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Social inequalities in multimorbidity, frailty, disability, and transitions to mortality: A 24-year follow-up of the Whitehall II cohort study

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Research in Context

Evidence before this study

We searched PubMed for publications until September 25, 2019, using the Medical Subject Headings search terms “Inequalities”, “socioeconomic status (SES)”, “ageing”, “frailty”, “multimorbidity”, “disability”, “morbidity”, and “mortality”. There is robust evidence of social inequalities in multimorbidity, frailty, disability, and mortality, with some recent data showing increases in inequalities in life expectancy in some high-income countries. Although studies have investigated the role of mediators in explaining social inequalities, we did not find studies that examined whether socioeconomic factors play a role both in the incidence of adverse health conditions (multimorbidity, frailty, or disability) and their progression to mortality. Separate studies have shown multimorbidity, frailty, or disability to increase risk of mortality but they have not been examined in the same study population.

Added value of this study

Our analysis of the temporal progression from a healthy state at age 50 to adverse health conditions (multimorbidity, frailty, disability) and subsequent mortality over 23.6 years suggests SES to affect risk of multimorbidity, frailty, and disability but not the risk of death after the onset of these conditions. Another key finding is the strong association between multimorbidity and mortality, with the strength of this association being similar across SES groups. In persons free of multimorbidity, frailty, and disability there was evidence of social inequalities in mortality, primarily due to deaths from cancer. The strength of our analysis is use of multi-state models to model transitions from a healthy state to adverse health conditions and subsequent mortality in a single analytic framework in order to examine how socioeconomic factors shape health trajectories.

Implications of all the available evidence

Our analyses highlight the importance of primary prevention, before the onset of multimorbidity, frailty, or disability, in reducing social inequalities in mortality.

ABSTRACT

BACKGROUND Social inequalities in mortality persist in high-income countries with universal health care; increases in life expectancy have led many more persons to experience old age but how inequalities in life expectancy are generated remains unclear. Accordingly, we examined whether social inequalities were present before or after the onset of adverse health conditions (multimorbidity, frailty, and disability).

METHODS Data on 6,425 persons were drawn from the Whitehall II cohort study. Three indicators of socioeconomic status (SES: education, occupational position, literacy) were assessed at age 50. Participants underwent clinical examinations (2002-2004, 2007-2009, 2012-2013, and 2015-2016) for assessment of frailty (2 or more of low physical activity, slow walking speed, poor grip strength, weight loss, and exhaustion) and disability (2 or more difficulties in bathing, dressing, toileting, transferring, feeding, and walking). In addition, linkage to electronic health records until 31st August 2017 was used for incidence of multimorbidity (2 or more of diabetes, coronary heart disease, stroke, chronic obstructive pulmonary disease, depression, arthritis, cancer, dementia, Parkinson's disease) and mortality. In analyses adjusted for sociodemographic factors, we used multi-state models to examine social inequalities in transitions from a healthy state to adverse health conditions and then to mortality.

FINDINGS A total of 1,694 (26.4%) participants developed multimorbidity, 1,733 (27.0%) became frail, 692 had disability (10.8%), and 611 (9.5%) died over a median follow-up of 23.6 years (Interquartile range (IQR): 19.6, 28.9). Multimorbidity (Hazard ratio (HR) 4.12, 95% Confidence interval (CI): 3.41, 4.98), frailty (HR 2.38, 95%CI: 1.93, 2.93), and disability (HR 1.73, 95%CI: 1.34, 2.22) were associated with increased risk of mortality; these associations were not modified by SES. In multi-state models, occupation was the SES indicator which was most strongly associated with inequalities in the transition from a healthy state to multimorbidity (HR 1.54, 95%CI: 1.37,

1.73), frailty (HR 2.08, 95%CI: 1.85, 2.33), and disability (HR 1.44, 95%CI: 1.18, 1.74). SES indicators did not affect transitions to mortality in those with multimorbidity, frailty, or disability.

INTERPRETATION Our findings highlight the need for primary prevention for reducing social inequalities in mortality as SES did not affect mortality after onset of multimorbidity, frailty, or disability. Of the three health conditions, multimorbidity had the strongest association with mortality, making it a key target for improving population health.

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INTRODUCTION

The ageing of populations worldwide highlights the importance of understanding drivers of health at older ages. Data on morbidity trends at older ages suggest continuing increases in the prevalence of chronic diseases with some evidence of a decrease in functional limitations.¹ The risk of mortality is higher in both those with chronic disease,² and those with functional limitations assessed by frailty³ or disability.⁴ At the same time, social inequalities in mortality persist⁵ with data on recent trends from some high income countries, including England⁶ and the US⁷, suggest a widening of these inequalities. The extent to which adverse health conditions in the course of ageing are generators of inequalities in mortality remains unknown as research in this domain is piecemeal, in that studies examine inequalities in morbidity and mortality, without considering the social patterning in progression from adverse health conditions to mortality.

The aim of our study is to examine whether social inequalities in mortality are generated before or after the onset of adverse health conditions such as multimorbidity, frailty, and disability in participants aged 50 at start of a median follow-up of 23.6 years. We use multi-state models which allow estimation of the role of socioeconomic status (SES) in transitions from a healthy state to adverse health conditions and subsequent transitions to mortality. A further aim is to identify key indicators of SES that shape the risk of multimorbidity, frailty, disability and mortality. Education and occupation are widely used indicators of SES but other measures may be more salient for health at older ages. Longer lifespans, the increasing complexity of managing multiple health conditions require consideration of measures such as literacy, defined as the capacity to obtain and process health information and services needed to make appropriate health decisions.⁸ We use these three SES indicators (education, occupation, literacy) to examine inequalities in transitions to mortality via multimorbidity, frailty, and disability in order to identify prevention targets to reduce social inequalities in mortality.

