

## Original article

# Risk factors and mortality associated with multimorbidity in people with stroke or transient ischaemic attack: a study of 8,751 UK Biobank participants

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## Abstract

**Background:** Multimorbidity is common in stroke, but the risk factors and effects on mortality remain poorly understood. **Objective:** To examine multimorbidity and its associations with sociodemographic/lifestyle risk factors and all-cause mortality in UK Biobank participants with stroke or transient ischaemic attack (TIA). **Design:** Data were obtained from an anonymized community cohort aged 40–72 years. Overall, 42 comorbidities were self-reported by those with stroke or TIA. Relative risk ratios demonstrated associations between participant characteristics and number of comorbidities. Hazard ratios demonstrated associations between the number and type of comorbidities and all-cause mortality. Results were adjusted for age, sex, socioeconomic status, smoking, and alcohol intake. Data were linked to national mortality data. Median follow-up was 7 years. **Results:** Of 8,751 participants (mean age 60.9±6.7 years) with stroke or TIA, the all-cause mortality rate over 7 years was 8.4%. Over 85% reported ≥1 comorbidities. Age, socioeconomic deprivation, smoking and less frequent alcohol intake were associated with higher levels of multimorbidity. Increasing multimorbidity was associated with higher all-cause mortality. Mortality risk was double for those with ≥5 comorbidities compared to those with none. Having cancer, coronary heart disease, diabetes, or chronic obstructive pulmonary disease significantly increased mortality risk. Presence of any cardiometabolic comorbidity significantly increased mortality risk, as did any non-cardiometabolic comorbidity. **Conclusions:** In stroke survivors, the number of comorbidities may be a more helpful predictor of mortality than type of condition. Stroke guidelines should take greater account of comorbidities, and interventions are needed that improve outcomes for people with multimorbidity and stroke.

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**Keywords:** stroke, comorbidity, multimorbidity, mortality, risk factors

## Introduction

It is well known that the prevalence of multimorbidity (the presence of two or more long-term conditions) is

rising and that this creates challenges for those providing healthcare [1]. People with higher levels of multimorbidity are more likely to be prescribed higher numbers of medications [2,3], placing them at greater risk of disease–disease and disease–drug interactions [4,5]. It has been shown that multimorbidity is more common and occurs earlier in those who are more socioeconomically deprived [1]. Management of patients with multimorbidity can be challenging for clinicians due to a lack of evidence about how these factors relate to health-related outcomes.

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Multimorbidity is common in stroke. Approximately 94% of those who have suffered a stroke have at least one other long-term condition and 10% suffer from seven or more [2]. Current stroke guidelines and healthcare services are not designed optimally for those with multimorbidity. As a result, those with stroke describe their healthcare as fragmented and poorly coordinated [6]. Information about which individuals with stroke are at risk of multimorbidity and examination of the relationship with health-related outcomes is essential to inform the design of stroke services.

There currently is a poor understanding of the risk factors and consequences of multimorbidity in stroke. Older age has been shown to be associated with higher numbers of morbidities [7], but little is known about the relationships, if any, with other sociodemographic and lifestyle factors, such as socioeconomic deprivation. Importantly, studies that examine the impacts of multimorbidity on mortality in people with stroke are scant. A small number of studies have demonstrated an increased risk of mortality with higher numbers of morbidities [8–12]. These studies have been limited in that they have included low participant numbers [9–12], considered the effects of a limited number of comorbidities, involved a short length of follow-up, and were not adjusted for confounding factors [8–12]. Whether outcomes vary depending on the type of comorbidity, *i.e.* concordant and discordant, remains unclear.

## Objectives

This paper aims to enhance our understanding of the risk factors for multimorbidity in those with stroke and, importantly, any effects on mortality. Here we examine, in those with stroke or transient ischaemic attack (TIA):

- The relationship between sociodemographic and lifestyle characteristics, and multimorbidity
- The relationship between multimorbidity and all-cause mortality
- Which comorbid health conditions, if any, have a stronger association with all-cause mortality.

