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Multimorbidity and associations with clinical outcomes in a middle-aged population in Iran: a longitudinal cohort study

Maria Lisa Odland ,[1,2,3] Samiha Ismail,[1] Sadaf G Sepanlou,[4] Hossein Poustchi,[5] Alireza Sadjadi,[4] Akram Pourshams,[4] Tom Marshall,[1] Miles D Witham,[6,7] Reza Malekzadeh,[4] Justine I Davies[1,8]

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MLO and SI are joint first authors.
RM and JID are joint senior authors.

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For numbered affiliations see end of article.

Correspondence to
Dr Maria Lisa Odland;
m.l.odland@bham.ac.uk

ABSTRACT

Background As the populations of lower-income and middle-income countries age, multimorbidity is increasing, but there is little information on its long-term consequences. We aimed to show associations between multimorbidity and outcomes of mortality and hospitalisation in Iran, a middle-income country undergoing rapid economic transition.

Methods We conducted a secondary analysis of longitudinal data collected in the Golestan Cohort Study. Data on demographics, morbidities and lifestyle factors were collected at baseline, and information on hospitalisations or deaths was captured annually. Logistic regression was used to analyse the association between baseline multimorbidity and 10-year mortality, Cox-proportional hazard models to measure lifetime risk of mortality and zero-inflation models to investigate the association between hospitalisation and multimorbidity. Multimorbidity was classified as ≥2 conditions or number of conditions. Demographic, lifestyle and socioeconomic variables were included as covariables.

Results The study recruited 50 045 participants aged 40–75 years between 2004 and 2008, 47 883 were available for analysis, 416 (57.3%) were female and 12 736 (27.94%) were multimorbid. The odds of dying at 10 years for multimorbidity defined as ≥2 conditions was 1.99 (95% CI 1.86 to 2.12, p<0.001), and it increased with increasing number of conditions (OR of 3.57; 95% CI 3.12 to 4.08, p<0.001 for ≥4 conditions). The survival analysis showed the hazard of death for those with ≥4 conditions was 3.06 (95% CI 2.74 to 3.43, p<0.001). The number of hospital admissions increased with number of conditions (OR of not being hospitalised of 0.36; 95% CI 0.31 to 0.52, p<0.001, for ≥4 conditions).

Conclusion The long-terms effects of multimorbidity on mortality and hospitalisation are similar in this population to those seen in high-income countries.

WHAT IS ALREADY KNOWN ABOUT THE SUBJECT?

⇒ In high-income countries (HICs), multimorbidity is prevalent and has been associated with serious long-term consequences such as mortality and increased hospitalisation.
⇒ As life expectancy increases, multimorbidity is now increasing in lower-income and middle-income countries (LMICs), but little is known about the long-term consequences.
⇒ These consequences may not be the same as in HICs, and given the effects of poverty, preceding undernutrition, and infectious diseases in LMIC settings, there is a chance the long-term consequences could be even worse.

WHAT DOES THIS STUDY ADD?

⇒ This is one of the first studies to show the long-term effects of multimorbidity outside of a HIC setting.
⇒ This study shows that in Iran, a country going through rapid economic growth and transitioning from a lower-middle to an upper-middle income country, multimorbidity gives increased risk of mortality and hospitalisation.
⇒ The study quantifies the effects of difference demographic and behavioural factors on long-term outcomes of multimorbidity.

HOW MIGHT THIS IMPACT ON CLINICAL PRACTICE?

⇒ This study shows multimorbidity has a detrimental effect on long-term outcomes in a middle-income country going through rapid economic growth. Future research is needed to determine whether low-income countries will face similar issues as they develop.
⇒ The quantification of the effects of demographic and behavioural factors on long-term outcomes, allows better planning of health interventions.
⇒ Politicians and policy-makers in low-income countries, and global health funding, need to focus on chronic conditions and multimorbidity in the years to come in order to avoid the massive burden multimorbidity is likely to place on health systems.

INTRODUCTION

Multimorbidity is most commonly conceptualised as the presence of two or more conditions in an individual or it can be defined in

other ways such as count of conditions.[1 2] It encompasses comorbidity, which refers to two or more chronic conditions that are causally or pathologically linked.[1 2] In high-income countries (HICs)—where most of the research on multimorbidity has focused[1 3] it is increasingly recognised as a major health issue. Several longitudinal studies have shown strong associations between the presence of multimorbidity and adverse outcomes such as death or hospitalisation.[4–8] Understanding the relationship between multimorbidity and outcomes and developing interventions to improve management of patients with multimorbidity to moderate outcomes is a major research focus in HICs.[1 3]

Multimorbidity has received less attention in lower-income and middle-income countries (LMICs).[1 3 9–13] During the Millennium Development Goal era, health research and financial aid in LMICs focused on reducing communicable diseases, and improving maternal, neonatal and child health.[14] These successful efforts have combined with increasing country economic development and reductions in poverty resulted in a growing population of older people, who are more likely to have multimorbidity, in LMICs.[15] In addition, urbanisation, increasingly sedentary life styles and changes in dietary habits towards consumption of larger amounts of calorie dense food have led to a growth in population prevalence of obesity and associated chronic non-communicable diseases (NCDs).[11 16] These chronic NCDs often co-occur in the same individual, but also occur on a background of a high prevalence of communicable diseases.[1 10] Hence, multimorbidity in LMICs is growing in prevalence.

Nevertheless, outside of the HIC setting, the epidemiology and consequences of multimorbidity is a relatively unexplored area, and evidence on the health consequences of multimorbidity in LMIC settings is needed to increase the priority given to this issue. These consequences may not be the same as in HICs, and given the effects of poverty, preceding undernutrition and infectious diseases in LMIC settings, there is a chance the long-term consequences could be even worse.[1]

Cross-sectional analyses have shown a high prevalence of multimorbidity in a few countries, although most of these studies defined multimorbidity using only a limited number of conditions.[10 11] Some studies have shown cross sectional associations of multimorbidity with disability, low quality of life, poor physical performance, number of hospitalisations and mortality.[11 17 18] We are only aware of two longitudinal studies on the outcomes of multimorbidity, both of which were done in China, with limited numbers of participants.[12 13] In order to prioritise planning for health systems that can deal adequately with the increasing burden of multimorbidity in LMICs, it is important to understand the relationship between multimorbidity and long-term health outcomes.

A lack of longitudinal, routinely collected, data in many LMICs limits the ability to report long-term outcomes of multimorbidity. However, data collected as part of a longitudinal cohort study in Iran over the time period where the country transitioned from lower-middle-income to upper-middle-income status, afford the opportunity to assess the outcomes of multimorbidity in a middle-income country going through rapid economic growth. Iran became an upper-middle-income country (UMIC) in 2009, as a result of a rapid and continued period of development. This economic transition and accompanying demographic change is likely reflective of that which will be experienced by many LMICs in the near future. Our aim was to show how presence of multimorbidity is associated with longitudinal outcomes of mortality and hospitalisation in Iran, and explore how this relationship is affected by individuals' demographic and economic characteristics and behavioural factors.

METHODS

This is a secondary analysis of data from the Golestan Cohort Study (GCS), a prospective study which was set up to study risk factors for oesophageal cancer (a highly prevalent cancer in this region). The extensive data collection protocol allows comprehensive study of multimorbidity.

Study setting

During the study period, The Islamic Republic of Iran was a lower-middle-income country in Western Asia with 83 million inhabitants.[19] In the last 20 years, it has developed and urbanised, life expectancy has risen and there is an increased risk of exposure to tobacco, unhealthy diets and physical inactivity.[20 21] Poverty is decreasing, but poverty headcount rates remain higher in rural areas (27%) than urban areas (6%).[19] The prevalence of NCDs has increased along with economic growth; multimorbidity is prevalent.[20 22]

Golestan province is in the north-east of Iran. Urban participants of GCS were recruited from Gonbad City, (population 126 797 inhabitants in 2004) and rural participants from villages in Gonbad, Kaleleh and Aq-Qala counties. The life expectancy in Golestan (Women 72.36 and Men 67.71) in 2004 was similar to the rest of the country.[23] The majority of the population live in urban areas and are educated.[24] Access to healthcare has improved after the introduction of the 'Health transformation plan (HTP)', an initiative from the government to increase universal health coverage (UHC).[25]

Participants and sampling

The GCS recruited participants aged 40–75 years who were free from any gastrointestinal (GI) cancer between January 2004 and June 2008. The study aimed to recruit equal numbers of men and women, with 20% from urban areas, and 80% from Turkmen ethnicity.[21] People unwilling to participate, temporary residents, or those with a current or previous diagnosis of any upper GI cancer were excluded. The sampling strategy has been described in detail elsewhere.[21 26] In brief, in Gonbad city, participants were selected randomly from the five areas in Gonbad by systematic clustering based on household

numbers. For rural areas, all 236 villages contained within Golestan province were included in the sampling frame and participants within these villages were selected by cluster sampling. All consenting adults in each household were invited to participate.

Data collection

For the baseline data collection, participants were contacted by trained healthcare workers and invited to attend the GCS Centre for completion of a questionnaire and collection of anthropometric and blood pressure data. The questionnaire collected information including: (1) Demographic characteristics: sex, age, ethnicity, marital status, educational level, rural or urban location, and information on 15 household assets; (2) personal history of all medication use in the last 6 months (participants were asked to bring medications to the visit); (3) self-report of the following diseases: rheumatic heart disease; angina, myocardial infarction, or heart failure; stroke; hypertension; diabetes; chronic obstructive pulmonary disease; kidney disease; intestinal disease; liver disease; serious infectious diseases (mainly tuberculosis); major disabilities; and history of surgery; (4) tobacco use; and (5) physical activity.[27]

Height in centimetres was measured while standing upright using a stadiometer and weight in kilograms was measured without shoes and in loose clothing using a Mechanical Seca 762. Blood pressure was measured using a Richter mercury sphygmomanometer twice on both arms while the participant was seated. The average of all four readings was used to derive blood pressure.

All participants in the study were followed up by telephone call every 12 months from enrolment to the present and any hospital admission since the last follow-up was recorded, and annual follow-up is ongoing. Participants were also instructed to notify the study team at the time of hospitalisation to limit issues with recall. The dataset used in this analysis was locked for analysis on 29th December 2019, which gave a minimum 10-year follow-up period for all recruited participants.

Definition of variables

Demographic characteristics and lifestyle factors

Age was described as a categorical variable, in groups <40, 40–49, 50–59, 60–69 and ≥70 (the age group <40 was created to include people who on attending the study centre indicated that they were younger than 40—most were people aged 38 and 39). It was used as a continuous variable in the models. Education level was dichotomised into no-education (no education) or education (including one or more years of education). Marital status was categorised as single (including single, widowed, divorced or separated) or married. Wealth quintiles were calculated from data on household assets ownership using multiple correspondence analysis which is widely accepted and used method.[28 29] Ethnicity was dichotomised into Turkmen or other. Smoking was categorised as non-smoker, ex-smoker or current smoker. Alcohol consumption was low and this variable was not used in the analysis.