METHODS

Data are drawn from the Whitehall II study, an ongoing cohort study, established in 1985 to investigate the role of socioeconomic circumstances for health by following a cohort of 10,308 civil servants (6,895 men and 3,413 women) aged 35-55 in 1985-1988. All participants responded to a comprehensive questionnaire and underwent a uniform, structured clinical evaluation at baseline, and approximately every 5 years. Participant consent and research ethics approvals are renewed at each contact; the latest approval was by the NHS London - Harrow Research Ethics Committee, reference number 85/0938.

Indicators of SES

Occupational position at age 50 was available from employment records of British Service grade employment; it is a comprehensive measure which reflects education, occupational status and income which was categorized as high (administrative grades), intermediate (professional or executive grades) and low (clerical or support grades) position.

Highest attained education was categorised in three levels: high (university or higher degree), intermediate (higher secondary school) and low (lower secondary school or less).

Literacy at age 50 was assessed using a vocabulary test as recommended in a recent review.⁹ We used the Mill Hill vocabulary test, consisting of a list of 33 stimulus words ordered by increasing difficulty with the person required to choose the meaning of each word from six response choices.

Ascertainment of adverse health conditions

Participants were followed for three partially overlapping adverse health conditions, each of these was defined as an adverse health condition if 2 or more of the condition specific criteria were met. This is the standard definition of multimorbidity but not frailty and disability, sensitivity analyses were undertaken to ensure that results were not affected by this choice.

Multimorbidity: Nine chronic diseases, which are part of the leading causes of death in high-income countries, were ascertained using data from multiple sources: clinical examinations in the study and linkage to electronic health records using the National Health Service (NHS) identification number; four national databases were used: the national hospital episode statistics (HES) database with in- and out-patient data, the Mental Health Services Data Set which in addition to in- and out-patient data also has data on care in the community, the cancer registry, and the mortality register.

The chronic conditions considered were: diabetes (fasting glucose ≥ 7.0 mmol/l, reported doctor-diagnosed diabetes, use of diabetes medication, ICD10: E10-E14), coronary heart disease (12-lead resting ECG recording, ICD10: I20-I25, procedures K40-K49, K50, K75, U19), stroke (MONICA-Ausburg stroke questionnaire, ICD10: I60-I64), chronic obstructive pulmonary disease (ICD10: J41-J44), depression (use of antidepressants, ICD10: F32-F33), arthritis (self-report of longstanding illness, ICD10: M15-M19), cancer (cancer registry with malignant cancer ICD10: C00–C97 to include colorectal, lung, breast, prostate, smoking related cancers and melanoma skin cancers), dementia (ICD10: F00-F03, F05.1, G30, G31), and Parkinson's disease (ICD10: G20).

Frailty: was measured at clinical examinations (2002-2004, 2007-2009, 2012-2013, and 2015-2016) using the Fried frailty scale, the threshold for each criterion was based on the original frailty score.¹⁰ This strategy allows comparison of findings across studies as opposed to use of thresholds based on the distribution in the study population being examined. The criteria for frailty included (appendix): low physical activity, slow walking speed, poor grip strength, weight loss, and exhaustion. Participants were classified as “frail” if they had at least 2 of the frailty criteria.

Disability: In 2002-2004, 2007-2009, 2012-2013, and 2015-2016 a modified version of the Katz Index of Independence in Activities of Daily Living (ADL) was included in the study questionnaire to measure disability.¹¹ Disability was defined as reporting difficulty (yes/no) in performing 2 or more of the following 6 ADLs: bathing, dressing, toileting, transferring, feeding, and walking.

Mortality follow-up

Death from any cause was our primary outcome. Mortality data until 31st August 2017 were drawn from the British national mortality register (National Health Services Central Registry). The tracing exercise was carried out using the National Health Service identification number of each participant.

Covariates

These included age, sex, race (white, non-white), and marital status at 50 years.

Statistical Analyses

Data on SES and covariates were extracted from the wave of data collection when the participant was aged 50 (± 5 years) and free of adverse health conditions. Participants were followed from age 50 until the record of death or August 31st 2017, whichever came first (flowchart in **Figure 1**).

There was no evidence of sex differences (all $p > 0.05$) in the association between SES indicators and adverse health conditions (multimorbidity, frailty, disability), leading us to combine men and women in the analysis. As education and occupation were measured on a 3-point scale, literacy was also categorized into three equal groups. After verification for linearity, categories of SES indicators were recoded (0, 0.5, and 1) so that when entered as a continuous variable the reported hazard corresponds to the increased risk in those with the lowest compared to the highest

socioeconomic group. All analyses were undertaken on transitions, first using survival analysis and then multi-state models.

Survival analysis - 2 states: Proportional hazards models were used to examine the association of SES (education, occupation, literacy) with adverse health conditions and mortality in separate models. We then examined the association of time-varying multimorbidity, frailty, disability (separate models) with subsequent mortality. These analyses were undertaken in the total sample, and an interaction term was used to assess whether this association differed according to SES. We repeated these analyses using time-varying, total number of adverse health conditions as the exposure (0, 1, 2, or 3).