## Materials and methods

### Study design and data collection

This study examined data from the UK Biobank cohort. UK Biobank participants are volunteers who have given full informed consent to provide information about their health for the purposes of research, and for prospective data linkage. The UK Biobank has full ethical approval from the NHS National Research Ethics Service (16/NW/0274).

Participants included in this study were 8,751 adults aged 40–72 years in the UK with self-reported stroke or TIA. All attended one of 22 assessment centres across England, Scotland, or Wales. Detailed sociodemographic, lifestyle, and medical information was collected from these individuals between 2006 and 2010 at an assessment centre by means of touch screen questionnaires and nurse-led interviews.

### Clinical variables and outcomes

Sociodemographic information included sex, age, and socioeconomic status based on the Townsend score (a measure of deprivation in the UK) [13]. Self-reported lifestyle characteristics included alcohol intake (never or on special occasions only, one to three times a month, or at least once a week) and smoking status (never, current or previous). These baseline assessment centre data were linked to national mortality registries; and the median length of follow-up was 7 years from baseline data (interquartile range 75–93 months).

Data included information on self-reported morbidities. For the purpose of examining the number of comorbidities reported, a count (1, 2, 3, 4 or  $\geq 5$ ) was taken from a list of 42 morbidities originally established for a previous large epidemiological study, through systematic review, the Quality and Outcomes Framework, NHS Scotland, and an expert panel [1], and subsequently amended for the UK Biobank [14] (see Supplementary File).

### Statistical analysis

Frequencies, percentages, cross-tabulations, and graphical display were used for descriptive analysis. Relative risk ratios (RRRs; multinomial regression) were used to examine the associations between participant characteristics and number of comorbidities. Hazards ratios (HRs; Cox proportional hazards regression) were used to examine associations between number of comorbidities and time to all-cause mortality. Participants with no comorbidities were used as the reference category. A Kaplan–Meier plot was used to compare cumulative mortality between participants with stroke or TIA with different numbers of comorbidities. Models containing all variables (sex, age, socioeconomic status, smoking, alcohol intake) with and without comorbidity count were compared by goodness of fit ( $R^2$ ) to ascertain if knowledge of comorbidity improved prediction of mortality.

Individual Cox proportional hazards multivariable regression models were also used to study the adjusted effect size for the presence of each individual comorbidity (excluding those with a prevalence of less than 1% among participants with stroke or TIA) on all-cause mortality as

the outcome variable. Similarly, the adjusted effect size for the presence of any cardiometabolic comorbidity (diabetes, coronary heart disease [CHD], atrial fibrillation [AF], chronic heart failure [CHF], chronic kidney disease [CKD], or hypertension) and any non-cardiometabolic comorbidity (all other conditions) were examined. RRRs and HRs were fully adjusted for age, sex, deprivation, smoking status, and alcohol intake. Individuals with missing values were excluded from the analyses. Statistical analyses were conducted using R software (version 3.2.2) using the packages ‘survival’ [15] and ‘nnet’ [16]. All analyses were independently checked by another member of the team.

## Results

### Patient characteristics

Participants were 8,751 people who reported stroke or TIA. A total of 8,854 had reported these conditions in the UK Biobank; 103 of these were excluded from all analyses due to missing values. Mean age of included participants was 60.9 (standard deviation [SD] 6.7); 57.5% were male; 95.6% were white British; mean Townsend score was 3.29 (SD 1.43); 7,497 (85.1%) had at least one comorbidity; mean number of comorbidities was 2.0 (SD 1.6). Of those with stroke or TIA, 734 (8.4%) participants died over the period of follow-up. Participant details are shown in Table 1.

### Patient characteristics and number of comorbidities

Fully adjusted RRRs for number of comorbidities in relation to patient characteristics are shown in Table 2. Higher numbers of comorbidities were found in those who were female, older, socio-economically deprived, smokers, and less frequent consumers of alcohol. These relationships remained positive after full adjustment for confounding factors.

