevertheless, 11% of the sample was excluded due to missing or withheld ethnicity data. Those without ethnicity data had considerably fewer conditions and a lower percentage died during follow-up so would not contribute large number of events to survival models though we cannot rule out the possibility that the association between multiple conditions and mortality is not the same for those excluded.

We included five years of follow-up and ended the study before the start of the Covid-19 pandemic as our focus was on inequalities in a period of usual care. It is well-documented that Covid-19 mortality risk was highest for people from minoritised ethnic groups and people with existing long-term conditions [49]. Our analysis may underestimate ethnic differences in the impact of multiple conditions in the context of Covid-19.

Reverse causality due to diagnosis of conditions when a person is seriously ill is one possible explanation for an association between number of conditions and mortality risk. We are not aware of evidence that this bias differs across ethnic groups but cannot rule out this possibility. Other limitations of our study include lack of data on the severity of conditions; this is a limitation common to most studies that employ data from routine health records. Routine health data also has the potential for bias due to differences in how healthcare staff record symptoms, diagnose conditions, or offer pharmacological therapies. If these are done less frequently for some groups then our analysis may have undercounted their actual number of conditions. This would lead to underestimation of the mortality risk associated with having more conditions. Our assessment of the contribution of new conditions emerging during follow-up was limited. We included the number of conditions at study start and end, which effectively models onset of new conditions as a covariate. Other studies have modelled transition to multimorbidity or to an additional condition separately from transition to death [50]. Ethnic identity is related to several constructs such as migration status and preferred language, that may affect interaction with health care, ability to manage long-term conditions, and survival. These constructs are not well-captured in our data, but other studies have shown stark differences in mortality for people from minoritised ethnic groups that were born in the UK or Republic of Ireland and those that were born elsewhere [24, 25].

Conclusion

Given the finding of poorer survival with multiple conditions among some minoritised ethnic groups, work is now needed to identify factors that contribute to these inequalities. Within the health care setting, there may be opportunities to target clinical and self-management support. This could include helping them to have a better understanding of their long-term conditions and the treatments they are recommended to adhere to, providing context-specific advice for lifestyle changes, and improving the way local services work together so that the health system is more straightforward to navigate [37].

In the longer term, solutions that prevent and delay the onset of multiple long-term conditions in communities that are ethnically or socioeconomically disadvantaged are needed. These will include local and national strategies that address the wider determinants of health within and beyond the health care system.

Supporting information

S1 Table. Long-term conditions counted in the current study. (DOCX)

S2 Table. Characteristics of analytical sample by ethnicity. (DOCX)

S3 Table. Number of conditions and complex multimorbidity prevalence by age and ethnicity.

(DOCX)

S4 Table. Cox regression estimates for models including number of conditions. Model 1 for constant association between number of conditions and mortality risk same across ethnic groups; Model 2 including interaction between ethnicity and number of conditions; Model 3 including possible explanatory factors. (DOCX)

S5 Table. Cox regression estimates for model including complex multimorbidity. (DOCX)

S6 Table. Cox regression estimates for model including circulatory/ endocrine/ respiratory conditions.

(DOCX)

S1 Fig. Linear association between number of long-term conditions and mortality. (TIF)

Acknowledgments

This work uses data provided by patients and collected by the NHS as part of their care and support. We also thank the Data Management Team at the Health Foundation.

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References

 Stirland LE, González-Saavedra L, Mullin DS, Ritchie CW, Muniz-Terrera G, Russ TC. Measuring multimorbidity beyond counting diseases: systematic review of community and population studies and guide to index choice. BMJ 2020;368. https://doi.org/10.1136/bmj.m160 PMID: 32071114