Body mass index (BMI) kg/m^2 was calculated from height and weight and defined as underweight (<18.5 kg/m^2), normal (18.5–25 kg/m^2) and overweight or obese (≥25 kg/m^2). Physical activity categories were derived by combining activities during employment, leisure and transport based on the amount (intensity and duration) of activity performed during a week based on metabolic equivalents of task, and categorised as previously described into tertiles: low (1), medium (2) and high (3).[30]

Definition of disease states

Hypertension was defined as either self-reported diagnosis, being on treatment or average measured systolic blood pressure of ≥140 mm/Hg or diastolic blood pressure ≥90 mm/Hg. Liver disease was identified by symptoms (jaundice), self-reported diagnosis or being on medication. All other conditions were identified by self-report or use of medication history as follows. First, medications which were specific to conditions self-reported by participants were removed from the list of an individual's treatment. Then, if the participant was on medications specific for a condition not captured on self-report, they were assigned that condition. Remaining medications that were not used to treat specific diagnoses, but potentially used for a diagnosis that the participant had already been assigned were assumed to be given for that diagnosis and removed from the medication list. Finally, patients on any remaining medications that had not been accounted for by the above processes were assigned the condition which the medication is most likely to be used to treat. This process was conducted using reference to the British National Formulary and by agreement between authors (see online supplemental appendix tables 1 and 2 for assignment of diseases to participants).

Participants were categorised as having any (or no) conditions in the domains of NCDs (conditions in the system categories of cancer, cardiovascular disease (CVD), endocrine, GI, respiratory, renal, neurology, rheumatology, unspecified conditions needing immunosuppressant or other NCDs (vitamin/mineral deficiency or benign prostatic hyperplasia)); communicable diseases (tuberculosis, hepatitis or HIV); or any mental health conditions.

Defining multimorbidity

Multimorbidity was defined using two internationally accepted definitions: first as the count of conditions, second as two or more conditions.[1]

Outcomes

The primary outcome was mortality, defined as death within 10 years of study entry. Secondary outcomes were (1) time to death and (2) number of hospitalisations. We chose to study both odds of death within 10 years of enrolment and survival (time to death), given different

likely uses of this information. While odds of death may be useful to clinicians when discussing future outcomes with patients, survival analyses may provide information that is more useful for healthcare planners.

Statistical analysis

All analyses were done using R Studio software V.1.2.5019 using 'survival', 'pscl', 'ggplot2' and 'boot' packages. Variables were described using mean and SD if normally distributed and median and IQR if not. Categorical variables are given as numbers (n) and percentages (%). Heat maps were developed to show multimorbidity pairings for the most common disease systems. We used complete cases of independent variables in the analyses. For each analysis, we used backwards elimination and included an interaction term for age and sex dependent on the effect on the model fit, captured by the Akaike information criterion (AIC). In all analyses, multimorbidity was defined in two ways; as a count of conditions, or binary outcome (yes or no). For ordinal variables, we selected the lowest variable category as the reference category, or for other variables the reference category was chosen arbitrarily.

Primary outcome

Binary logistic regression models were fitted to explore the associations between multimorbidity and death within a 10-year period after study entrance, controlling for sex, age (as a continuous variable), education level, marital status, urban or rural location, wealth, ethnicity and behavioural factors of smoking status BMI, physical activity status. The best model was chosen, using χ^2 tests and through backward elimination ending when all the variables in the model were significant. Only participants who were followed up for the full 10-year period or died within the 10-year period were used in this analysis. Results are given in odds ratios (ORs) with (95% CIs).

Secondary outcomes

Cox proportional hazards models were fitted to explore the associations between multimorbidity and survival during the 10-year study period after checking the plausibility of the proportional hazard assumption. Covariables entered into the model were sex, age (as a continuous variable), education level, marital status, urban or rural location, wealth, ethnicity and behavioural factors of smoking status, BMI, and physical activity status. The best model was selected by improving the AIC through backward elimination. Backward elimination ended when all the variables in the models were significant. An interaction term between age and sex was inserted to improve the model fit. Participants who were lost to follow-up were censored at the last date of follow-up. Results are shown as hazard ratios (HRs) with 95% CI.

Poisson logistic regression models with a zero-inflation component were used to explore the associations between multimorbidity as a count of conditions and number of hospitalisations in a 10-year period. The AIC was used to justify the addition of the zero-inflation component to this model. Backwards elimination was done for both the binary model and the count model ending when all the variables in the models were significant. Results were generated using bootstrapping and are given as ORs with 95% CI for the zero-inflation component of the model, and incidence rates with 95% CI for the hospitalisation count part of the model. Only participants who were followed up for the full 10-year period or died within the 10-year period were used in this analysis. Covariates entered into the model were sex, age, education level, marital status, urban or rural location, wealth, ethnicity and NCD risk factors of smoking status, BMI and physical activity status.

Patient and public involvement statement

Participants were not directly involved in planning the study.

RESULTS

Out of the 50 045 individuals in the original sample, 2162 participants were removed before analysis; 8 were missing BMI data, 2096 were missing physical activity data, and 58 had incorrect follow-up data (follow-up date entered incorrectly) leaving 47 883 cases for the analysis. 2297 participants were lost to follow-up during the 10-year period and were excluded from the binary logistic regression for 10-year mortality and analysis of numbers of hospitalisations within 10 years of follow-up (leaving n=45 586 complete cases for these analyses). These individuals were, however, included in the survival analysis (n=47 883) (figure 1). The demographic, lifestyle and disease characteristics of participants are shown in table 1.

Among the 45 586 individuals included in the complete case analysis, most were female (57.04%) and the mean age was 51.93 (SD 8.85) years. The majority of the participants had no schooling (69.88%), and most were married (88.09%). Eighty per cent of the sample lived in rural areas, and 75.53% were of Turkmen ethnicity. 14.08% were current smokers with a mean of 16.90 (18.25) pack years. 59.28% of people were overweight or obese with a BMI ≥25 kg/m^2.

The average number of morbidities per participant was 1.05 (SD 1.19) and 59.45% had a least one morbidity. When categorising multimorbidity as two or more conditions 12 736 (27.94%) of the participants had multimorbidity (table 1). The most common disease domain was NCDs (56.65%) with CVD (37.15%) being the most common NCD system affected and hypertension (27.90%) the most common condition (online supplemental appendix table 3 shows conditions within disease domains). Having at least one condition in the GI system was also common (22.13%). At least one mental health condition was present in 8.62% of the population, but the condition was not possible to ascertain from the survey or medication information. The percentage of communicable diseases in the study population was 3.22% and

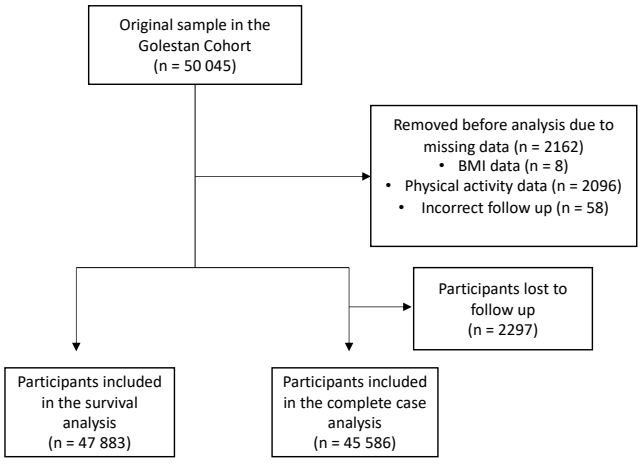

Figure 1 Study flow diagram showing the numbers of people who were included in the survival analyses and the complete case analysis. BMI, body mass index.

tuberculosis constituted the majority (99.59%) of these. No medications were taken by 41.29% of the population, while 9.76% were on ≥4 medications. The most common combination of diseases systems was mental health and CVD (figure 2).

When considering complete cases, during the 10 years of follow-up, 5 411 participants died, 17 855 had one or more hospitalisations and the mean time to death was 5.52 years for those that died. The demographic information of the participants who died during the study period and occurrence of outcomes by demographics, lifestyle factors, condition and multimorbidity are shown in online supplemental appendix table 4. The characteristics of multimorbid versus not multimorbid participants in complete cases are found in online supplemental appendix table 5.

In multivariable analysis (table 2), the odds of being dead within 10 years after study entry increased significantly with increasing number of conditions, after controlling for age, sex, education, wealth, physical activity, smoking history and BMI. The OR was 3.57 (95% CI 3.12 to 4.08, p<0.001) for participants with four or more conditions compared with those with no conditions at baseline. Being male, older, unmarried, poorer, ever having smoked, less physically active and having a lower BMI were all significantly associated with greater odds of death within 10 years compared with their referent categories; area of living and ethnicity were not significantly associated with the outcome and was therefore excluded from the model. When categorising multimorbidity as a dichotomous variable (two or more conditions vs fewer than two conditions), multimorbidity was again significantly associated with increased odds of being dead within 10 years (OR 1.99, 95% CI 1.86 to 2.12, p<0.001) when controlling for other variables (online supplemental appendix table 6).

Results from the Cox regression analysis to explore association between multimorbidity and survival, including a term capturing the extra risk each year experienced by males to optimise model fit, are shown in table 3. Area of living was again excluded from the model due to lack of significance. The factors associated with the highest HR were multimorbidity with four or more conditions (HR 3.06, 95% CI 2.74 to 3.43), male (HR 3.17 95% CI 2.22 to 4.53), ever having smoked (HR 1.37, 95% CI 1.28 to 1.47) and older age (HR 1.08, 95% CI 1.07 to 1.08). The Kaplan-Meier plot for participants with 0, 1, 2, 3 or 4+ conditions is shown in figure 3. When categorising multimorbidity as a dichotomous variable (two or more conditions vs fewer than two conditions), multimorbidity was again significantly associated with an increased hazard of dying when controlling for other variables (HR 1.81, 95% CI 1.71 to 1.91, p<0.001) (online supplemental appendix table 7 and figure 1).

The binary component of the zero inflation model (table 4) showed that the OR for being in the group who were not hospitalised decreased with number of conditions and also decreased with age, wealth, being non-Turkman ethnicity and ever having smoked. Having education, having a BMI between 18.5–25 kg/m^2, and

Table 1 Demographic characteristics, NCD risk factors and morbidity categories of the participants included in the study (n=47 883)

	Individuals used in survival analysis (including 2297 lost to follow-up)		Lost to follow-up*		Complete cases	
	n	%	n	%	n	%
	47 883	**100**	**2297**	**4.80%**	**45 586**	**95.20**
Demographic variables						
Males	20 467	42.74	884	38.48	19 583	42.96
Females	27 416	57.26	1413	61.52	26 003	57.04
Age, mean (SD)	51.86 (8.83)		50.48 (8.48)		51.93 (8.85)	
<40	785	1.64	63	2.74	722	1.58
40–49	23 196	48.44	1258	54.77	21 938	48.12
50–59	14 848	31.01	621	27.04	14 227	31.21
60–69	6797	14.20	281	12.23	6516	14.29
≥70	2257	4.71	74	3.22	2183	4.79
Education level†						
No-education	33 313	69.57	1457	63.43	31 856	69.88
Education	14 570	30.43	840	36.57	13 730	30.12
Marital status						
Single	5687	11.88	258	11.23	5429	11.91
Married	42 196	88.12	2039	88.77	40 157	88.09
Geography						
Urban	9718	20.30	257	11.19	9461	20.75
Rural	38 165	79.70	2040	88.81	36 125	79.25
Wealth						
1	10 095	21.08	348	15.15	9747	21.38
2	8866	18.52	358	15.59	8508	18.66
3	10 440	21.80	531	23.12	9909	21.74
4	9132	19.07	477	20.77	8655	18.99
5	9350	19.53	583	25.38	8767	19.23
Ethnicity						
Torkman	35 570	74.29	1139	49.59	34 431	75.53
Other	12 313	25.71	1158	50.41	11 155	24.47
NCD risk factors						
Smoking						
Non-smoker	39 574	82.65	1975	85.98	37 599	82.48
Ex-smoker	1637	3.42	70	3.05	1567	3.44
Current smoker	6672	13.93	252	10.97	6420	14.08
Pack years for smokers, mean (SD)	16.89 (18.37)		16.65 (21.06)		16.90 (18.25)	
BMI (kg/m^2)						
Underweight (<18.5)	2267	4.73	98	4.27	2169	4.76
Normal weight (18.5≤weight<25)	17 155	35.83	760	33.09	16 395	35.96
Overweight (≥25)	28 461	59.44	1439	62.65	27 022	59.28
Physical activity status*						
1	16 552	34.57	664	28.91	15 888	34.85
2	15 416	32.20	809	35.22	14 607	32.04
3	15 915	33.24	824	35.87	15 091	33.10
Morbidity						