### Number of comorbidities and mortality

Compared with those with no comorbidities, the risk of all-cause mortality was significantly higher for those with 2, 3, 4 or  $\geq 5$  comorbidities, and the risk increased as the number of morbidities increased. Fully adjusted HRs for mortality in relation to number of comorbidities are shown in Figure 1. A Kaplan–Meier plot showing probability of all-cause mortality among participants with different numbers of multimorbidity is shown in Figure 2.

Prediction of mortality improved by 15.6% ( $R^2$  0.037 as opposed to 0.032) when comorbidity count was added into the model that included sex, age, socioeconomic status, smoking, and alcohol intake.

**Table 1** Sample characteristics ( $n=8,751$ ).

Patient characteristic	<i>n</i> (%)
Male	5,028 (57.5)
Age groups, years	
40–49	692 (7.9)
50–59	2,243 (25.6)
60–72	5,816 (66.5)
Ethnicity	
White	8,333 (95.6)
Other	387 (4.4)
Townsend quintiles	
1 (most deprived)	2,528 (28.9)
2	1,752 (20)
3	1,612 (18.4)
4	1,509 (17.2)
5 (least deprived)	1,350 (15.4)
Smoking status	
Never	3,684 (42.1)
Current or previous	5,067 (57.9)
Alcohol intake	
Never or special occasions only	2,552 (29.2)
One to three times a month	946 (10.8)
At least once a week	5,253 (60.0)
Number of comorbidities	
0	1,254 (14.3)
1	2,416 (27.6)
2	2,313 (26.4)
3	1,407 (16.1)
4	734 (8.4)
$\geq 5$	627 (7.2)

### Type of comorbidity and mortality

Fully adjusted HRs for the presence of individual comorbidities are presented in Table 3. When compared with no comorbidities, presence of the following individual conditions alongside stroke or TIA significantly increased the risk of all-cause mortality: cancer, CHD, diabetes, or chronic obstructive pulmonary disease (COPD).

Compared with no comorbidities, the presence of any cardiometabolic comorbidity significantly increased the risk of all-cause mortality (fully adjusted HR 1.42; 95% CI 1.19–1.69) as did the presence of any non-cardiometabolic comorbidity (HR 1.38; 95% CI 1.17–1.61).

## Discussion

### Summary of results

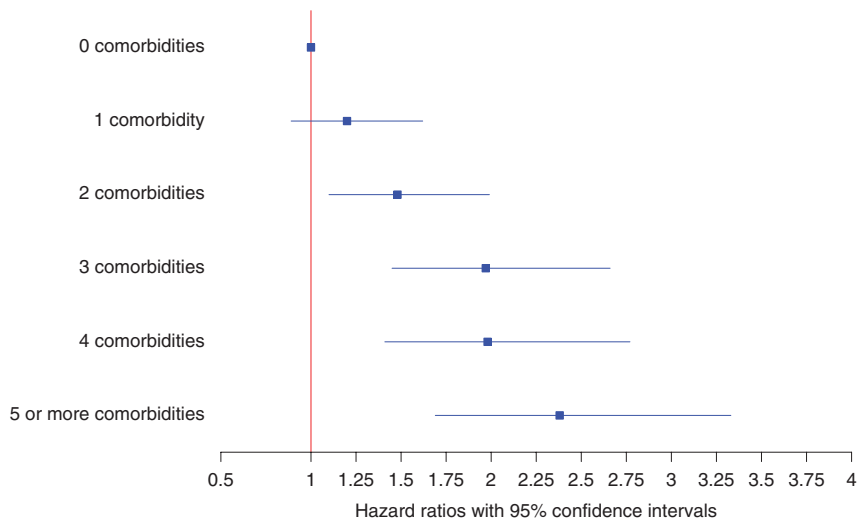
In those with stroke or TIA, number of comorbidities was associated with female sex, older age, socioeconomic deprivation, smoking, and less frequent alcohol consumption.