Multi-state models - 3 states: Analyses were undertaken using weighted multistate models (MSM) with a semi-Markov model (Weibull distribution)¹² to estimate the role of SES in transitions (**Figure 2**) from A) a healthy state to adverse health condition (multimorbidity, frailty, or disability), B) a healthy state to death in those without the adverse health condition in question, and C) from the adverse health condition to death. As transition C was underpowered when the adverse health outcomes are considered separately we undertook sensitivity analyses using “any of the three adverse health conditions”. All three transitions were allowed over the entire follow-up but once a person transitioned into an adverse health state, they stayed there until the transition to death, if present. The semi-Markov models take into consideration time since the previous state in the analyses. Analyses were adjusted for age, sex, marital status, race, and birth cohort.

In both the survival analyses and multi-state models interval censoring was used as assessment of some adverse health conditions was not continuous, in that the exact date of onset could lie in the interval between two clinical examinations. Another feature of the analyses was use of inverse-probability-weighting (IPW) for missing data.¹³ This involved estimating the probability of being included in the analytic sample (6,425 vs. target population of 10,183, **Figure**

1) using data on sociodemographic factors (age, sex, race, education, height, occupational position, marital status), health behaviours (smoking, alcohol consumption, physical activity, fruit and vegetable consumption), cardiometabolic risk factors (body mass index, systolic and diastolic blood pressure, cholesterol), mental health from study baseline (1985), chronic conditions along with mortality over the follow-up (1985 to 2017) and their interactions with covariates. The inverse of these probabilities were used to weight the analyses. In order to allow interval censoring, Weibull distribution was used both in the survival analyses and the multi-state models.¹⁴

Multi-state models were performed using the multistate package of R software; all other analyses used Stata version 15. A two-sided p-value < 0.05 was considered statistically significant.

Data Sharing: Data available on request, <https://www.ucl.ac.uk/epidemiology-health-care/research/epidemiology-and-public-health/research/whitehall-ii/data-sharing>

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. AD and ASM had full access to all of the data and the final responsibility to submit for publication.

RESULTS

Analyses were based on 6,425 participants (**Figure 1**), weighted to reflect the target population of 10,183 participants due to differences in characteristics of these two groups (eTable 1). Participants were followed over a median 23.6 (Interquartile range (IQR): 19.6, 28.9) years; **Table 1** presents their characteristics at age 50 as a function of adverse health conditions and mortality at the end of the follow-up. Further details of the components of adverse health

conditions are provided in eTable 2; coronary heart disease, physical inactivity, and difficulties in dressing were the most frequent components in measures of multimorbidity, frailty, and disability respectively.

The median age was 69.1 years at occurrence of multimorbidity (IQR: 63.6, 74.1), 69.1 years for frailty (IQR: 63.1, 74.7), 70.5 years for disability (IQR: 64.9, 75.5), and 75.4 years for mortality (IQR: 69.1, 79.0). Of the 2,877 participants with at least one adverse health condition, 65.6% had a single and 34.4% two or three adverse health conditions (eTable 3). Of the 611 deaths, 33.9% had none of the three adverse health conditions, 38.6% had one, 27.5% had two or three adverse health conditions (eTable 3). Primary causes of death were cancer (48.3%) and cardiovascular disease (23.7%) (eTable 4). Among the 1,694 participants with multimorbidity, 326 (19.2%) died over a median follow-up of 3.7 years (IQR: 1.0, 7.3). Among the 1,733 frail participants, 195 (11.3%) died over a median follow-up of 4.4 years (IQR: 2.3, 7.5). Among the 692 participants with disability, 89 (12.9%) died over a median follow-up of 3.4 years (IQR: 1.7, 6.5). Cancer rather than cardiovascular disease was the primary cause of death in persons with multimorbidity (50.9% vs. 19.6%), frailty (36.4% vs. 25.1%) and disability (36.0% vs. 19.1%), eTable 4.

The kappa coefficients (education and occupation or literacy: 0.24, occupation and literacy: 0.25) did not suggest strong overlap in the SES measures. **Table 2** shows their associations with mortality, with the indicators modelled both as categorical and continuous variables. There was no evidence of deviations from linearity, allowing all SES indicators to be modelled as continuous variables to reflect excess risk in those in lowest compared to highest SES group. Lower occupational position was associated with increased mortality (HR 1.57, 95% CI: 1.19, 2.07). No associations were observed for education and literacy. eTable 5 also shows occupation to have the strongest association with multimorbidity, frailty, and disability.

Sensitivity analyses with varying thresholds to define frailty (2 or 3 of the 5 components of Fried's frailty score) and disability (1 or 2 or 3 ADLs) did not affect associations with mortality

(eTable 6), allowing us to retain the 2 or more of the condition specific criteria for all adverse health outcomes. Multimorbidity had the strongest association with mortality (HR 4.12; 95%CI: 3.41, 4.98), and disability the weakest (HR 1.73; 95% CI: 1.34, 2.22), **Table 3**. There was no evidence of stronger associations between adverse health conditions and mortality in the lower SES groups. When accumulation of adverse health conditions (0, 1, 2, or 3) was the exposure (eTable 7), there was also no evidence of stronger associations in the lower SES groups.

Subsequent analyses were based on transitions; **Figure 2** shows the natural history of disease progression, without accounting for SES differences. Of the three adverse health outcomes, the incidence of disability was lowest; mortality was highest in those with multimorbidity. We then examined the role of SES in transitions of health states, results shown in **Table 4**. There were social inequalities in transition A (from a healthy state to multimorbidity, frailty, and disability) for all SES indicators except education in transition to frailty. Occupation had the strongest association with transition from a healthy state to multimorbidity (HR 1.54; 95%CI: 1.37, 1.73), frailty (HR 2.08; 95%CI: 1.85, 2.33), and disability (HR 1.44; 95%CI: 1.18, 1.74).