Continued

Table 1 Continued

	Individuals used in survival analysis (including 2297 lost to follow-up)		Lost to follow-up*		Complete cases	
	n	%	n	%	n	%
	47 883	**100**	**2297**	**4.80%**	**45 586**	**95.20**
No of diseases, mean (SD)	1.06 (1.19)		1.18 (1.28)		1.05 (1.19)	
Count of morbidities						
0	19 344	40.40	861	37.48	18 483	40.55
1	15 069	31.47	702	30.56	14 367	31.52
2	7873	16.44	395	17.20	7478	16.40
3	3534	7.38	215	9.36	3319	7.28
4+	2063	4.31	124	5.40	1939	4.25
Multimorbidity (defined as 2+ morbidities in any domain or system)						
Not multimorbid	34 413	71.87%	1563	68.05%	32 850	72.06%
Multimorbid	13 470	28.13%	734	31.95%	12 736	27.94%
At least one disease (N)	28 539	59.60%	1436	62.52%	27 103	59.45%
Non-communicable diseases (at least one)	27 198	56.80%	1373	59.77%	25 825	56.65%
Cancer	160	0.33%	4	0.17%	156	0.34%
Cardiovascular disease (at least one condition)	17 815	37.21%	881	38.35%	16 934	37.15%
Endocrine (at least one condition)	885	1.85%	55	2.39%	830	1.82%
Gastrointestinal (at least one condition)	10 698	22.34%	610	26.56%	10 088	22.13%
Respiratory (at least one condition)	2948	6.16%	114	4.96%	2834	6.22%
Renal - chronic kidney disease	90	0.19%	4	0.17%	86	0.19%
Neurology (at least one condition)	965	2.02%	51	2.22%	914	2.01%
Rheumatology (at least one condition)	127	0.27%	8	0.35%	119	0.26%
Unspecified conditions needing Immunosuppressants	3691	7.71%	208	9.06%	3483	7.64%
Other*‡	1290	2.69%	86	3.74%	1204	2.64%
Mental health (any)	4188	8.75%	258	11.23%	3930	8.62%
Communicable diseases (at least one)	1534	3.20%	64	2.79%	1470	3.22%
Medications						
0	19 567	40.86%	743	32.35%	18 824	41.29%
1	12 705	26.53%	620	26.99%	12 085	26.51%
2	7073	14.77%	351	15.28%	6722	14.75%
3	3780	7.89%	274	11.93%	3506	7.69%
4+	4758	9.94%	309	13.45%	4449	9.76%

*Physical activity tertiles have been calculated based on the intensity of physical activity, based on METs.
†Education includes 1 or more years of education.
‡Vitamin or mineral deficiency or benign prostate hyperplasia.
BMI, body mass index; METs, metabolic equivalents of task; NCD, non-communicable disease.

having a higher level of physical activity were protective against being hospitalised. Backwards elimination of the binary component of the zero-inflation model removed gender, marital and area of living. Also BMI categories were changed to BMI 18.5–25 kg/m^2 vs not to improve model fit. The count component of the zero inflation model (table 4) showed that the number of hospital admissions an individual had significantly increased with the number of conditions when controlling for demographic and behavioural factors. The number of hospitalisations also increased with male sex, age and having education, being non-Turkman, smoker and BMI ≥25. The number of hospitalisations decreased with increased physical activity. Backwards elimination for the count part removed marital status, area of living and wealth. Also BMI was changed to BMI 0–25 kg/m^2 vs 25+, and

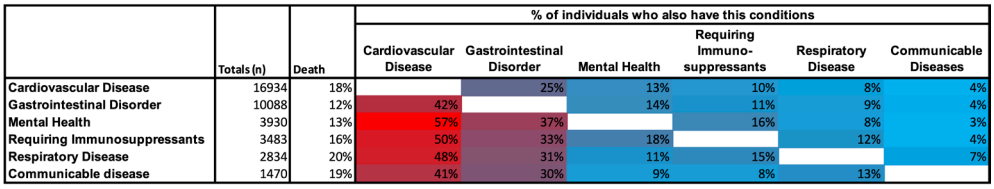

Figure 2 Multimordibity pairings for the most common disease systems (complete cases only n=45 586). The most common disease systems and their pairings are shown. Red indicates common pairings and blue, less common.

physical activity was changed to 1–2 vs 3 to improve the fit.

DISCUSSION

We found that multimorbidity was common in this large population of older adults from Iran. It was strongly associated with a greater chance of death within 10 years of follow-up, a lower hazard of survival, and a greater chance of hospitalisation and number of hospitalisations within the study period. The lack of access to good quality data from electronic health records in most LMICs means that most studies of multimorbidity use survey data—as we have done—which limits the ability to include severity of conditions in any analyses. Nevertheless, the definition of multimorbidity of the presence of two or more chronic conditions in an individual is internationally accepted.[1 2] We chose to additionally categorise multimorbidity as a count of conditions. There was a strong dose response relationship between adverse outcomes and increasing number of conditions, with odds of death for those with four or more conditions being almost double that for those categorised as having multimorbidity based on having two or more conditions. Hence, this demonstrates that the impact of

Table 2 The OR of dying within 10 years, by demographic characteristics, NCD risk factors and number of conditions

Variable		OR		
Count of morbidities	**0 diseases**	**Referent**	**95% CI**	**P value**
	1 disease	1.62	(1.50 to 1.76)	<0.001
	2 diseases	2.31	(2.11 to 2.53)	<0.001
	3 diseases	2.72	(2.42 to 3.04)	<0.001
	4+diseases	3.57	(3.12 to 4.08)	<0.001
Sex	Females	Referent		
	Males	2.16	(1.98 to 2.36)	<0.001
Age	Age at entrance	1.08	(1.08 to 1.09)	<0.001
Education	No-education	Referent		
	Education	0.79	(0.72 to 0.86)	<0.001
Marital status	Not married	Referent		
	Married	0.84	(0.77 to 0.92)	<0.001
Wealth quintiles	Wealth quintile 1	Referent		
	Wealth quintile 2	0.90	(0.82 to 0.98)	0.02
	Wealth quintile 3	0.68	(0.62 to 0.74)	<0.001
	Wealth quintile 4	0.69	(0.62 to 0.76)	<0.001
	Wealth quintile 5	0.58	(0.52 to 0.64)	<0.001
Smoking status	Never smoked	Referent		
	Current/ex-smoker	1.46	(1.35 to 1.59)	<0.001
BMI	BMI <18.5	Referent		
	BMI: 18.5≤x<25	0.66	(0.58 to 0.74)	<0.001
	BMI: ≥25	0.58	(0.51 to 0.65)	<0.001
Physical activity	Physical activity 1	Referent		
	Physical activity 2	0.77	(0.71 to 0.84)	<0.001
	Physical activity 3	0.71	(0.65 to 0.77)	<0.001

BMI, body mass index; NCD, non-communicable disease.

Table 3 The HR of dying within the study period by demographic characteristics, NCD risk factors and number of conditions

Variable		HR		
Count of morbidities	0 diseases	Referent	95% CI	P value
	1 disease	1.54	(1.43 to 1.65)	<0.001
	2 diseases	2.08	(1.92 to 2.26)	<0.001
	3 diseases	2.36	(2.14 to 2.60)	<0.001
	4+diseases	3.06	(2.74 to 3.43)	<0.001
Sex	Females	Referent		
	Males	3.17	(2.22 to 4.53)	<0.001
Age	Age at entrance	1.08	(1.07 to 1.08)	<0.001
Education	No-education	Referent		
	Education	0.81	(0.75 to 0.87)	<0.001
Marital status	Not married	Referent		
	Married	0.87	(0.80 to 0.94)	<0.001
Wealth quintiles	Wealth quintile 1	Referent		
	Wealth quintile 2	0.91	(0.84 to 0.98)	0.02
	Wealth quintile 3	0.71	(0.65 to 0.77)	<0.001
	Wealth quintile 4	0.72	(0.66 to 0.78)	<0.001
	Wealth quintile 5	0.62	(0.56 to 0.68)	<0.001
Ethnicity	Turkmen	Referent		
	Not Turkmen	0.88	(0.83 to 0.94)	<0.001
Smoking status	Never smoked	Referent		
	Current/ex-smoker	1.37	(1.28 to 1.47)	<0.001
BMI	BMI <18.5	Referent		
	BMI: 18.5≤x<25	0.70	(0.63 to 0.77)	<0.001
	BMI: ≥25	0.62	(0.56 to 0.69)	<0.001
Physical activity	Physical activity 1	Referent		
	Physical activity 2	0.79	(0.74 to 0.85)	<0.001
	Physical activity 3	0.74	(0.69 to 0.79)	<0.001
Interaction between sex and age	Extra risk for each age year for females	Referent		
	Extra risk for each age year for males	0.99	(0.99 to 1.00)	0.01

BMI, body mass index; NCD, non-communicable disease.

multimorbidity risks being under-estimated if the count of conditions is not used.

Many countries are attempting to achieve the Sustainable Development Goals (SDGs) by 2030, and in the last few decades Iran has implemented various reforms in order to achieve UHC, which is a key component of the health-related SDGs.[31] The HTP which was initiated in 2014 has contributed by expanding insurance coverage, and enhancing financial protection.[31] In fact, the out-of-pocket (OOP) expenditure on health in Iran was halved from 1995 to 2018, although it remained high at 35.83% in 2018 (the most recent year for which there are data).[19 32] The Iranian healthcare system has a well-defined three-tier structure of primary, secondary and tertiary facilities, and even though the HTP was initially only implemented in hospital-based settings, it was later expanded to primary healthcare, which is where most patients with multimorbidity receive routine care. Thus health services development in Iran has accompanied economic growth. Although, some issues more familiar to countries that have less developed health services or economies remain, for example, there are no mechanisms to collect health insurance contributions from people without consistent income, thus compulsory health insurance coverage is not fully implemented.[31] Moreover, many diagnostic services are only offered by the private healthcare sector which is not supported by the HTP, leading to high OOP for some people, and more mechanisms are needed to extend free health insurance coverage to the ones in need.[31] Multimorbidity has been shown to be associated with greater mortality, hospitalisations, disability and low quality of life in HICs,[1 5 17 33–35] but has been a neglected area in health research in LMICs with little evidence available on long-term outcomes of multimorbidity in these settings.