Increasing multimorbidity was associated with an increasing risk of all-cause mortality, with mortality risk more than doubled for those with at least 5 morbidities

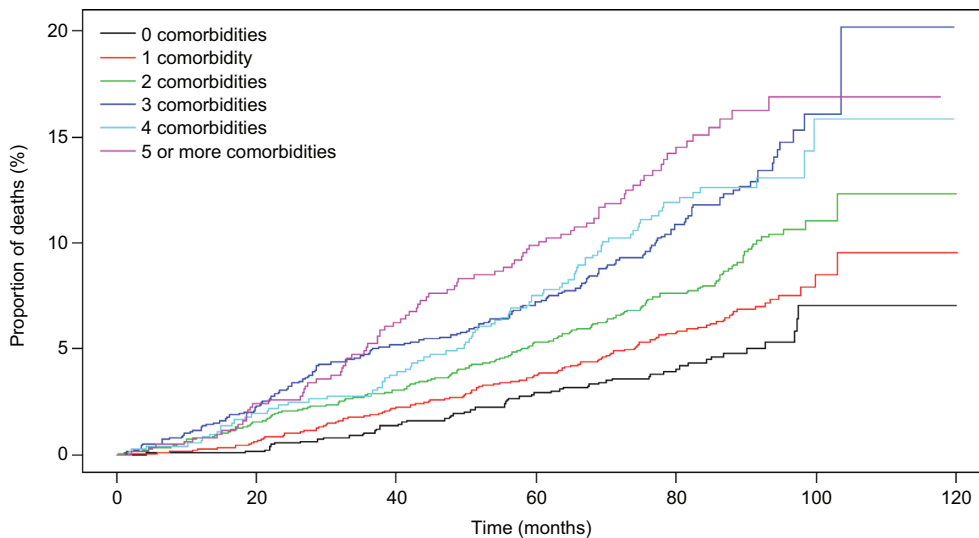
**Table 2** Participant characteristics in relation to the number of comorbidities\* (RRR adjusted for sex, age, deprivation, smoking status, and alcohol intake).