There were social inequalities in Transition B (from a healthy state to mortality in those without an adverse health condition, **Table 4**). Cancer deaths (eTable 4), the primary cause of death in persons who died without multimorbidity (45.3%), frailty (53.8%), and disability (50.4%) may be an explanation for these findings. There was no evidence of excess mortality in the lower socioeconomic groups in those with multimorbidity, frailty, or disability (Transition C, **Table 4**). Age at onset of adverse health conditions did not modify associations, range of p-values for interactions between SES indicators and age at onset: 0.13 to 0.96. Sensitivity analyses on transition C, undertaken using any of the three adverse health conditions as the transition state with 404 deaths in 2,877 participants, also showed education (HR 0.89; 95%CI: 0.78, 1.02), occupation (HR 1.13; 95%CI: 0.95, 1.34), and literacy (HR 0.99; 95%CI: 0.94, 1.04) not to be associated with mortality in this transition.

DISCUSSION

The main finding of our analyses on temporal progression from a healthy state at age 50 to adverse health conditions (multimorbidity, frailty, disability) and subsequent mortality is that social inequalities are generated before rather than after the onset of these conditions. These analyses suggest SES to affect risk of multimorbidity, frailty, and disability but not the risk of death in those with these conditions. Our approach differs from mediation models where the goal is to estimate the extent to which adverse health conditions explain social inequalities in mortality rather than to investigate how SES affects the onset and progression of adverse health conditions. Results from our study show social inequalities in the aetiology rather than prognosis of the studied conditions.

Of the three adverse health conditions in our study, multimorbidity had the strongest association with mortality; the strength of this association was similar across SES groups. A total of 175 of 611 deaths (28.6%) in our study were in persons with multimorbidity only and a further 151 deaths (24.7%) in those with multimorbidity and frailty and/or disability. There is increasing recognition of the importance of multimorbidity,^{15,16} particularly at older ages,¹⁶ although there is no clear consensus on the precise number or nature of diseases that ought to be included in defining multimorbidity. Similarly, the concept of frailty is increasingly promoted as a simple measure of health status of older adults,¹⁷ but definitions vary across studies as reflected in alternative conceptualisations such as the Frailty Index.¹⁸ In general terms, frailty is seen to be the result of cumulative decline in multiple physiological systems, reflecting a state of heightened vulnerability to environmental stressors.^{10,17} Disability is widely used in research on ageing, often measured using difficulties in daily living,¹ and predicts future outcomes.¹⁹ Although there was no consistent evidence of heterogeneity across SES groups in the association between adverse health conditions and mortality, there was a suggestion of stronger associations in the high occupation and education groups (Table 3 & eTable 7). This counter-intuitive finding could be explained by

functional limitations being more normative in low SES group or better reporting of these conditions in the high SES group.

There is robust evidence of social inequalities in multimorbidity,¹⁶ frailty²⁰ and disability;²¹ all three conditions have been associated with greater risk of mortality.²⁻⁴ Recent analysis of data from the World Health Surveys¹ suggests that trends in loss of functioning and disability over the life course may be improving but chronic disease patterns appear to be worsening. Our findings suggest multimorbidity to be important because of its high prevalence, supported by findings in previous studies,¹⁶ and its strong association with mortality. Although the prevalence of multimorbidity increases with age, it is not uncommon prior to old age.¹⁶ Thus, better monitoring of multimorbidity and timely interventions may help improve population health. This is feasible due to contact with the healthcare provider for management of the first non-fatal chronic disease, i.e. before a first chronic disease progresses to multimorbidity. Our choice of 9 chronic diseases is based on their importance for mortality; among those without multimorbidity in our study a majority of death (73.7%, eTable 4) was due to cardiovascular disease or cancer – both on our list of 9 chronic diseases.

Recent findings challenge the view that health change progresses through stages: risk factors → diseases/conditions → loss of function → disability → death.²² This temporal sequence is not seen in our study as the median age at onset of multimorbidity, frailty, and disability was similar. Furthermore, nearly two-thirds of those with adverse health conditions experienced only one of the three conditions. Using a follow-up starting at age 50, we considered multimorbidity, frailty, and disability along with subsequent mortality in the same study whereas most previous research has not examined all three adverse health conditions so their relative importance for mortality and social inequalities in mortality could not be assessed. Our results identify multimorbidity as the most pertinent prevention target to improve population health and prolong life expectancy. Even when all adverse health conditions were considered together in sensitivity analyses, there was no

evidence of social inequalities in transitions to mortality in those with one or more of these conditions.