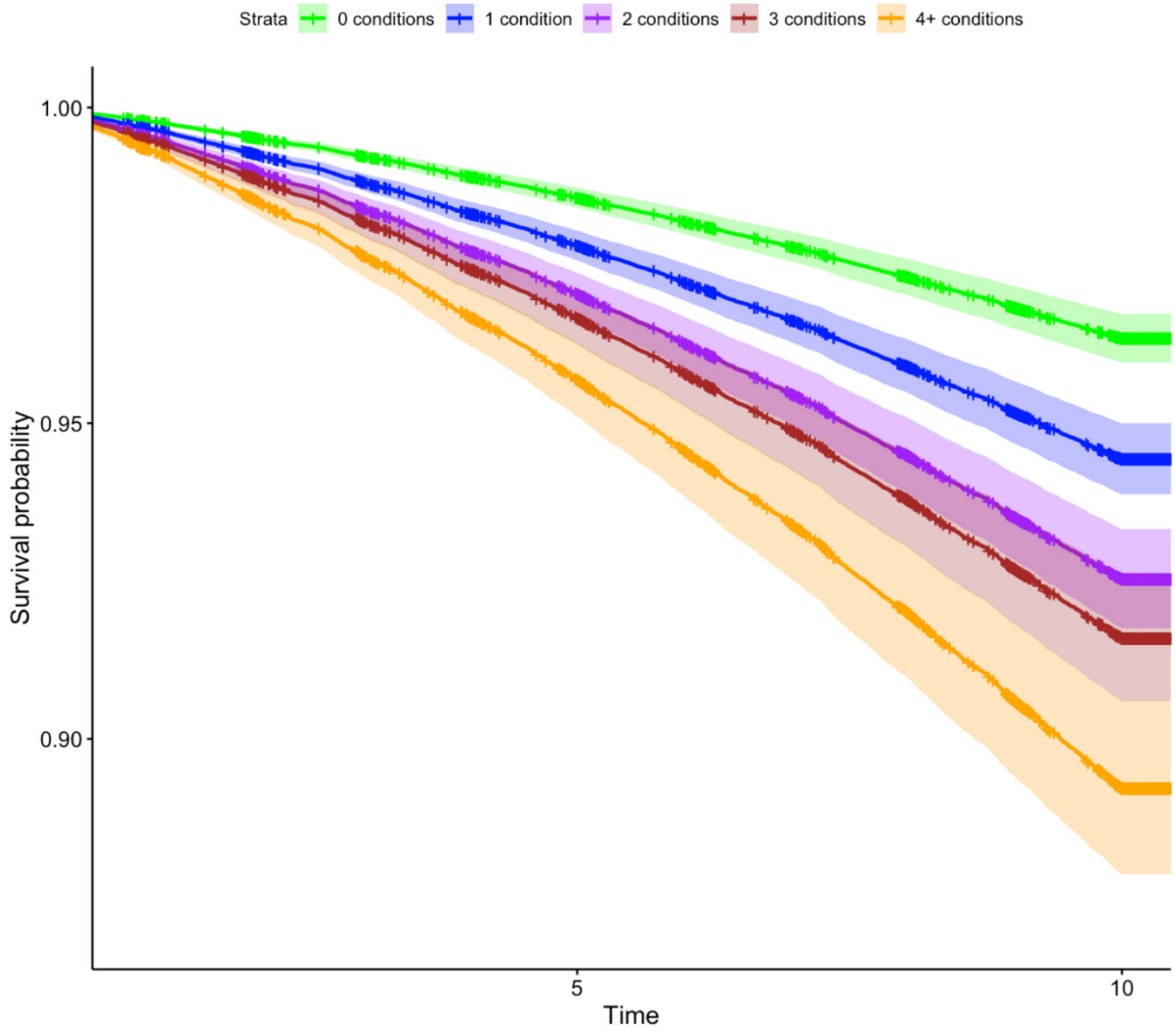

Figure 3 Survival of participants by number of conditions (n=47 883). Plots are shown controlling for demographic characteristics and behavioural factors.

Although it is likely that the long-term consequences of multimorbidity will be at least as hazardous in LMICs as in HICs, it is important to show this to raise the priority of managing multimorbidity in health system planning. Iran, being a rapidly developing country which has transitioned from being a lower-middle-income country to an UMIC during the study period may be an exemplar of the situation in other developing LMICs. Additionally, given the double burden of prevalent infectious diseases and rapidly rising prevalence of NCDs on a background of poverty, it is possible that the outcomes of multimorbidity will be worse in LMICs than HICs. Indeed, although the HRs found in our study were within the range of what was found in the previous studies from China,[12 13] the association between number of conditions and mortality was stronger in our study than seen in studies done in HICs.[36–38]

As far as we are aware, our study is the first to look at hospitalisation as a long-term consequence of multimorbidity outside of an HIC setting. Our results from Iran are similar to what has been found in HICs, with increased number of conditions being associated with greater chance of hospitalisation per se and increased number of hospitalisations.[35 39] These findings may well be an indication of what will be experienced in many other rapidly developing LMICs in the near future, and our evidence of the high proportion of multimorbidity and its strong association with serious long-term consequences, is therefore troubling.

The baseline proportion of multimorbidity (defined as two or more conditions) in our study is similar to previously estimated in Iran and other LMICs in similar age groups.[9 11 40 41] Our finding that NCDs, especially CVDs, were the most common is to be expected, given global disease patterns.[42] We have also shown that diseases in different domains (non-communicable, mental health or communicable) or disease system categories (eg, cardiovascular, GI, neurological) often co-occur. This lends weight to calls to develop health system-platforms of care, requiring a shift in emphasis from providing care for single diseases to an array of diseases.[43] It is also important that UHC is broad in its coverage of conditions

Table 4 Zero inflation model of number of hospitalisations within a 10-year period of entering the study

		Zero inflation model					
		Binary part*			Count part†		
Variable		OR	95% CI	P value	Risk ratio	95% CI	P value
Count of morbidities	**0 diseases (ref)**						
	1 disease	0.73	(0.67 to 0.80)	<0.001	1.24	(1.18 to 1.31)	<0.001
	2 diseases	0.57	(0.52 to 0.63)	<0.001	1.53	(1.45 to 1.62)	<0.001
	3 diseases	0.51	(0.45 to 0.58)	<0.001	1.70	(1.59 to 1.80)	<0.001
	4+ diseases	0.36	(0.31 to 0.42)	<0.001	2.01	(1.88 to 2.17)	<0.001
Sex	Females (ref)						
	Males	–	–	–	1.03	(0.99 to 1.07)	0.05
Age	Age at entrance	0.96	(0.95 to 0.96)	<0.001	1.01	(1.01 to 1.01)	<0.001
Education	No-education (ref)						
	Education	1.22	(1.13 to 1.31)	<0.001	0.95	(0.91 to 0.99)	0.01
Wealth quintiles	Wealth quintile 1 (ref)						
	Wealth quintile 2	0.89	(0.82 to 0.97)	0.007	–	–	–
	Wealth quintile 3	0.89	(0.82 to 0.96)	0.003	–	–	–
	Wealth quintile 4	0.86	(0.80 to 0.94)	<0.001	–	–	–
	Wealth quintile 5	0.86	(0.79 to 0.95)	<0.001	–	–	–
Ethnicity	Turkmen (ref)						
	Not Turkmen	0.76	(0.70 to 0.81)	<0.001	1.15	(1.11 to 1.20)	<0.001
Smoking status	Never smoked (ref)						
	Current/ex-smoker	0.86	(0.79 to 0.94)	<0.001	1.07	(1.02 to 1.12)	0.001
BMI	BMI <18.5 or ≥25 (ref)						
	BMI: 18.5≤x<25	1.16	(1.08 to 1.24)	<0.001	–	–	–
BMI	BMI <25(ref)						
	BMI: ≥25	–	–	–	1.11	(1.07 to 1.16)	<0.001
Physical activity	Physical activity 1 (ref)						
	Physical activity 2	1.20	(1.13 to 1.28)	<0.001	–	–	–
	Physical activity 3	1.24	(1.15 to 1.35)	<0.001	–	–	–
Physical activity	Physical activity 1–2 (ref)						
	Physical activity 3	–	–	–	0.93	(0.89 to 0.97)	<0.001

The following changes were made through backwards elimination.
Area of living and marital status were excluded from both models due to insignificance.
Sex was not a significant predictor of the outcome in the binary part of the model and was therefore excluded.
Wealth was not a significant predictor of the outcome in the count part of the model and was therefore excluded; BMI categories were changed to BMI 18.5–25 vs not for the binary part and <25 vs not for the count part.
Physical activity categories were changed to 1–2 vs 3 for the count part.
The zero inflation (binary) part shows ORs of how variables affect a participant being in the inflated zero-hospitalisations group, then a count model is fitted to show risk ratios for the number of hospitalisations which occur if a participant could have more than 0 hospitalisations.
*Predicting if a participant had certainly 0 hospitalisations in study period.
†Number of times of hospitalisations, if participant did not have certainly 0 hospitalisations.
BMI, body mass index.

to address the issue of multimorbidity.[44] However, caring for patients with multimorbidity is challenging, putting a burden on the health services and patients—who often are required to attend for multiple medical follow-up appointments. Delivering patient centred care—with fewer healthcare visits—needs to be balanced with the financial reality that many developing health systems face. As explained previously, Iran is still struggling to achieve UHC even after implementation of the HTP, and some of the poorest or more fragile people in the community might not be accessing healthcare due to lack of insurance and high OOP. To achieve UHC and deal with the burden of multimorbidity and its consequences which we have found will require continued political and financial

commitment. The drive to ensure that care for chronic conditions is focused in primary healthcare settings will help achieve this balance, indeed, other middle income countries, such as South Africa, have embraced this approach with their Ideal Clinic programme.[45] The Ideal Clinic programme was initiated in 2013 to improve the quality of primary healthcare facilities, even though the programme is new, and has to be strengthened, the preliminary results are promising.[46] Moreover, stakeholders and policy-makers in LMICs can learn from some of the triumphs and errors of HICs.[47]

Although our main aim was to explore associations between multimorbidity and outcomes, there are other findings worthy of note. In particular odds of death were three times as high for men as for women when defining multimorbidity as count of conditions. Sex did not influence the risk of being hospitalised in our study, but did have an effect on the number of hospitalisations, with men having more hospitalisations. Our results are thus similar to findings in other studies.[4 12 13 48] Even though women are generally more likely to have multimorbidity than men,[11 35 49] differences in healthcare utilisation between women and men may be the reason for worse outcomes in men compared with women.[50 51] We also found that wealth was associated with a lower risk of adverse outcomes—as have other studies using cross sectional data from LMICs.[11 52] Low socioeconomic status is a well-known risk factor for CVD, multimorbidity and mortality in HICs.[2 13 52 53] Hence ignoring the increasing burden of multimorbidity may increase inequalities in Iran and other LMICs.[19]

Although studies in HICs have found a U-shaped relationship between BMI and outcomes,[54] we found that low BMI was associated with the highest risk of death within 10 years, reduced survival and increased number of hospitalisations. Being overweight had the lowest risk of adverse outcomes. Our findings are in thus line with studies which have demonstrated the 'obesity paradox', that is, being overweight is associated with improved survival in older age groups.[54] Also the finding that low BMI is associated with a higher odds of death in our study may be due to reverse causality, with lower BMI occurring in people who are more severely ill. Being in a higher tertile of physical activity was associated with better outcomes, a finding which is in line with others who have shown that exercise, even when ageing, improves outcomes.[55 56]