Patient characteristic	Number of comorbidities, RRR (95% CI) ( <i>n</i> =8,751)				
	1 <i>n</i> =2,416	2 <i>n</i> =2,313	3 <i>n</i> =1,407	4 <i>n</i> =734	≥5 <i>n</i> =627
Gender					
Male	1	1	1	1	1
Female	0.96 (0.83–1.11); <i>p</i> =0.60	0.93 (0.80–1.07); <i>p</i> =0.29	1.07 (0.91–1.26); <i>p</i> <0.05	1.32 (1.09–1.60); <i>p</i> <0.05	1.41 (1.15–1.72); <i>p</i> <0.05
Age groups, years					
40–49	1	1	1	1	1
50–59	1.49 (1.18–1.89); <i>p</i> <0.05	1.98 (1.53–2.57); <i>p</i> <0.05	2.37 (1.74–3.24); <i>p</i> <0.05	2.83 (1.88–4.25); <i>p</i> <0.05	2.36 (1.61–3.46); <i>p</i> <0.05
60–72	2.05 (1.65–2.56); <i>p</i> <0.05	3.40 (2.67–4.33); <i>p</i> <0.05	4.33 (3.23–5.81); <i>p</i> <0.05	4.89 (3.32–7.20); <i>p</i> <0.05	3.51 (2.44–5.05); <i>p</i> <0.05
Townsend quintiles					
1 (most deprived)	1.30 (1.05–1.62); <i>p</i> <0.05	1.70 (1.35–2.12); <i>p</i> <0.05	2.19 (1.71–2.81); <i>p</i> <0.05	2.41 (1.78–3.27); <i>p</i> <0.05	3.85 (2.70–5.48); <i>p</i> <0.05
2	1.27 (1.01–1.59); <i>p</i> <0.05	1.49 (1.19–1.88); <i>p</i> <0.05	1.43 (1.09–1.85); <i>p</i> <0.05	1.61 (1.17–2.23); <i>p</i> <0.05	2.33 (1.61–3.40); <i>p</i> <0.05
3	1.05 (0.84–1.30); <i>p</i> =0.68	1.11 (0.88–1.39); <i>p</i> =0.37	1.06 (0.82–1.38); <i>p</i> =0.66	1.44 (1.04–1.97); <i>p</i> <0.05	1.51 (1.03–2.22); <i>p</i> <0.05
4	1.10 (0.88–1.38); <i>p</i> =0.38	1.28 (1.01–1.61); <i>p</i> <0.05	1.22 (0.94–1.59); <i>p</i> =0.14	1.16 (0.82–1.63); <i>p</i> =0.40	1.63 (1.09–2.42); <i>p</i> <0.05
5 (least deprived)	1	1	1	1	1
Smoking status					
Never	1	1	1	1	1
Current or previous	1.22 (1.06–1.40); <i>p</i> <0.05	1.42 (1.23–1.64); <i>p</i> <0.05	1.55 (1.32–1.82); <i>p</i> <0.05	1.79 (1.48–2.18); <i>p</i> <0.05	1.90 (1.54–2.33); <i>p</i> <0.05
Alcohol intake					
Never or special occasions only	1	1	1	1	1
One to three times a month	11.08 (0.83–1.40); <i>p</i> =0.55	0.94 (0.73–1.22); <i>p</i> =0.64	0.71 (0.54–0.95); <i>p</i> =0.02	0.61 (0.43–0.85); <i>p</i> <0.05	0.61 (0.44–0.85); <i>p</i> <0.05
At least once a week	0.98 (0.82–1.16); <i>p</i> =0.79	0.66 (0.56–0.79); <i>p</i> <0.05	0.49 (0.41–0.59); <i>p</i> <0.05	0.43 (0.35–0.54); <i>p</i> <0.05	0.25 (0.20–0.32); <i>p</i> <0.05

\*1,254 patients did not have any comorbidities. CI, confidence interval; RRR, relative risk ratios.



**Figure 1** Fully adjusted hazards ratios for mortality in relation to the number of comorbidities.



**Figure 2** Kaplan–Meier graph of death proportion versus comorbidities ( $n=8,751$ ).

compared with those with none. The presence of cancer, CHD, diabetes, or COPD significantly increased the risk of mortality for those with stroke or TIA. Interestingly, the presence of any cardiometabolic comorbidity significantly increased the risk of all-cause mortality, as did the presence of any non-cardiometabolic comorbidity, with little difference in effect size between these two groups.

### How findings compare with other studies

Studies of risk factors for multimorbidity in stroke or TIA are limited. Only one could be found that examined age as a risk factor [7]. This found a significant association between age and Charlson Comorbidity Index (CCI),

which includes 17 morbidities and is weighted, i.e. a higher score is given for morbidities deemed to be more severe. To the best of our knowledge, ours is the first study to examine other sociodemographic and lifestyle factors in individuals with stroke or TIA and multimorbidity. The finding that multimorbidity is associated with age and socioeconomic deprivation correlates with the wider literature on multimorbidity [1,17,18].

Five studies were found that have examined mortality in relation to multimorbidity in stroke [8–12], but none were adjusted for such a broad range of potential confounders. All had a higher mean age (68–82 years) [8–12] and all but one [8] included smaller numbers of participants (175–2,402) and a shorter length of follow-up (the longest was 1 year) than presented in

**Table 3** Effects on mortality (fully adjusted hazards ratios) for the presence of individual comorbidities\* (*n*=8,751).