In our data occupation reflects education, salary, and social status and it had robust associations with all health conditions. The use of three SES indicators allows comparison between them and suggests that comprehensive measures of socioeconomic circumstances are more strongly associated with health conditions. Challenges of longer life expectancy, requiring self-management of health for long periods, has led to interest in health literacy.²³ It reflects an individual's capacity to obtain, process, and understand health information as opposed to indicators of socioeconomic circumstances that reflect access to resources. In our data, literacy was not associated with mortality and its association with adverse health conditions was weak. The important finding in relation to all SES indicators is that they did not affect the risk of mortality after the onset of multimorbidity, frailty or disability. Two previous studies reported similar findings in relation to comprehensive measures of socioeconomic circumstances and frailty, one based in China,²⁴ and the other based on the Honolulu Aging Study.²⁵ We previously used a narrow definition, cardiometabolic multimorbidity, where we found health behaviours rather than SES to play a major role in the transition from multimorbidity to mortality.²⁶

Our findings need to be considered in light of the study strengths and limitations. The strengths comprise large sample size, multiple measures of SES, long follow-up to allow analyses of the natural history of health conditions using suitable methods, and availability of complete data on health conditions. Although multiple sources were used to ascertain health conditions, it is possible that data on some conditions is missing as we did not have access to emergency care. However, it is unlikely that chronic conditions are treated only in emergency care and the resulting imprecision in date of onset is accounted for in the interval censoring used in our analyses. A further strength is consideration of missing data using inverse probability weighting; availability of data on occupational position and mortality for everyone in the target population (1,830 deaths in

10,183 persons) allowed us ensure that the association in this population (HR=1.54, 95% CI: 1.32, 1.78) was similar to that in our sample after IPW (HR=1.57, 95% CI: 1.19, 2.07, Table 2).

The primary limitation is that our findings are likely to apply only to high-income countries with universal health care where the onset of disease/poor health triggers the involvement of health and social care systems. A further limitation is use of an occupational cohort study where participants tend to be healthier than those in the general population, not allowing comparison of prevalence rates with studies based on the general population. However, this is an unlikely source of bias in risk factor-disease associations as we have previously shown estimates from our study to be similar to those reported in general population-based studies.²⁷ Although occupation in our study reflects income, it is not a measure of family wealth, living conditions, or other financial difficulties. Similarly, the measure of literacy used in the study is only a proxy of health literacy and it is possible that some of its associations with health are poorly estimated. Finally, as there are no “gold-standard” definitions for the adverse health conditions we decided to use the criteria of 2, used primarily in studies on multimorbidity, for all three conditions and this may also impact results. The complex interrelationship between multimorbidity, frailty, and disability over time, including reversal from these conditions was not considered in our analyses due to computational complexity and limited statistical power.

Changes in behaviours and improvements in treatment of major diseases have led to increases in life expectancy in past decades. Our analysis of the natural history of adverse health conditions to mortality shows multimorbidity to be an important target to improve population health and reduce social inequalities in mortality. The concern is that healthcare systems remain organised around single system illness that do not reflect the multi-organ dysfunction experienced by older adults. Our results highlight the importance of prevention, either via management of risk factors or screening and effective treatment of early stages of disease.

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Declaration of interest: We declare no competing interests.

Contributors: AD & ASM developed the hypothesis and study design. AD performed the statistical analysis, with contributions from AF & SS. AD & ASM wrote the first and successive drafts of the manuscript. AD, AF, JD, KB, TBR, AS, MK, SS, and ASM contributed to study concept and design, analysis and interpretation of data, and drafting or critical revision of the manuscript for important intellectual content, or in addition, data acquisition. ASM and MK obtained funding. AD & ASM had full access to the data in the study and had final responsibility for the decision to submit for publication.

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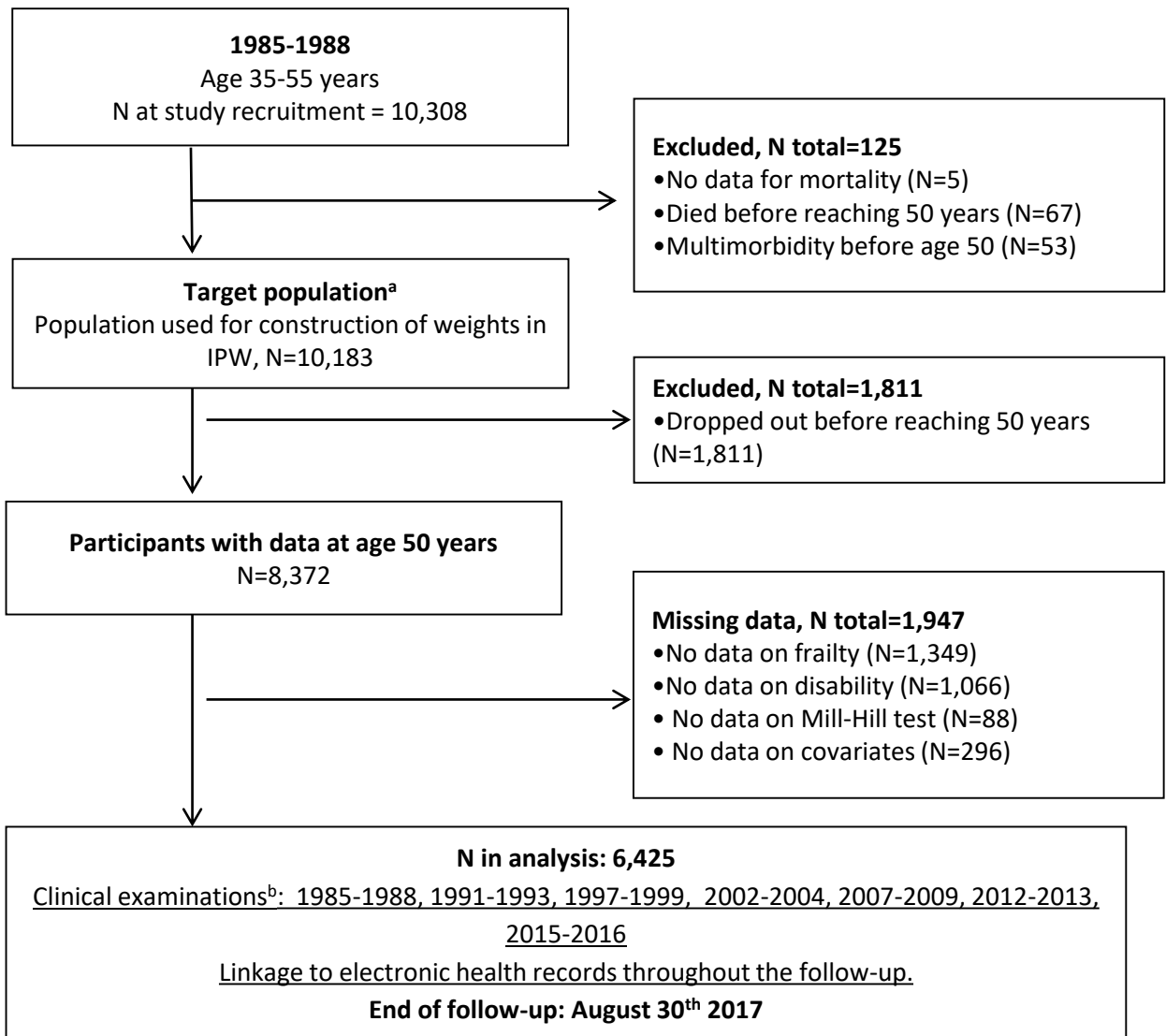
Figure 1. Flowchart of sample selection.