Our study has several limitations. Polypharmacy has been associated with an increased risk of death in other studies.[57] However, given that we defined the presence of conditions based on the use of medications it was not possible to reliably disentangle the contributions of polypharmacy or multimorbidity to outcomes in this study. Unfortunately, our study did not investigate the association with concordant (two or more conditions in one disease domain) or discordant (two or more conditions in a different disease domain) multimorbidity. Discordant multimorbidity has been found to have adverse outcomes on frailty, disability, and quality of life in a previous cross-sectional study from Burkina Faso.[11] However, information on numbers of conditions in the communicable or mental health domains was not sufficient to enable such an analysis in this study. A major limitation is that we only had access to data on multimorbidity and physical measurements at baseline, and were not able to determine the effects of changes in multimorbidity status over the course of follow-up on outcomes. Another major limitation is that the study was set in the Golestan province which is largely populated by Turkmen, especially in the rural areas. Turkmen is a minor ethnic group in Iran forming around 2% of the total population. Turkmen may have a different diet, lifestyle and socioeconomic status to that of ethnic Persians which means our results may not be generalisable to the rest of Iran. Indeed, although ethnicity did not influence the odds of being dead in 10 years, there were—contrasting—effects of ethnicity on the hazard of death and hospitalisations. Nevertheless, removing ethnicity from our models did not substantially alter the relationship between our main independent variable of interest, multimorbidity and the outcomes (data not shown). Other limitations from our study include that the competing risk of death could have reduced the association between multimorbidity and hospitalisations, meaning that our estimates on hospitalisation are conservative. The prevalence of mental health conditions was surprisingly low, which could be due to under-reporting and stigma, meaning that the reported prevalence of mental health conditions (and hence multimorbidity) could be an underestimate. An additional reason for underestimation of multimorbidity is that the sample in the cohort was collected to study the incidence of oesophageal cancer, hence patients with GI cancers were excluded from the baseline sample. Upper GI cancer is a common cause of cancer related death in Iran, with gastric cancers being the most prevalent (0.2 and 100 per 100 000).[58]

That most of the conditions in this cohort were self-reported could introduce a risk of recall bias. However, the questionnaire was validated in a pilot and there was good correlation between self-reported food intake or opium use and biomarker measurements.[26 59] Additionally, medications—which were recorded by data collectors—provided additional objective evidence of disease; although medications were assigned to diseases informed by the British National Formulary and clinical expert opinion, these assignments may not have been accurate in all cases. We could not ascertain reason for hospitalisation and specific cause of death using our data. Finally, to provide data in an important area where data are currently lacking, our study used a convenience cohort which was not nationally representative.

Conclusions

This is one of the first studies to report on longitudinal effects of multimorbidity in a middle-income country. Our study shows that the long-terms effects of multimorbidity on outcomes, such as mortality and hospitalisation,

are just as hazardous, and potentially worse, in Iran as in HICs. Our results are relevant for future health policy and planning as there is a growing body of evidence on the increasing burden of NCDs and multimorbidity in LMICs, and given similar socioeconomic trajectories, low-income countries may face the similar issues of deleterious consequences of multimorbidity to Iran in the future. We recommend focusing more resources and global health funds around improving health system preparedness in LMIC settings to treat patients with multimorbidity in the years to come.

Author affiliations
[1]Institute of Applied Health Research, University of Birmingham, Birmingham, UK
[2]Department of Obstetrics and Gynecology, St. Olavs University Hospital, Trondheim, Norway
[3]Malawi-Liverpool-Wellcome Trust Research Institute, Blantyre, Malawi
[4]Digestive Diseases Research Center, Digestive Diseases Research Institute, Tehran University of Medical Sciences, Tehran, Iran
[5]Liver and Pancreatobiliary Diseases Research Center, Digestive Diseases Research Institute, Tehran University of Medical Sciences, Tehran, Iran
[6]AGE Research Group, NIHR Newcastle Biomedical Research Centre, Newcastle University, Newcastle upon Tyne, UK
[7]Newcastle Upon Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne, UK
[8]Medical Research Council/Wits University Rural Public Health and Health Transitions Research Unit, School of Public Health, University of the Witwatersrand, Johannesburg-Braamfontein, South Africa

Twitter Justine I Davies @drjackoids

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Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

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Ethics approval This was a secondary analysis of deidentified participant data. The initial study was approved by the ethics committee of the Digestive Diseases Research Institute, Tehran, University of Medical Sciences (OHRP-IRB-00001641). Before participation, a written informed consent was obtained from each participant, allowing investigators to use anonymised data for future analysis. Participants gave informed consent to participate in the study before taking part.

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Data availability statement Data are available on reasonable request. Information about the study design, updated interim analyses, ongoing substudies and relevant publications are available at www.ddrc.ac.ir. Specific proposals for national and international collaborations are welcomed. Initial proposals, which include the aim of the proposed study, the required data and a time-table, should be submitted to RM (ri.ca.sma@kelam) or PB (rf.crai@atteffob). The proposals will be discussed within the steering committee, which includes the principal investigators of the study and, if necessary, other experts according to the proposal's theme.

Author note RK and JID are joint last authors.

ORCID iD
Maria Lisa Odland http://orcid.org/0000-0003-4340-7145

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Appendix table 1. Elements used in construction of each morbidity variable

Domain	System	Condition	Definition, if needed	Method of derivation	1st pass drugs (Assign condition if drug is present)	2nd pass drugs (Remove drugs if condition present)		3rd pass drugs (Assign condition if drug present after step 2)
NCDs	Cancer	Cancer	Any cancer	1- Self reported 2- Medication process	Chemotherapy Radiotherapy Tamoxifen Vinblastin Amp Megestrol Acetate Imatinib	Gabapentin Vinblastin Amp Cyclophosphamide Cyclophosphamide Amp Tamoxifen Chemotherapy Megestrol Acetate Imatinib Radiotherapy	Cyproterone Cyproterone Compound Calcitonin nasal spray Haloperidol Trazodone Perphenazine Fluoxetine Trifluoperazine	Cyclophosphamide Cyclophosphamide Amp
	Cardiovascular	Diabetes		1- Self reported 2- Medication process	Acarbose Other “anti-diabetes” medication Insulin Insulin NPH Insulin Regular Glibenclamide chlorpropamide Metformin	Acarbose Other “anti-diabetes” medication Metformin Insulin Insulin NPH	Insulin Regular Glibenclamide Chlorpropamide	
		Dyslipidaemia		1- Medication process	Other “anti-lipid” medication Nicotinic Acid Clofibrate Gemfibrozil	Nicotinic Acid Other “anti-lipid” medication Clofibrate Gemfibrozil	Atorvastatin Lovastatin Simvastatin	Atorvastatin Lovastatin Simvastatin

		Hypertension		1- Self Report 2- Examination (Average BP readings above 140/90*) 3- Medication process	Anti HTN Methyldopa	Methyldopa Prazosin Trazosin Enalapril Captopril Lisinopril Carvedilol Losartan Atenolol Propranolol Metoprolol Sotalol Sotalol	Amlodipine Diltiazem Nifedipine Verapamil Metoral Furosemide Diuretic Hydrochlorothiazide Triamterene H Anti HTN Clonidine Methyldopa	Clonidine

		Heart Disease	Ischaemic Heart Disease/ Heart Failure/ Arrhythmia	1- Self reported 2- Medication process	Amiodarone Digoxin Isosorbide TNG Pearl Nitrocantin Nitroglycerin	Captopril Lisinopril Carvedilol Warfarin Clopidogrel Dipyridamole Ticlopidine Aspirin Losartan Atenolol Propranolol Metoprolol Sotalol Other “cardiac” medication Amlodipine Diltiazem Nifedipine Verapamil Metoral Furosemide	Enalapril Prazosin Trazosin Diuretic Hydrochlorothiazide Triamterene H Pentoxiphylline Hydralazine Atorvastatin Lovastatin Simvastatin Clonidine TNG Pearl Amiodarone Digoxin Isosorbide Nitrocantin Nitroglycerin Amilodipine Flurazepam Lorazepam	
		Rheumatic Heart Disease		1- Self report				
		Stroke	Both haemorragic and ischaemic	1- Self reported 2- Medication process		Warfarin Clopidogrel Dipyridamole Ticlopidine	Aspirin Atorvastatin Lovastatin Simvastatin	

		CV Unspecified	On Cardiovascular related medication but no assigned cardiovascular conditon	1- Medication process		Carvedilol Warfarin Clopidogrel Dipyridamole Ticlopidine Aspirin Losartan Atenolol Propranolol Metoprolol Sotalol Other “cardiac” medication Amlodipine Diltiazem	Spironolactone Enalapril Captopril Lisinopril Nifedipine Verapamil Metoral Furosemide Diuretic Hydrochlorothiazide Triamterene H Pentoxiphylline Hydralazine Amlodipine	Enalapril Captopril Lisinopril Spironolactone Carvedilol Warfarin Clopidogrel Dipyridamole Ticlopidine Aspirin Losartan Atenolol Propranolol Metoprolol Sotalol Cardiac Amlodipine Diltiazem Nifedipine Verapamil Metoral Furosemide Diuretic Hydrochlorothiazide Triamterene H Pentoxiphylline Hydralazine

	Endocrine	Thyroid Disease	Hypo- or hyperthyroid	1- Medication process	Anti Hyperthyroidism Anti Thyroidism Propylthiouracil Levothyroxine Radioactive Iodine Methimazole Metimazole	Anti Hyperthyroidism Anti Thyroidism Methimazole Metimazole Propylthiouracil Levothyroxine Radioactive Iodine		
		Endocrine Unspecified	Endocrine disorders excluding thyroid disease (On Endocrine related medication but no assigned Endocrine condition)	1- Medication process	Testosterone Growth Hormone Hormone Somatostatin Clomifene HCG HMG Esterogen Estradiol Estrogen Conjugated Ethinyl Estradiol Progesterone Desmopressin	Testosterone Growth Hormone Hormone Somatostatin Clomifene Bromocriptine Finasteride HCG HMG	Esterogen Estradiol Estrogen Conjugated Ethinyl Estradiol Progesterone Desmopressin Cyproterone Cyproterone Compound Calcitonin nasal spray	Cyproterone Cyproterone Compound Calcitonin nasal spray
	GI	Diarrhoea	Symptom	1- Medication process	Loperamide Diphenoxylate	Loperamide Diphenoxylate		

		GI Small Bowel	Ulcers, Reflux, IBS	1- Medication process	Anti Acid Anti Acid Syrup Bismuth Subcitrate AL MG Sucralfate ranitidine Cimetidine Famotidine H2 Blocker	Anti Acid Anti Acid Syrup Sucralfate ranitidine Cimetidine Famotidine	H2 Blocker Omeprazole Lansoprazole pantoprazole Bismuth Subcitrate AL MG	Omeprazole Lansoprazole pantoprazole
		IBD	Inflammatory Bowel Disease	1- Medication process	Mesalazine Asacol	Mesalazine Asacol	Sulfasalazine	Sulfasalazine
		Liver Disease	Alcoholic related liver disease, NAFLD, PBC, PSC	1- Self reported 2- Symptoms (Jaundice) 2- Medication process	Ursodeoxycholic Acid	Spironolactone Chlordiazepoxide Penicillamine Pentoxiphylline Prednisone Perdnisolone Azathioprine Prednisolone Ursodeoxycholic Acid	Vitamin B Complex Vitamin B Vitamin B1 Vitamin B12 Vitamin B6 Folic Acid Naltrexone Vitamin E rifampin	
		Pancreatic disorders	Requirement of pancreatic enzyme supplement	1- Medication process	Pancreatin	Pancreatin		