Comorbidity	<i>n</i> (%)	Hazard ratio	Confidence intervals	<i>p</i> value
Hypertension	4,936 (56.4)	1.15	0.99–1.34	0.07
Painful condition	1,903 (21.7)	0.96	0.81–1.15	0.68
<b>Coronary heart disease</b>	<b>1,510 (17.3)</b>	<b>1.60</b>	<b>1.36–1.88</b>	<b>&lt;0.05</b>
<b>Diabetes</b>	<b>1,190 (13.6)</b>	<b>1.72</b>	<b>1.45–2.04</b>	<b>&lt;0.05</b>
Asthma	1,155 (13.2)	1.17	0.95–1.43	0.14
Dyspepsia	1,026 (11.7)	0.93	0.75–1.17	0.58
<b>Cancer</b>	<b>882 (10.0)</b>	<b>2.16</b>	<b>1.80–2.60</b>	<b>&lt;0.05</b>
Depression	757 (8.7)	1.25	0.98–1.60	0.07
Thyroid disorder	634 (7.2)	0.79	0.56–1.10	0.16
<b>COPD</b>	<b>388 (4.4)</b>	<b>1.48</b>	<b>1.13–1.92</b>	<b>&lt;0.05</b>
Epilepsy	332 (3.8)	1.03	0.71–1.50	0.86
Rheumatoid arthritis and other connective tissue diseases	331 (3.8)	1.22	0.86–1.74	0.27
Migraine	293 (3.3)	0.79	0.47–1.32	0.37
Psoriasis/eczema	291 (3.3)	1.19	0.82–1.73	0.35
Prostate disease	260 (3.0)	1.01	0.70–1.46	0.96
Osteoporosis	260 (3.0)	1.12	0.74–1.70	0.57
Atrial fibrillation	257 (2.9)	0.80	0.50–1.28	0.36
Anxiety	179 (2.0)	0.81	0.46–1.43	0.46
Inflammatory bowel disease	173 (2.0)	1.01	0.48–2.12	0.98
Diverticular disease	162 (1.9)	0.62	0.32–1.20	0.16
Glaucoma	142 (1.6)	0.70	0.36–1.35	0.28

\*Results in bold are significant. COPD, chronic obstructive pulmonary disease.

this paper. All had baseline data collected in the acute setting, whereas this study examined a community cohort. All reported a positive relationship between comorbidity and mortality [8–12]. All used the CCI to measure comorbidity and one additionally used two other unweighted measures of a larger number of comorbidities [10]. Unweighted measures performed better than the CCI when predicting 6-month mortality. Two of the above studies also examined mortality risk in relation to the presence of individual comorbidities [8,11]. The smaller of these two studies (*N*=332) [11] found a significant in-hospital mortality risk associated with CHF, cancer, and CKD. The larger study (*N*=219,354) [8] found a significant 5-year mortality risk associated with CHF, AF, peripheral vascular disease, dementia, COPD, ulcer disease, liver disease, diabetes, moderate-to-severe renal disease, and cancer. In our study, a smaller number of conditions was found to have a significant effect on mortality. This could be explained by the inclusion of a larger number of potential confounders in the analyses. To our knowledge, this is the first study to examine the effects on mortality of cardiometabolic versus non-cardiometabolic comorbidity in people with stroke.

Studies of the wider population have similarly shown a strong relationship between number of morbidities and mortality. This holds true for studies that have examined older adults [19] and those that have included younger participants [20]; however, like those that have examined stroke populations, studies have included small sample sizes or examined low numbers of conditions,

and adjustment for potentially confounding factors is often lacking [19].

### Implications

This paper is novel because, for the first time, to our knowledge, it scrutinizes, in a large community cohort of people with stroke or TIA, the risk factors for multimorbidity and the relationship that multimorbidity has with mortality, whilst taking into account the potential confounding effects of sociodemographic and lifestyle factors. A strong relationship was seen between the number of comorbidities and mortality, with those who had the highest number of multimorbidities being at the highest risk. Addition of number of comorbidities to the model (comprising age, sex, socioeconomic deprivation, smoking, and alcohol intake) improved prediction of mortality by 15%. However, presence of only a handful of individual comorbidities significantly increased risk of mortality, and little difference was seen between the effects of cardiometabolic and non-cardiometabolic comorbidity on mortality. These results suggest that the number of comorbidities is a more helpful predictor of mortality than type of condition. This has potentially important implications for the risk stratification of people with stroke, and merits further exploration. Examination of whether particular combinations of comorbidities are associated with worse health-related outcomes is an important next step.