^aInverse probability weighting was used to reflect this target population.

^bInterval censoring was used in the analysis because the exact date on onset of adverse health conditions drawn from clinical examinations could lie in the interval between two clinical examinations.

Figure 2. Incidence rate per 1000 person years in each transition from a healthy state at age 50 to adverse health conditions (multimorbidity, frailty, disability) and mortality.

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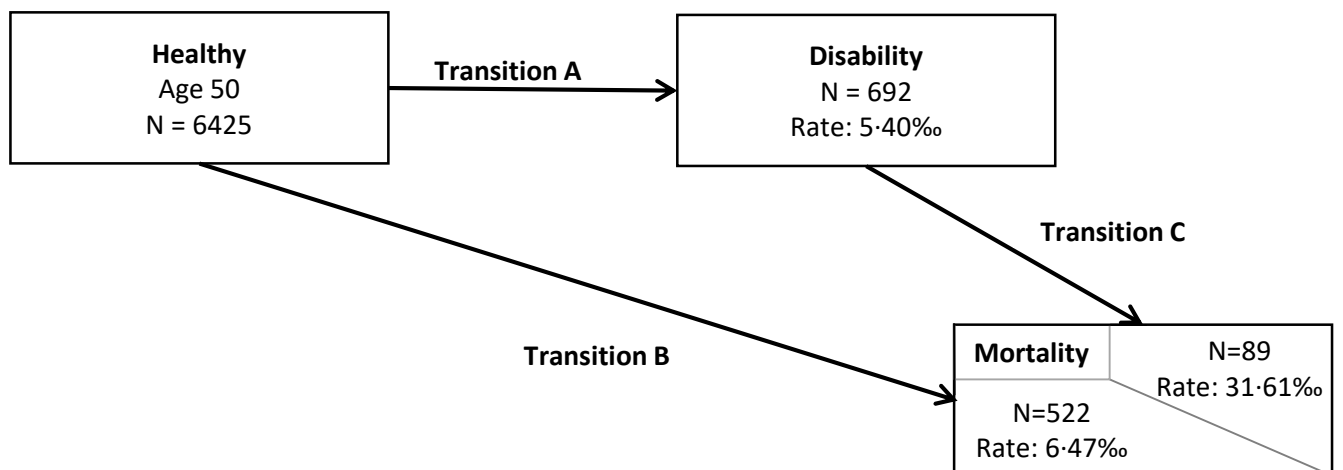
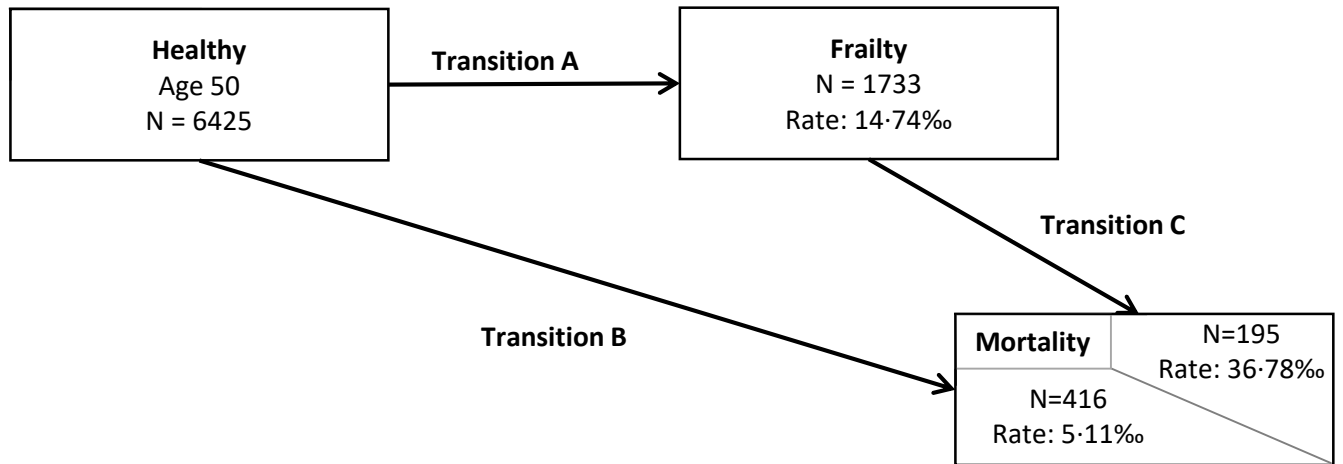
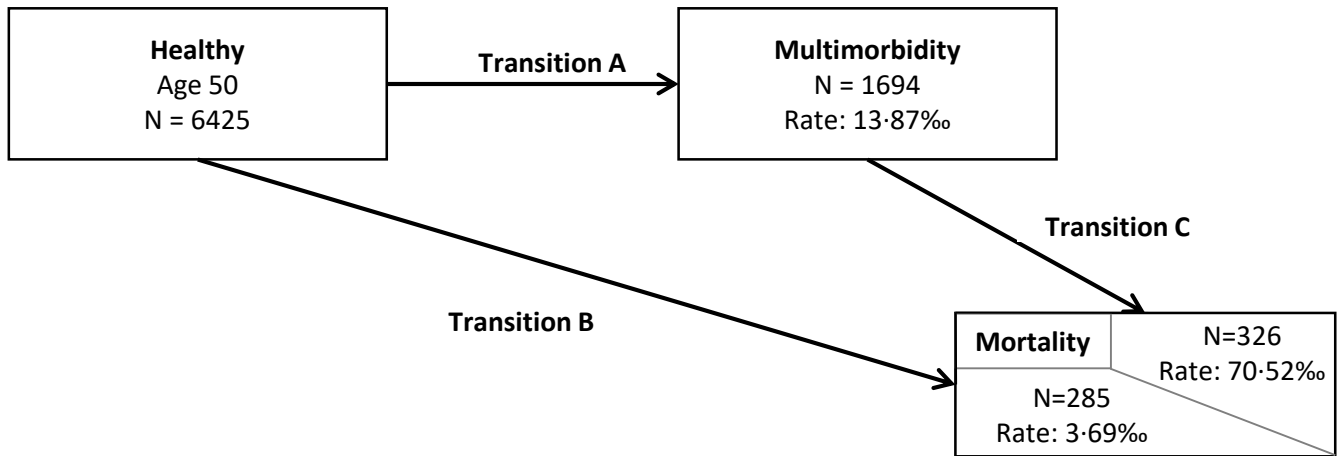