		GI Unspecified	On gastrointestinal related medication but no assigned gastrointestinal condition	1- Medication process	Sorbitol Clidinium C Dicyclomine Hyoscine Cholestyramine Digestive Psyllium GI Cisapride Lactulose Bisacodyl C Lax	Sorbitol Clidinium C Dicyclomine Hyoscine Cholestyramine Digestive Psyllium	GI Cisapride Lactulose Bisacodyl C Lax Thiethylperazine	Thiethylperazine
	Respiratory	Asthma		1- Medication process	Anti-Asthmatic	Beclomethasone Corticosteroid spray Fluticasone Belladonna Ipratropium Bromide Anti Asthmatic	Formetrol Fumarate Salbutamol Salmeterol Terbutaline Aminophylline theophylline	
		COPD		1 - Self Report 2- Medication process		Beclomethasone Corticosteroid spray Fluticasone Belladonna Ipratropium Bromide Formetrol Fumarate	Salbutamol Salmeterol Terbutaline Aminophylline Theophylline	

		Respiratory Unspecified	On Respiratory related medication but no assigned respiratory condition	1- Medication process	Expectorant Bromhexine Pseudoephedrine	Expectorant Bromhexine Pseudoephedrine Ipratropium Bromide Formetrol Fumarate	Salbutamol Salmeterol Terbutaline Aminophylline Theophylline	Ipratropium Bromide Formetrol Fumarate Salbutamol Salmeterol Terbutaline Aminophylline Theophylline
	Renal	CKD	Chronic kidney disease	1 - Self Report 2- Medication process		Enalapril Captopril Lisinopril Losartan	Atorvastatin Lovastatin Simvastatin	
	Neurology	Dementia		1- Medication process	Rivastigmine	Rivastigmine Haloperidol	Risperidone	
		Epilepsy		1- Medication process	Anti-Convulsant Phenytoin Phenobarbital Topiramate Primidone	Anti-Convulsant Carbamazepine Gabapentin Lamotrigine Phenytoin Sodium Valproate Topiramate	Phenobarbital Primidone Acetazolamide Benzodiazepine Clonazepam Diazepam	Carbamazepine Gabapentin Lamotrigine Sodium Valproate Clonazepam
		Headaches		1- Medication process	Dihydroergotamine Ergotamine	Dihydroergotamine Ergotamine	Amitriptyline	
		Myaesthenia Gravis		1- Medication process	Neostigmine Pyridostigmine	Neostigmine Pyridostigmine		

		Parkinsons		1- Medication process	Biperiden Trihexyphenidyl Levodopa Selegiline Amantadine	Biperiden Trihexyphenidyl Levodopa Selegiline	Amantadine Bromocriptine pramipexole Clozapine	Bromocriptine Pramipexole
	Rheumatology	Gout		1- Medication process	Colchicine Allopurinol	Colchicine Allopurinol		
		Arthritis		1- Medication process	Hydroxychloroquine Glucosamine	Hydroxychloroquine Glucosamine Cyclophosphamide Cyclophosphamide Amp Sulfasalazine Penicillamine Omeperazole Lansoprazole Pantoprazole Aspirin	Diclofenac Ibuprofen Celecoxib Indomethacin Mefenamic Acid Naproxen NSAIDS Piroxicam Tolmetin	Penicillamine

	Other inflammatory conditions	Immunosuppressants	Conditions needing immunosuppresents or antinflammatories (Not including conditons with drugs specifically for Rheumatoid arthritis or IBD)	1- Medication process	Methotrexate Methotrexate Amp Betamethasone Clobetasol Propionate Dexamethasone Dexamethasone Amp Fludrocortisone Hydrocortisone Triamcinolone Cellcept Cyclosporin IVIG Cromolyn Sodium	Methotrexate Methotrexate Amp Betamethasone Clobetasol Propionate Dexamethasone Dexamethasone Amp Fludrocortisone Hydrocortisone Triamcinolone Cellcept Cyclosporin IVIG Cromolyn Sodium Diclofenac Ibuprofen Celecoxib	Indomethacin Mefenamic Acid Naproxen NSAIDS Piroxicam Tolmetin Prednisone Azathioprine Beclomethasone Corticosteroid spray Fluticasone Prednisolone Omeperazole Lansoprazole Pantoprazole	Prednisone Azathioprine Beclomethasone Corticosteroid spray Fluticasone Prednisolone Diclofenac Ibuprofen Celecoxib Indomethacin Mefenamic Acid Naproxen NSAIDS Piroxicam Tolmetin

Other	Other	Vit Min Deficiency	Vitamin/Mineral Deficiency	1- Medication process	Alendronate Calcium Calcium Carbonate Calcium D Calcium Fort Calcium Gluconate Fefol Ferrous Sulfate Hematinic Acid Venofer Potassium Cholride	Potassium Cholride Alendronate Calcium Calcium Carbonate Calcium D Calcium Fort Calcium Gluconate Fefol Ferrous Sulfate Hematinic Acid Venofer Multivitamin Omega3	vitamin A Vitamin C Vitamin D3 Vitaminmineral Zinc sulfate Vitamin B Complex Vitamin B Vitamin B1 Vitamin B12 Vitamin B6 Folic Acid Vitamin E	Vitamin B Complex Vitamin B Vitamin B1 Vitamin B12 Vitamin B6 Folic Acid Vitamin E
		BPH	Benign Prostate Hyperplasia	1- Medication process	Tamsulosin	Tamsulosin Finasteride	Prazosin Trazosin	Finasteride Prazosin trazosin

Mental Health	Mental health (Depression, Anxiety, Psychosis)	MH	Mental health (Depression, Anxiety, Psychosis)	1- Medication process	Doxepin Methadone Busprione Anti Depressant Chlorpromazine Fluphenazine Olanzapin Thioridazine Alprazolam Midazolam Oxazepam Lithium Carbonate Mental Tranylcypromine Sedative Citalopram Fluvoxamine Sertraline Imipramine Nortriptyline Clomipramine Desipramine Maprotiline Maprotiline TCA Trimipramine	Naltrexone Methadone Carbamazepine Lamotrigine Sodium Valproate Busprione Anti Depressant Trazodone Trifluoperazine Chlorpromazine Clozapine Fluphenazine Haloperidol Olanzapin Perphenazine Risperidone Thioridazine Chlordiazepoxide Alprazolam Benzodiazepine Clonazepam Diazepam Flurazepam	Lorazepam Midazolam Oxazepam Lithium Carbonate Mental Tranylcypromine Sedative Fluoxetine Citalopram Fluvoxamine Sertraline Imipramine Nortriptyline Amitriptyline Clomipramine Desipramine Maprotiline Maprotiline TCA Trimipramine Doxepin Thiethylperazine	Naltrexone Clozapine Trifluoperazine Trazodone Haloperidol Perphenazine Risperidone Chlordiazepoxide Benzodiazepine Diazepam Flurazepam Lorazepam fluoxetine amitriptyline

Chronic communicable Diseases	Respiratory	TB	Tuberculosis	1 - Self Report 2- Medication process	Anti TB Streptomycin Ethambutol Isoniazid Para-aminosalcicyclic acid Pyrazinamide	Streptomycin Anti TB Ethambutol Isoniazid	Para-aminosalcicyclic acid Pyrazinamide Rifampin	Rifampin
	Hepatitis/ HIV	Hepatitis or HIV		1- Medication process	Interferon lamivudine	Interferon lamivudine		

Appendix table 2. Number of conditions assigned to participants through the medication process

	Participants before Medication process	**New assignments found in Medication process**	**Final Number of Participants**
Cancer	149	11	160
Cardiovascular Disease			
Diabetes	3,248	98	3,346
Dyslipidaemia	-	693	693
Hypertension	13,302	34	13,336
Heart Disease	2,851	187	3,038
Rheumatic Heart Disease	66	-	66
Stroke	379	-	379
Unspecified CV Disease	-	2,022	2,022
Endocrine			
Thyroid Disease	-	694	694
Unspecified Endocrine Disease	-	196	196
Gastrointestinal			
Diarrhoea	-	33	33

Reflux, Ulcers, IBS	-	9,130	9,130
Inflammatory Bowel Disease	-	27	27
Liver Disease	1,307	6	1,313
Pancreatic disorders	-	50	50
Unspecified GI Conditions	-	1,333	1,333
Respiratory			
Asthma	-	18	18
COPD	2,848	-	2,848
Unspecified Respiratory Disease	-	115	115
Renal - Chronic Kidney Disease	90	-	90
Neurology			
Dementia	-	1	1
Epilepsy	-	358	358
Headaches	-	475	475
Myaesthenia Gravis	-	4	4
Parkinsons	-	150	150
Rheumatology			

Gout	-	29	29
Arthritis	-	99	99
Unspecified conditions needing Immunosuppressants	-	3,691	3,691
Other			
Vitamin or Mineral Deficiency	-	1,249	1,249
Benign Prostate Hyperplasia	-	41	41
Mental Health (any)	-	4,188	4,188
Communicable Diseases			
Tuberculosis	1,455	70	1,525
Hepatitis / HIV	-	9	9

Appendix Table 3. Conditions included within each disease domain category						
	Individuals Used in Survival Analysis (Including 2297 lost to follow up)		**Lost to Follow up**		**Complete Cases**	
	n	%	**n**	%	**n**	%
n	47883		2297	4.80%	45586	95.20%
Morbidity						
Number of diseases, Mean (SD)	1.06 (1.19)		1.18 (1.28)		1.05 (1.19)	
Any Disease (N)	28539	59.60%	1436	62.52%	27103	59.45%
Non-communicable Diseases (at least one)	27198	56.80%	1373	59.77%	25825	56.65%
Cancer	160	0.33%	4	0.17%	156	0.34%
Cardiovascular Disease (at least one condition)	17815	37.21%	881	38.35%	16934	37.15%
Diabetes	3346	6.99%	173	7.53%	3173	6.96%
Dyslipidaemia	693	1.45%	77	3.35%	616	1.35%
Hypertension	13336	27.85%	618	26.90%	12718	27.90%
Heart Disease	3038	6.34%	174	7.58%	2864	6.28%
Rheumatic Heart Disease	66	0.14%	3	0.13%	63	0.14%
Stroke	379	0.79%	13	0.57%	366	0.80%
Unspecified CV Disease	2022	4.22%	102	4.44%	1920	4.21%
Endocrine (at least one condition)	885	1.85%	55	2.39%	830	1.82%
Thyroid Disease	694	1.45%	45	1.96%	649	1.42%
Unspecified Endocrine Disease	196	0.41%	10	0.44%	186	0.41%
Gastrointestinal (at least one condition)	10698	22.34%	610	26.56%	10088	22.13%
Diarrhoea	33	0.07%	2	0.09%	31	0.07%
Reflux, Ulcers, IBS	9130	19.07%	525	22.86%	8605	18.88%
Inflammatory Bowel Disease	27	0.06%	2	0.09%	25	0.05%
Liver Disease	1313	2.74%	87	3.79%	1226	2.69%
Pancreatic disorders	50	0.10%	3	0.13%	47	0.10%
Unspecified GI Conditions	1333	2.78%	75	3.27%	1258	2.76%