The associations seen here between multimorbidity and all-cause mortality support the premise that



prioritization should be given to the optimization of services provided for those with stroke affected by high levels of multimorbidity. Current clinical guidelines for stroke do not address management of multimorbidity [21–24] due to a lack of evidence on health-related outcomes and interventions that improve these outcomes. Individuals with multimorbidity could benefit from targeted interventions, such as increased clinician time [25]. Current risk stratification of individuals with multimorbidity is suboptimal; for example, the CCI is frequently used by clinicians and researchers, yet this does not include CHD, a condition that we found to be associated with a significantly increased risk of mortality, and previous work has shown unweighted measures to be superior to the CCI for predicting mortality in the acute setting [10]. Further work should compare the utility of different measures of multimorbidity in a community setting. Additionally, examination of any associations between multimorbidity and other rehabilitation outcomes, such as functional change, merits examination [26]. Further research is needed to allow: (1) better risk stratification of individuals with multimorbidity with a history of stroke or TIA; and (2) development and testing of complex interventions aimed at improving health-related outcomes for these individuals.

### Possible limitations

The use of self-reported health data could be a potential limitation; however, participants were supported by a nurse when reporting their health conditions [27]. The average age of this cohort was younger than the average stroke patient [2]. Younger individuals with stroke have, to date, been under-investigated. Participants were mostly white British, therefore ethnic minorities living in the UK were under-represented, and the participant sample was relatively affluent. These limitations are almost certainly due to participation bias and are likely to provide a more conservative picture of multimorbidity and effects on mortality [2,28]. For example, in a previous study of primary care records that included a more socio-economically deprived sample representative of the Scottish population, 94% of people with stroke had multimorbidity [2]; and in this study, 85% had multimorbidity. An under-representation of socially deprived individuals in the UK Biobank and the relatively younger age range are likely to contribute to the lower prevalence of multimorbidity in this study of people with stroke. The UK Biobank is representative of the UK population in regard to gender. The large sample size was a strength of the study.

The examination of patient characteristics in relation to number of morbidities was cross-sectional and therefore it was not possible to determine temporal

relationships. As discussed above, multimorbidity has received much attention in the literature, yet no consensus has been reached on the optimal method of measurement [29]. A simple count was deemed suitable due to the availability of data on a wide range of morbidities; however, this count was unweighted, which could be viewed as a limitation. The use of a wide range of confounding factors is a strength of this study. The negative relationship between multimorbidity and frequency of alcohol consumption may be due to poor correlation between frequency of consumption and amount consumed. A sensitivity analysis on a subset of individuals with data available on weekly unit consumption was conducted, but unfortunately interpretation was limited due to a small sample size and wide confidence intervals.

### Conclusions

Survival in participants aged 40–72 years with self-reported stroke or TIA was strongly correlated with the number of comorbidities, suggesting that greater emphasis on patient-centred rather than disease-centred care is merited. Significantly worse outcomes were seen in those who had cancer, CHD, diabetes, or COPD alongside their stroke or TIA. There was little difference between the effects of cardiometabolic and non-cardiometabolic comorbidity on mortality; both were significant. The number of comorbidities may be a better predictor of mortality than type of comorbidity. Those with stroke or TIA who were older, socio-economically deprived, smokers, and less frequent alcohol consumers were at higher risk of multimorbidity. Clinical guidelines need to place greater emphasis on the issues of multimorbidity in stroke and TIA.

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### Conflicts of interest

BN, DL, FM and KG received grants from the Chief Scientist Office (CSO), Scottish Government Health Directorates', during the conduct of the study. KG also received a grant from the Carnegie Trust for the Universities of Scotland during the conduct of the study. RM and BJ have nothing to declare.

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