Table 1. Characteristics at age 50 as a function of multimorbidity, frailty, disability, and mortality status at the end of follow-up. N=6,425

	Multimorbidity ^a		Frailty		Disability		Mortality	
	No	Yes	No	Yes	No	Yes	No	Yes
N	4731	1694	4692	1733	5733	692	5814	611
Men, N (%)	3435 (72.6)	1142 (67.4)	3489 (74.4)	1088 (62.8)	4132 (72.1)	445 (64.3)	4149 (71.4)	428 (70.1)
Non-white, N (%)	313 (6.6)	200 (11.8)	279 (6.0)	234 (13.5)	439 (7.7)	74 (10.7)	464 (8.0)	49 (8.0)
Single, N (%)	1065 (22.5)	397 (23.4)	911 (19.4)	551 (31.8)	1274 (22.2)	188 (27.2)	1300 (22.4)	162 (26.5)
Low education, N (%)	1878 (39.7)	842 (49.7)	1884 (40.2)	836 (48.2)	2357 (41.1)	363 (52.5)	2442 (42.0)	278 (45.5)
Low occupation, N (%)	526 (11.1)	309 (18.2)	465 (9.9)	370 (21.4)	694 (12.1)	141 (20.4)	739 (12.7)	96 (15.7)
Literacy, ^b Mean (SD)	25.2 (4.3)	24.2 (5.1)	25.1 (4.1)	24.4 (5.4)	25.0 (4.4)	23.9 (5.3)	24.9 (4.5)	25.0 (4.4)

^aMultimorbidity defined as 2 or more of the following chronic conditions: diabetes, coronary heart disease, stroke, chronic obstructive pulmonary disease, depression, arthritis, cancer, dementia, and Parkinson's disease.

^bAssessed using the Mill Hill vocabulary test.

Table 2. Association of socioeconomic indicators at age 50 with subsequent mortality (N= 611 in 6,425 participants).^a

	HR (95% CI)
Education	
High	1 (ref)
Medium	1.22 (0.98, 1.52)
Low	1.13 (0.92, 1.38)
<i>P non-linearity</i>	0.13
Education scale ^b	1.09 (0.89, 1.32)
Occupation	
High	1 (ref)
Medium	1.24 (1.04, 1.49)
Low	1.57 (1.18, 2.09)
<i>P non-linearity</i>	0.93
Occupation scale ^b	1.57 (1.19, 2.07)
Literacy^c	
High	1 (ref)
Medium	1.00 (0.82, 1.22)
Low	1.19 (0.96, 1.48)
<i>P non-linearity</i>	0.37
Literacy scale ^b	1.02 (0.93, 1.12)

^aAnalyses using proportional hazards regression with Weibull distribution and inverse probability weighting. Models adjusted for age, sex, race, marital status, and birth cohort.

^bCategories of SES indicators were recoded (0, 0.5, and 1) so that when entered as a continuous variable the reported hazard ratio corresponded to increased risk in the lowest compared to the highest socioeconomic group.

^cAssessed using the Mill Hill vocabulary test.