Respiratory (at least one condition)	2948	6.16%	114	4.96%	2834	6.22%
Asthma	18	0.04%	0	0.00%	18	0.04%
COPD	2848	5.95%	110	4.79%	2738	6.01%
Unspecified Respiratory Disease	115	0.24%	4	0.17%	111	0.24%
Renal - Chronic Kidney Disease	90	0.19%	4	0.17%	86	0.19%
Neurology (at least one condition)	965	2.02%	51	2.22%	914	2.01%
Dementia	1	0.00%	0	0.00%	1	0.00%
Epilepsy	358	0.75%	23	1.00%	335	0.73%
Headaches	475	0.99%	23	1.00%	452	0.99%
Myaesthenia Gravis	4	0.01%	0	0.00%	4	0.01%
Parkinsons	150	0.31%	7	0.30%	143	0.31%
Rheumatology (at least one condition)	127	0.27%	8	0.35%	119	0.26%
Gout	29	0.06%	0	0.00%	29	0.06%
Arthritis	99	0.21%	8	0.35%	91	0.20%
Unspecified conditions needing Immunosuppressants	3691	7.71%	208	9.06%	3483	7.64%
Other (at least one condition)	1290	2.69%	86	3.74%	1204	2.64%
Vitamin or Mineral Deficiency	1249	2.61%	85	3.70%	1164	2.55%
Benign Prostate Hyperplasia	41	0.09%	1	0.04%	40	0.09%
Mental Health (any)	4188	8.75%	258	11.23%	3930	8.62%
Communicable Diseases (at least one condition)	1534	3.20%	64	2.79%	1470	3.22%
Tuberculosis	1525	3.18%	61	2.66%	1464	3.21%
Hepatitis / HIV	9	0.02%	3	0.13%	6	0.01%

Cardiovascular disease (CV)
Inflammatory bowel disease (IBS)
Gastrointestinal (GI)
Chronic obstructive pulmonary disease (COPD)

Appendix Table 4. Occurrence of each outcome during the ten year study period by demographic, lifestyle, disease, and multimorbidity categories, using complete cases only

	Total	Number of individuals who died *		Time to Death		Number of individuals who had any hospitalisations		Number of hospital visits considering only individuals who were hospitalised		Number of hospital visits (considering all participants)	
	n	n	%	Mean	SD	n	%	Mean	SD	Mean	SD
	45586	5411	11.87%	5.50	2.79	17855	39.17%	1.94	1.39	0.76	1.28
Demographic variables											
Gender											
Females	26003	2333	8.97%	5.60	2.75	10596	40.75%	1.97	1.47	0.80	1.35
Males	19583	3078	15.72%	5.42	2.81	7259	37.07%	1.88	1.26	0.70	1.19
Age of entrance											
<40	722	11	1.52%	6.42	2.37	169	23.41%	1.68	1.14	0.39	0.90
40-49	21938	1094	4.99%	5.50	2.85	6709	30.58%	1.79	1.29	0.55	1.09
50-59	14227	1666	11.71%	5.55	2.80	5959	41.89%	1.97	1.43	0.82	1.34
60-69	6516	1707	26.20%	5.50	2.78	3658	56.14%	2.11	1.48	1.19	1.53
≥70	2183	933	42.74%	5.38	2.71	1360	62.30%	2.08	1.34	1.30	1.46
Education level											
Illiterate	31856	4289	13.46%	5.50	2.78	13341	41.88%	1.96	1.42	0.82	1.34
Not illiterate	13730	1122	8.17%	5.50	2.83	4514	32.88%	1.86	1.29	0.61	1.14
Marital Status											
Not Married	5429	993	18.29%	5.48	2.68	2594	47.78%	2.08	1.50	0.99	1.47
Married	40157	4418	11.00%	5.50	2.81	15261	38.00%	1.91	1.37	0.73	1.25
Geography											
Urban	9461	1036	10.95%	5.38	2.76	4136	43.72%	2.04	1.49	0.89	1.41
Rural	36125	4375	12.11%	5.52	2.79	13719	37.98%	1.91	1.35	0.72	1.25

Wealth											
1	9747	1595	16.36%	5.51	2.78	3729	38.26%	1.90	1.33	0.73	1.24
2	8508	1141	13.41%	5.43	2.81	3304	38.83%	1.93	1.34	0.75	1.26
3	9909	1042	10.52%	5.61	2.80	3888	39.24%	1.93	1.38	0.76	1.28
4	8655	909	10.50%	5.42	2.70	3455	39.92%	1.97	1.44	0.78	1.32
5	8767	724	8.26%	5.50	2.86	3479	39.68%	1.97	1.45	0.78	1.33
Ethnicity											
Torkman	34431	4003	11.63%	5.50	2.78	12744	37.01%	1.88	1.34	0.70	1.22
Other	11155	1408	12.62%	5.48	2.82	5111	45.82%	2.08	1.48	0.95	1.44
Lifestyle											
Smoking											
Non-smoker	37599	3947	10.50%	5.55	2.75	14700	39.10%	1.94	1.41	0.76	1.29
Ex-smoker	1567	319	20.36%	4.97	2.85	697	44.48%	1.94	1.32	0.86	1.31
Current smoker	6420	1145	17.83%	5.46	2.88	2458	38.29%	1.92	1.27	0.73	1.22
BMI (kg/m^2)											
<18.5	2169	465	21.44%	5.31	2.82	872	40.20%	1.80	1.15	0.72	1.15
18.5≤x<25	16395	2273	13.86%	5.48	2.82	5899	35.98%	1.85	1.25	0.66	1.16
≥25	27022	2673	9.89%	5.54	2.75	11084	41.02%	2.00	1.47	0.82	1.36
Physical Activity Status											
1	15888	2786	17.54%	5.38	2.77	7555	47.55%	2.05	1.49	0.98	1.45
2	14607	1204	8.24%	5.67	2.80	5417	37.08%	1.91	1.38	0.71	1.25
3	15091	1421	9.42%	5.58	2.79	4883	32.36%	1.78	1.22	0.58	1.08
Morbidity											
Non-communicable Diseases (at least one)	25825	3903	15.11%	5.44	2.80	12163	47.10%	2.08	1.51	0.98	1.46
Cancer	156	45	28.85%	3.96	3.10	84	53.85%	2.20	1.57	1.19	1.59

Cardiovascular Disease (at least one condition)	16934	3023	17.85%	5.35	2.79	8785	51.88%	2.17	1.58	1.12	1.57
Diabetes	3173	771	24.30%	5.34	2.76	2121	66.85%	2.59	1.90	1.73	1.97
Dyslipidaemia	616	91	14.77%	5.77	2.48	381	61.85%	2.53	1.87	1.56	1.92
Hypertension	12718	2327	18.30%	5.39	2.79	6515	51.23%	2.15	1.58	1.10	1.56
Heart Disease	2864	799	27.90%	4.98	2.85	1926	67.25%	2.54	1.81	1.71	1.90
Rheumatic Heart Disease	63	17	26.98%	5.72	3.36	42	66.67%	2.48	1.67	1.65	1.80
Stroke	366	131	35.79%	4.92	2.65	238	65.03%	2.23	1.59	1.45	1.67
Unspecified CV Disease	1920	254	13.23%	5.03	2.77	904	47.08%	2.02	1.37	0.95	1.38
Endocrine (at least one condition)	830	62	7.47%	5.62	2.69	388	46.75%	2.09	1.64	0.98	1.53
Thyroid Disease	649	54	8.32%	5.39	2.75	310	47.77%	2.11	1.69	1.01	1.57
Unspecified Endocrine Disease	186	9	4.84%	6.72	2.12	81	43.55%	2.02	1.44	0.88	1.38
Gastrointestinal (at least one condition)	10088	1249	12.38%	5.57	2.77	4587	45.47%	2.06	1.49	0.94	1.43
Diarrhoea	31	6	19.35%	6.57	3.20	15	48.39%	1.53	0.92	0.74	1.00
Reflux, Ulcers, IBS	8605	1038	12.06%	5.65	2.75	3927	45.64%	2.05	1.49	0.94	1.43
Inflammatory Bowel Disease	25	2	8.00%	6.96	1.40	11	44.00%	2.09	1.04	0.92	1.26
Liver Disease	1226	156	12.72%	5.43	2.79	536	43.72%	2.09	1.45	0.91	1.41
Pancreatic disorders	47	7	14.89%	5.55	1.93	20	42.55%	2.10	1.65	0.89	1.49
Unspecified GI Conditions	1258	175	13.91%	4.97	2.90	597	47.46%	2.08	1.55	0.98	1.49
Respiratory (at least one condition)	2834	555	19.58%	5.13	2.85	1499	52.89%	2.33	1.71	1.23	1.71
Asthma	18	7	38.89%	3.55	2.40	14	77.78%	2.71	1.54	2.11	1.78

COPD	2738	533	19.47%	5.12	2.85	1441	52.63%	2.33	1.71	1.22	1.70
Unspecified Respiratory Disease	111	29	26.13%	4.93	2.98	68	61.26%	2.59	1.78	1.59	1.88
Renal - Chronic Kidney Disease	86	23	26.74%	4.83	3.24	49	56.98%	2.63	2.48	1.50	2.28
Neurology (at least one condition)	914	96	10.50%	5.45	2.71	406	44.42%	2.07	1.64	0.92	1.50
Dementia	1	1	100%	6.47	NA	1	100.00%	1.00	NA	1.00	NA
Epilepsy	335	53	15.82%	5.62	2.67	163	48.66%	2.30	1.85	1.12	1.73
Headaches	452	16	3.54%	6.09	2.57	177	39.16%	1.89	1.46	0.74	1.30
Myaesthenia Gravis	4	1	25.00%	5.28	NA	3	75.00%	1.00	0.00	0.75	0.50
Parkinsons	143	27	18.88%	4.52	2.88	75	52.45%	2.07	1.46	1.08	1.48
Rheumatology (at least one condition)	119	17	14.29%	4.44	3.32	64	53.78%	2.36	1.33	1.27	1.53
Gout	29	4	13.79%	3.79	3.44	15	51.72%	2.67	1.72	1.38	1.82
Arthritis	91	13	14.29%	4.64	3.40	49	53.85%	2.27	1.19	1.22	1.43
Unspecified conditions needing Immunosuppressants	3483	552	15.85%	5.63	2.74	1748	50.19%	2.21	1.63	1.11	1.60
Other (at least one condition)	1204	150	12.46%	5.16	2.83	596	49.50%	2.19	1.66	1.08	1.60
Vitamin or Mineral Deficiency	1164	143	12.29%	5.11	2.82	574	49.31%	2.21	1.68	1.09	1.62
Benign Prostate Hyperplasia	40	7	17.50%	6.22	3.05	22	55.00%	1.59	0.85	0.88	1.02
Mental Health (Any)	3930	499	12.70%	5.39	2.80	1916	48.75%	2.08	1.53	1.01	1.49
Communicable Diseases (at least one condition)	1470	281	19.12%	5.52	2.77	685	46.60%	2.10	1.57	0.98	1.50
Tuberculosis	1464	281	19.19%	5.52	2.77	683	46.65%	2.11	1.57	0.98	1.50

Hepatitis / HIV	6	0	0.00%	NA	NA	2	33.33%	1.00	0.00	0.33	0.52
Number of morbidities											
0	18483	1383	7.48%	5.66	2.74	5228	28.29%	1.63	1.01	0.46	0.91
1	14367	1747	12.16%	5.56	2.81	5707	39.72%	1.84	1.26	0.73	1.20
2	7478	1218	16.29%	5.50	2.80	3763	50.32%	2.10	1.51	1.06	1.50
3	3319	625	18.83%	5.30	2.76	1863	56.13%	2.28	1.70	1.28	1.70
4+	1939	438	22.59%	5.01	2.77	1294	66.74%	2.60	1.91	1.73	1.98
Multiple Morbidity (defined as 2+ morbidities in any domain or system)											
Not MM	32850	3130	9.53%	5.60	2.78	10935	33.29%	1.74	1.15	0.58	1.06
MM	12736	2281	17.91%	5.35	2.79	6920	54.33%	2.24	1.65	1.22	1.65

Body mass index (BMI)
Cardiovascular disease (CV)
Inflammatory bowel disease (IBS)
Gastrointestinal (GI)
Chronic obstructive pulmonary disease (COPD)
Multimorbidity (MM)