- Cassell A, Edwards D, Harshfield A, Rhodes K, Brimicombe J, Payne R, et al. The epidemiology of multimorbidity in primary care: A retrospective cohort study. Br J Gen Pract. 2018; 68(669):e245–51. https://doi.org/10.3399/bjgp18X695465 PMID: 29530918
- Barnett K, Mercer SW, Norbury M, Watt G, Wyke S, Guthrie B. Epidemiology of multimorbidity and implications for health care, research, and medical education: a cross-sectional study. Lancet 2012; 380(9836):37–43. https://doi.org/10.1016/S0140-6736(12)60240-2 PMID: 22579043
- Nunes BP, Flores TR, Mielke GI, Thumé E, Facchini LA. Multimorbidity and mortality in older adults: A systematic review and meta-analysis. Arch Gerontol Geriatr 2016; 67:130–8. https://doi.org/10.1016/j. archger.2016.07.008 PMID: 27500661
- Wei MY, Mukamal KJ. Multimorbidity, Mortality, and Long-Term Physical Functioning in 3 Prospective Cohorts of Community-Dwelling Adults. Am J Epidemiol. 2018; 187(1):103. <u>https://doi.org/10.1093/aje/ kwx198 PMID: 29309518</u>
- The Emerging Risk Factors Collaboration. Association of Cardiometabolic Multimorbidity With Mortality. JAMA 2015; 314(1):60. https://doi.org/10.1001/jama.2015.7008 PMID: 26151266
- Willadsen T, Siersma V, Nicolaisdóttir D, Køster-Rasmussen R, Jarbøl D, Reventlow S, et al. Multimorbidity and mortality: A 15-year longitudinal registry-based nationwide Danish population study. J Comorbidity 2018; 8(1):2235042X18804063. https://doi.org/10.1177/2235042X18804063 PMID: 30364387
- Caughey GE, Ramsay EN, Vitry AI, Gilbert AL, Luszcz MA, Ryan P, et al. Comorbid chronic diseases, discordant impact on mortality in older people: a 14-year longitudinal population study. J Epidemiol Community Health 2010; 64(12):1036–42. https://doi.org/10.1136/jech.2009.088260 PMID: 19854745
- Ferrer A, Formiga F, Sanz H, Almeda J, Padrós G. Multimorbidity as specific disease combinations, an important predictor factor for mortality in octogenarians: the Octabaix study. Clin Interv Aging 2017; 12:223. https://doi.org/10.2147/CIA.S123173 PMID: 28184153
- Storeng SH, Vinjerui KH, Sund ER, Krokstad S. Associations between complex multimorbidity, activities
 of daily living and mortality among older Norwegians. A prospective cohort study: the HUNT Study, Norway. BMC Geriatr 2020; 20(1).
- Zheng DD, Loewenstein DA, Christ SL, Feaster DJ, Lam BL, McCollister KE, et al. Multimorbidity patterns and their relationship to mortality in the US older adult population. PLoS One 2021; 16(1). https://doi.org/10.1371/journal.pone.0245053 PMID: 33471812
- Rocca WA, Grossardt BR, Boyd CM, Chamberlain AM, Bobo W V, Sauver JLS. Original research: Multimorbidity, ageing and mortality: normative data and cohort study in an American population. BMJ Open 2021; 11(3).
- Ryan B, Allen B, Zwarenstein M, Stewart M, Glazier R, Fortin M, et al. Multimorbidity and mortality in Ontario, Canada: A population-basedretrospective cohort study. J Comorbidity 2020; 10:2235042X2095059. https://doi.org/10.1177/2235042X20950598 PMID: 32923405
- Kanesarajah J, Waller M, Whitty JA, Mishra GD. Multimorbidity and quality of life at mid-life: A systematic review of general population studies. Maturitas 2018; 109:53–62. <u>https://doi.org/10.1016/j.</u> maturitas.2017.12.004 PMID: 29452782
- Williams JS, Egede LE. The Association Between Multimorbidity and Quality of Life, Health Status and Functional Disability. Am J Med Sci 2016; 352(1):45–52. <u>https://doi.org/10.1016/j.amjms.2016.03.004</u> PMID: 27432034
- 16. Whitty CJM. Triumphs and challenges in a world shaped by medicine. Clin Med 2017; 17(6):537–544.
- Pearson-Stuttard J, Ezzati M, Gregg EW. Multimorbidity—a defining challenge for health systems. Lancet Public Health 2019; 4(12):e599–600. https://doi.org/10.1016/S2468-2667(19)30222-1 PMID: 31812234
- Mondor L, Cohen D, Khan AI, Wodchis WP. Income inequalities in multimorbidity prevalence in Ontario, Canada: a decomposition analysis of linked survey and health administrative data. Int J Equity Health 2018; 17(1). https://doi.org/10.1186/s12939-018-0800-6 PMID: 29941034
- Kone AP, Mondor L, Maxwell C, Kabir US, Rosella LC, Wodchis WP. Rising burden of multimorbidity and related socio-demographic factors: a repeated cross-sectional study of Ontarians. Can J Public Health 2021; 112(4):737. https://doi.org/10.17269/s41997-021-00474-y PMID: 33847995
- Ashworth M, Durbaba S, Whitney D, Crompton J, Wright M, Dodhia H. Journey to multimorbidity: Longitudinal analysis exploring cardiovascular risk factors and sociodemographic determinants in an urban setting. BMJ Open 2019; 9(12).
- Verest WJGM, Galenkamp H, Spek B, Snijder MB, Stronks K, van Valkengoed IGM. Do ethnic inequalities in multimorbidity reflect ethnic differences in socioeconomic status? The HELIUS study. Eur J Public Health. 2019; 29(4):687–93. https://doi.org/10.1093/eurpub/ckz012 PMID: 30768174
- Watkinson RE, Sutton M, Turner AJ. Ethnic inequalities in health-related quality of life among older adults in England: secondary analysis of a national cross-sectional survey. Lancet Public Health 2021; 6(3):E145–154. https://doi.org/10.1016/S2468-2667(20)30287-5 PMID: 33516278