Table 3. Association of time varying adverse health conditions (multimorbidity, frailty, and disability) with subsequent mortality in the total study population and analysis stratified by SES.^a

	Adverse Health Condition	Multimorbidity ^b HR (95% CI)	Frailty HR (95% CI)	Disability HR (95% CI)
Total sample				
	No	1 (ref)	1 (ref)	1 (ref)
	Yes	4.12 (3.41, 4.98)	2.38 (1.93, 2.93)	1.73 (1.34, 2.22)
Education				
High	No	1 (ref)	1 (ref)	1 (ref)
	Yes	4.58 (3.27, 6.42)	3.04 (2.11, 4.40)	2.58 (1.67, 3.99)
Medium	No	1 (ref)	1 (ref)	1 (ref)
	Yes	4.22 (2.98, 5.96)	2.02 (1.37, 2.99)	1.49 (0.87, 2.55)
Low	No	1 (ref)	1 (ref)	1 (ref)
	Yes	3.90 (3.00, 5.06)	2.35 (1.77, 3.12)	1.62 (1.16, 2.25)
<i>p</i> for interaction^c		0.74	0.29	0.16
Occupation				
High	No	1 (ref)	1 (ref)	1 (ref)
	Yes	4.52 (3.47, 5.89)	3.00 (2.21, 4.07)	2.78 (1.97, 3.92)
Medium	No	1 (ref)	1 (ref)	1 (ref)
	Yes	4.04 (3.12, 5.24)	1.82 (1.36, 2.43)	1.48 (1.02, 2.15)
Low	No	1 (ref)	1 (ref)	1 (ref)
	Yes	3.63 (2.35, 5.61)	2.67 (1.65, 4.33)	1.31 (0.77, 2.22)
<i>p</i> for interaction^c		0.66	0.04	0.01
Literacy^d				
High	No	1 (ref)	1 (ref)	1 (ref)
	Yes	4.15 (3.18, 5.40)	2.45 (1.83, 3.29)	1.51 (1.04, 2.19)
Medium	No	1 (ref)	1 (ref)	1 (ref)
	Yes	3.61 (2.59, 5.03)	2.38 (1.64, 3.45)	2.28 (1.47, 3.52)
Low	No	1 (ref)	1 (ref)	1 (ref)
	Yes	4.49 (3.21, 6.28)	2.31 (1.61, 3.31)	1.56 (1.02, 2.38)
<i>p</i> for interaction^c		0.63	0.96	0.31

^aAnalyses (adjusted for age, sex, race, marital status, and birth cohort) using proportional hazards regression with Weibull distribution and with inverse probability weighting. Participants free of adverse health conditions who dropped out of the study were censored at the data wave that followed their last assessment.

^bMultimorbidity defined as 2 or more of the following chronic conditions: diabetes, coronary heart disease, stroke, chronic obstructive pulmonary disease, depression, arthritis, cancer, dementia, and Parkinson's disease.

^cThe interaction terms tests whether the association between adverse health conditions and mortality differs as a function of SES.

^dAssessed using the Mill Hill vocabulary test.

Table 4. Multi-state models for the transitions from a healthy state to adverse health condition (multimorbidity, frailty and disability) and mortality.^a

TRANSITIONS	N event/ N total	Education^b HR (95% CI)	Occupation^b HR (95% CI)	Literacy^{b,c} HR (95% CI)
Transition to Mortality via Multimorbidity^d				
A (Healthy to Multimorbidity)	1677/6425 ^e	1.24 (1.13, 1.35)	1.54 (1.37, 1.73)	1.11 (1.07, 1.14)
B (Healthy to Mortality)	285/6425	0.94 (0.67, 1.34)	2.02 (1.18, 3.44)	0.89 (0.74, 1.07)
C (Multimorbidity to Mortality)	326/1677	1.03 (0.89, 1.20)	1.14 (0.94, 1.39)	0.99 (0.94, 1.05)
Transition to Mortality via Frailty				
A (Healthy to Frailty)	1733/6425	1.08 (0.99, 1.18)	2.08 (1.85, 2.33)	1.05 (1.01, 1.09)
B (Healthy to Mortality)	416/6425	1.26 (1.05, 1.50)	1.82 (1.45, 2.30)	1.10 (1.03, 1.19)
C (Frailty to Mortality)	195/1733	0.92 (0.76, 1.11)	0.96 (0.76, 1.22)	0.96 (0.90, 1.02)
Transition to Mortality via Disability				
A (Healthy to Disability)	692/6425	1.29 (1.11, 1.50)	1.44 (1.18, 1.74)	1.21 (1.14, 1.27)
B (Healthy to Mortality)	522/6425	1.15 (1.01, 1.31)	1.39 (1.17, 1.65)	1.02 (0.97, 1.08)
C (Disability to Mortality)	89/692	0.69 (0.50, 0.95)	0.90 (0.59, 1.36)	1.00 (0.90, 1.12)

^aAnalyses using three states multi-state models with interval censored data; analyses undertaken using Weibull distribution and inverse probability weighting. Models adjusted for sex, race, marital status, birth cohort, and age at the adverse health condition in the transition C.

^bCategories of SES indicators were recoded (0, 0.5, and 1) so that when entered as a continuous variable the reported hazard ratio corresponded to increased risk in the lowest compared to the highest socioeconomic group.

^cAssessed using the Mill Hill vocabulary test.

^dMultimorbidity defined as 2 or more of the following chronic conditions: diabetes, coronary heart disease, stroke, chronic obstructive pulmonary disease, depression, arthritis, cancer, dementia, and Parkinson's disease.