* Out of complete cases who died in 10 years from admission to study

Appendix table 5

Characteristics of multimorbid vs not multimorbid in complete cases

	Complete Cases		**Not Multimorbid**		**Multimorbid**	
	n	%	**n**	%	**n**	%
n	45586		32850	72.06%	12736	27.94%
Demographic variables						
Males	19583	42.96%	15891	48.37%	3692	28.99%
Females	26003	57.04%	16959	51.63%	9044	71.01%
Age, Mean (SD)	51.93 (8.85)		51.1 (8.63)		54.08 (9.03)	
<40	722	1.58%	593	1.81%	129	1.01%
40-49	21938	48.12%	17106	52.07%	4832	37.94%
50-59	14227	31.21%	9775	29.76%	4452	34.96%
60-69	6516	14.29%	4018	12.23%	2498	19.61%
≥70	2183	4.79%	1358	4.13%	825	6.48%
Education level*						
Illiterate	31856	69.88%	22139	67.39%	9717	76.30%
Literate	13730	30.12%	10711	32.61%	3019	23.70%
Marital Status						
Single/Widowed/Divorced/Seperated	5429	11.91%	3223	9.81%	2206	17.32%
Married	40157	88.09%	29627	90.19%	10530	82.68%

Geography						
Urban	9461	20.75%	6195	18.86%	3266	25.64%
Rural	36125	79.25%	26655	81.14%	9470	74.36%
Wealth						
1	9747	21.38%	7146	21.75%	2601	20.42%
2	8508	18.66%	6264	19.07%	2244	17.62%
3	9909	21.74%	7233	22.02%	2676	21.01%
4	8655	18.99%	6203	18.88%	2452	19.25%
5	8767	19.23%	6004	18.28%	2763	21.69%
Ethnicity						
Torkman	34431	75.53%	25184	76.66%	9247	72.61%
Other	11155	24.47%	7666	23.34%	3489	27.39%
Lifestyle						
Smoking,						
Non-smoker	37599	82.48%	26617	81.03%	10982	86.23%
Ex-smoker	1567	3.44%	1083	3.30%	484	3.80%
Current smoker	6420	14.08%	5150	15.68%	1270	9.97%
Pack years for smokers, Mean (SD)	16.9 (18.25)		16.48 (17.68)		18.43 (20.1)	
BMI (kg/m^2)						

Underweight (<18.5)	2169	4.76%	1709	5.20%	460	3.61%
Normal Weight (18.5≤ weight <25)	16395	35.96%	12906	39.29%	3489	27.39%
Overweight (≥25)	27022	59.28%	18235	55.51%	8787	68.99%
Physical Activity Status**						
1	15888	34.85%	9859	30.01%	6029	47.34%
2	14607	32.04%	10593	32.25%	4014	31.52%
3	15091	33.10%	12398	37.74%	2693	21.14%
Morbidity						
Number of diseases, Mean (SD)	1.05 (1.19)		0.44 (0.5)		2.64 (0.95)	
Number of Morbidities						
0	18483	40.55%	18483	56.26%	0	0.00%
1	14367	31.52%	14367	43.74%	0	0.00%
2	7478	16.40%	0	0.00%	7478	58.72%
3	3319	7.28%	0	0.00%	3319	26.06%
4+	1939	4.25%	0	0.00%	1939	15.22%
Any Disease (N)	27103	59.45%	14367	43.74%	12736	100.00%
Non-communicable Diseases (at least one)	25825	56.65%	13109	39.91%	12716	99.84%
Cancer	156	0.34%	50	0.15%	106	0.83%
Cardiovascular Disease (at least one condition)	16934	37.15%	7045	21.45%	9889	77.65%

Endocrine (at least one condition)	830	1.82%	214	0.65%	616	4.84%
Gastrointestinal (at least one condition)	10088	22.13%	3740	11.39%	6348	49.84%
Respiratory (at least one condition)	2834	6.22%	782	2.38%	2052	16.11%
Renal - Chronic Kidney Disease	86	0.19%	19	0.06%	67	0.53%
Neurology (at least one condition)	914	2.01%	217	0.66%	697	5.47%
Rheumatology (at least one condition)	119	0.26%	12	0.04%	107	0.84%
Unspecified conditions needing Immunosuppressants	3483	7.64%	823	2.51%	2660	20.89%
Other*****	1204	2.64%	207	0.63%	997	7.83%
Mental Health (any)	3930	8.62%	765	2.33%	3165	24.85%
Communicable Diseases (at least one condition)	1470	3.22%	493	1.50%	977	7.67%
Medications						
0	18824	41.29%	18259	55.58%	565	4.44%
1	12085	26.51%	10082	30.69%	2003	15.73%
2	6722	14.75%	3401	10.35%	3321	26.08%
3	3506	7.69%	829	2.52%	2677	21.02%
4+	4449	9.76%	279	0.85%	4170	32.74%

* Non-illiterate includes any education

** Physical activity tertiles have been calculated based on the intensity of physical activity, based on METs

Appendix table 6. The odds ratio (OR) of being dead within ten years by demographic characteristics, NCD risk factors and multimorbidity (≥2 conditions)

Variable		**OR**	**95% CI**	**P-Value**
Multimorbid	<2 conditions	Referent		
	≥2 conditions	1.99	(1.86 - 2.12)	<0.001
Sex	Females	Referent		
	Males	2.06	(1.89 - 2.24)	<0.001
Age	Age at Entrance	1.09	(1.08 - 1.09)	<0.001
Education	Illiterate	Referent		
	Literate	0.80	(0.73 - 0.87)	<0.001
Marital Status	Not Married (ref)			
	Married	0.83	(0.76 - 0.91)	<0.001
Wealth Quintiles	Wealth Quintile 1	Referent		
	Wealth Quintile 2	0.90	(0.82 - 0.98)	0.02
	Wealth Quintile 3	0.68	(0.62 - 0.75)	<0.001
	Wealth Quintile 4	0.69	(0.63 - 0.76)	<0.001
	Wealth Quintile 5	0.58	(0.52 - 0.65)	<0.001
Smoking status	Never Smoked	Referent		
	Current/Ex-smoker	1.48	(1.37 - 1.61)	<0.001
BMI	BMI<18.5	Referent		
	BMI: 18.5≤x<25	0.66	(0.59 - 0.75)	<0.001
	BMI: ≥25	0.60	(0.53 - 0.68)	<0.001
Physical Activity	Physical Activity 1	Referent		
	Physical Activity 2	0.76	(0.70 - 0.82)	<0.001
	Physical Activity 3	0.69	(0.63 - 0.75)	<0.001

Non communicable disease (NCD)

Body mass index (BMI)

Appendix Table 7. The Hazard Ratio (HR) of dying within the study period by demographic characteristics, NCD risk factors and multimorbidity (≥2 conditions)

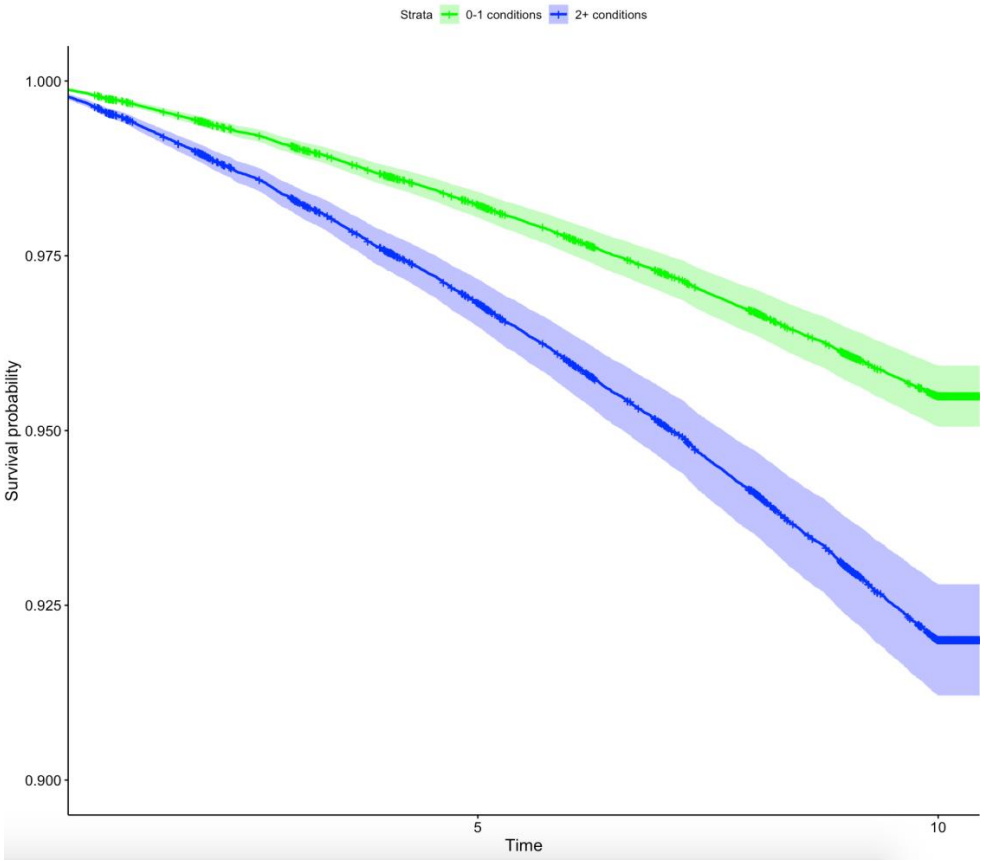
Variable		**HR**	**95% CI**	**P-value**
Sex	Females	Referent		
	Males	3.00	(2.10 - 4.28)	<0.001
Age	Age at Entrance	1.08	(1.08 - 1.09)	<0.001
Education	Illiterate	Referent		
	Literate	0.81	(0.75 - 0.88)	<0.001
Marital Status	Not Married	Referent		
	Married	0.86	(0.79 - 0.93)	<0.001
Wealth Quintiles	Wealth Quintile 1	Referent		
	Wealth Quintile 2	0.91	(0.84 - 0.98)	0.01
	Wealth Quintile 3	0.71	(0.66 - 0.77)	<0.001
	Wealth Quintile 4	0.72	(0.67 - 0.79)	<0.001
	Wealth Quintile 5	0.63	(0.57 - 0.69)	<0.001
Ethnicity	Torkmen	Referent		
	Not Torkmen	0.89	(0.84 - 0.95)	<0.001
Smoking status	Never Smoked	Referent		
	Current/Ex-smoker	1.39	(1.30 - 1.49)	<0.001
BMI	BMI<18.5	Referent		
	BMI: 18.5≤x<25	0.70	(0.64 - 0.78)	<0.001
	BMI: ≥25	0.64	(0.58 - 0.71)	<0.001
Physical Activity	Physical Activity 1	Referent		
	Physical Activity 2	0.78	(0.72 - 0.83)	<0.001
	Physical Activity 3	0.72	(0.67 - 0.77)	<0.001
Interaction between Sex and Age	Extra Risk for each age year for Females	Referent		

	Extra Risk for each age year for Males	0.99	(0.99 - 1.00)	0.01
Multimorbid	<2 conditions	Referent		
	≥2 conditions	1.81	(1.71 - 1.91)	<0.001

Non communicable disease (NCD)

Body mass index (BMI)

Appendix figure 1. Survival in the study period for multimorbidity defined as two or more conditions versus fewer than two conditions (n= 47,883)



Plots are shown controlling for demographic characteristics and behavioural factors