- Benjamins MR, Silva A, Saiyed NS, Maio FG De. Comparison of All-Cause Mortality Rates and Inequities Between Black and White Populations Across the 30 Most Populous US Cities. JAMA Network Open 2014; 4(1):e2032086–e2032086.
- 24. ONS. Ethnic differences in life expectancy and mortality from selected causes in England and Wales—Office for National Statistics [Internet]. 2020. [cited 24 Feb 2022]. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/articles/ethnicdifferencesinlifeexpectancyandmortalityfromselectedcausesinenglandandwales/2011to2014
- Bhopal RS, Gruer L, Cezard G, Douglas A, Steiner MFC, Millard A, et al. Mortality, ethnicity, and country
 of birth on a national scale, 2001–2013: A retrospective cohort (Scottish Health and Ethnicity Linkage
 Study). PLoS Med 2018; 15(3).
- Laditka JN, Laditka SB. Associations of multiple chronic health conditions with active life expectancy in the United States. Disabil Rehabil. 2016; 38(4):354–61. https://doi.org/10.3109/09638288.2015. 1041614 PMID: 25936731
- Quiñones AR, Newsom JT, Elman MR, Markwardt S, Nagel CL, Dorr DA, et al. Racial and Ethnic Differences in Multimorbidity Changes Over Time. Med Care 2021; 59(5):402–9. https://doi.org/10.1097/ MLR.000000000001527 PMID: 33821829
- Møller H, Henson K, Lüchtenborg M, Broggio J, Charman J, Coupland VH, et al. Short-term breast cancer survival in relation to ethnicity, stage, grade and receptor status: national cohort study in England. Br J Cancer 2016; 115(11):1408. https://doi.org/10.1038/bjc.2016.335 PMID: 27780193
- Das-Munshi J, Chang C-K, Schofield P, Stewart R, Prince MJ. Depression and cause-specific mortality in an ethnically diverse cohort from the UK: 8-year prospective study. Psychol Med 2019; 49(10):1639. https://doi.org/10.1017/S0033291718002210 PMID: 30180917
- Wolf A, Dedman D, Campbell J, Booth H, Lunn D, Chapman J, et al. Data Resource Profile Data resource profile: Clinical Practice Research Datalink (CPRD) Aurum UK primary care. Int J Epidemiol 2019;1740–1740. https://doi.org/10.1093/ije/dyz034 PMID: 30859197
- Payne Rupert A, Mendonca SC, Elliott MN, Saunders CL, Mbbs DAE, Marshall M, et al. Development and validation of the Cambridge Multimorbidity Score. CMAJ 2020; 3:107–21. https://doi.org/10.1503/ cmaj.190757 PMID: 32015079
- Head AL. CPRD_multimorbidity_codelists. [cited 24 Feb 2022]. Available from: https://github.com/annalhead/CPRD_multimorbidity_codelists
- Head AL, Fleming K, Kypridemos C, Schofield P, Pearson-Stuttard J, O'Flaherty M. Inequalities in incident and prevalent multimorbidity in England, 2004–19: a population-based, descriptive study. Lancet Healthy Longevity 2021; 2(8):E489–497.
- Harrison C, Britt H, Miller G, Henderson J. Examining different measures of multimorbidity, using a large prospective cross-sectional study in Australian general practice. BMJ Open 2014; 4(7):e004694. https://doi.org/10.1136/bmjopen-2013-004694 PMID: 25015470
- Mathur R, Bhaskaran K, Chaturvedi N, Leon DA, Van Staa T, Grundy E, et al. Completeness and usability of ethnicity data in UK-based primary care and hospital databases. J Public Health 2014; 36(4):684– 92. https://doi.org/10.1093/pubmed/fdt116 PMID: 24323951
- Quiñones AR, Botoseneanu A, Markwardt S, Nagel CL, Newsom JT, Dorr DA, et al. Racial/ethnic differences in multimorbidity development and chronic disease accumulation for middle-aged adults. Plos One 2019; 14(6). https://doi.org/10.1371/journal.pone.0218462 PMID: 31206556
- Sauver JLS, Boyd CM, Grossardt BR, Bobo W V, Rutten LJF, Roger VL, et al. Risk of developing multimorbidity across all ages in an historical cohort study: differences by sex and ethnicity. BMJ Open 2015; 5(2).
- ONS. Leading causes of death, UK—Office for National Statistics [Internet]. 2020 [cited 2021 Oct 8]. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/ causesofdeath/articles/leadingcausesofdeathuk/2001to2018#uk-leading-causes-of-death-for-allages
- Martins T, Hamilton W, Ukoumunne OC. Ethnic inequalities in time to diagnosis of cancer: A systematic review. BMC Fam Pract 2013; 14:197. https://doi.org/10.1186/1471-2296-14-197 PMID: 24359157
- 40. Mukadam N, Lewis G, Mueller C, Werbeloff N, Stewart R, Livingston G. Ethnic differences in cognition and age in people diagnosed with dementia: A study of electronic health records in two large mental healthcare providers. Int J Geriatr Psychiatry 2019; 34(3):504–10. <u>https://doi.org/10.1002/gps.5046</u> PMID: 30675737
- Public Health England. Local action on health inequalities. Understanding and reducing ethnic inequalities in health [Internet]. 2018. [cited 2022 Feb 24]Available from: https://assets.publishing.service.gov. uk/government/uploads/system/uploads/attachment_data/file/730917/local_action_on_health_ inequalities.pdf

- 42. Taskforce on Multiple Conditions. You only had to ask. What people with multiple conditions say about health equity. [Internet]. 2021 [cited 2021 Oct 8]. Available from: https://richmondgroupofcharities.org. uk/sites/default/files/youonlyhadtoask_fullreport_july2021_final.pdf
- Millett C, Gray J, Saxena S, Netuveli G, Khunti K, Majeed A. Ethnic Disparities in Diabetes Management and Pay-for-Performance in the UK: The Wandsworth Prospective Diabetes Study. Plos Med 2007; 4 (6):e191. https://doi.org/10.1371/journal.pmed.0040191 PMID: 17564486
- Mathur R, Farmer RE, Eastwood S V., Chaturvedi N, Douglas I, Smeeth L. Ethnic disparities in initiation and intensification of diabetes treatment in adults with type 2 diabetes in the UK, 1990–2017: A cohort study. Plos Med 2020; 17(5):e1003106. <u>https://doi.org/10.1371/journal.pmed.1003106</u> PMID: 32413037
- 45. Hall M, Dondo TB, Yan AT, Mamas MA, Timmis AD, Deanfield JE, 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):e1002501. https://doi.org/10.1371/journal.pmed. 1002501 PMID: 29509764
- 46. Das-Munshi J, Chang CK, Dutta R, Morgan C, Nazroo J, Stewart R, et al. Ethnicity and excess mortality in severe mental illness: a cohort study. The Lancet Psychiatry 2017; 4(5):389. <u>https://doi.org/10.1016/ S2215-0366(17)30097-4 PMID: 28330589</u>
- 47. Turra CM, Elo IT. The Impact of Salmon Bias on the Hispanic Mortality Advantage: New Evidence from Social Security Data. Popul Res Policy Rev 2008; 27(5):515. https://doi.org/10.1007/s11113-008-9087-4 PMID: 19122882
- ONS. Household wealth by ethnicity, Great Britain—Office for National Statistics [Internet]. 2020 [cited 2021 Oct 8]. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/ personalandhouseholdfinances/incomeandwealth/articles/householdwealthbyethnicitygreatbritain/ april2016tomarch2018
- 49. Sze S, Pan D, Nevill CR, Gray LJ, Martin CA, Nazareth J, et al. Ethnicity and clinical outcomes in COVID-19: A systematic review and meta-analysis. EClinicalMedicine 2020; 29:100630. https://doi.org/ 10.1016/j.eclinm.2020.100630 PMID: 33200120
- 50. Chan MS, Van Den Hout A, Pujades-Rodriguez M, Jones MM, Matthews FE, Jagger C, et al. Socioeconomic inequalities in life expectancy of older adults with and without multimorbidity: A record linkage study of 1.1 million people in England. Int J Epidemiol 2019; 48(4):1340–51. https://doi.org/10.1093/ije/ dyz052 PMID: 30945728