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Complete List of Authors:	Kabir, Alamgir; University of New South Wales - Kensington Campus, Centre for Primary Health Care and Equity Tran, An; University of New South Wales, Centre for Primary Health Care and Equity Ansari, Sameera; University of New South Wales, School of Population Health Conway, Damian; South Eastern Sydney Local Health District, Population and Community Health Directorate Barr, Margo; University of New South Wales, Centre for Primary Health Care and Equity
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Impact of multimorbidity and complex multimorbidity on mortality among older Australians aged 45 years and over: A large population-based record linkage study

Alamgir Kabir,[1] An Tran,[1] Sameera Ansari,[2,3] Damian P Conway,[4,5] Margo Linn Barr[1]

[1]Centre for Primary Health Care and Equity, UNSW Sydney, NSW, Australia

[2]School of Population Health, UNSW Sydney, NSW, Australia

[3]Faculty of Health Sciences and Medicine, Bond University, QLD, Australia

[4]The Kirby Institute, UNSW Sydney, NSW, Australia

[5]Population and Community Health Directorate, South Eastern Sydney Local Health District, NSW, Australia

Corresponding author: Alamgir Kabir, Centre for Primary Health Care and Equity, Level 3, AGSM Building, UNSW Sydney NSW 2052 Australia, a.kabir@unsw.edu.au

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ABSTRACT

Objectives: Multimorbidity (MM; co-occurrence of two or more chronic health conditions) and complex multimorbidity (CMM; three or more chronic conditions affecting three or more different body systems) are used in the assessment of complex healthcare needs and their impact on health outcomes. However, little is known about the impacts of MM and CMM on mortality in an Australian population.

Design: Community-based prospective cohort study.

Setting: New South Wales, Australia.

Participants: People aged 45 years and over from New South Wales, Australia who completed the baseline survey of the 45 and Up Study.

Measures: Baseline survey data from the 45 and Up Study were linked with deaths registry data during eight years of follow-up. Eleven self-reported chronic conditions (cancer, heart disease, diabetes, stroke, Parkinson's disease, depression/anxiety, asthma, allergic rhinitis, hypertension, thrombosis and musculoskeletal conditions) from the baseline survey were included in the MM classification. Chronic conditions were further classified into nine body system groups. Cox proportional hazard models were used to estimate adjusted and unadjusted 8-year mortality hazard ratios.

Results: Of 251,689 people in the cohort, 111,084 (44.1%) were classified as having MM and 39,478 (15.7%) as having CMM. During 8-year follow up, there were 25,891 deaths. Cancer (34.7%) was the most prevalent chronic conditions and cardiovascular (50.9%) was the most affect body system with a chronic condition. MM and CMM were associated with a 37% (Adj. HR:1.36, 95% CI: 1.32-1.40) and a 22% (Adj. HR:1.22, 95% CI: 1.18-1.25) increased risk of death, respectively.

Conclusions: MM and CMM were common in this large population-based cohort study of older Australian adults; and MM was a better predictor of all-cause mortality risk than CMM. Higher mortality risk in those aged 45-59 years indicates tailored, person-centred integrated care interventions and better access to holistic healthcare are needed for this age group.

Strengths and limitations of this study

- Complex multi-morbidity (CMM) has been proposed as an alternative and more specific metric to assess the complexity of health care needs, but little is known about how it compares to multimorbidity (MM) when examining mortality.
- This is the first population-based study in Australia reporting the effect of CMM on mortality in a large cohort of older adults.
- Tailored, person-centred integrated care interventions and better access to holistic healthcare for the 45–59-year-old age group is needed.
- Though the 45 and Up Study cohort has been shown to be representative of the population from which it is drawn, non-response at baseline may mean the cohort varies slightly from the broader population.
- Our analysis was restricted to the conditions listed in the baseline survey, however this included all of the most important chronic conditions.

INTRODUCTION

Multimorbidity (MM), the co-occurrence of two or more chronic health conditions in an individual, is often used in the assessment of complex healthcare needs and their impact on health outcomes.[1] As life expectancy increases over time due to advances in healthcare and living standards, the burden of chronic conditions is increasing globally.[2] Consequently, the proportion of national healthcare expenditure spent caring for people with MM has increased substantially. For example, managing MM accounts for 71% of total US healthcare spending.[3] While overall prevalence of MM is 33% globally,[4] prevalence among those aged 65 years or more is estimated to be 55-98% in high-income countries.[5] In Australia, estimated prevalence of MM is 20% overall and 51% among those aged 65 years or more.[6]

MM is associated with increased risk of adverse mental and physical health outcomes,[7 8] and poor quality of life overall.[9 10] However, reported effects of MM on mortality in older adults are mixed: some studies report MM is associated with greater risk of mortality,[11-16] while others report no significant association.[17 18] A systematic review found an increased risk of mortality among those with MM, but noted the majority of studies were not population-based, had relatively small sample sizes and/or lacked internal validity.[14] Also, many studies reported the impact of MM on mortality among older adults overall without stratifying outcomes by age group. Though some Australian studies demonstrated an association between MM and mortality, these studies were not population-based and have limited generalisability.[19 20]

Some authors have proposed complex multimorbidity (CMM; co-occurrence of three or more chronic conditions affecting three or more different body systems) as an alternative and more specific metric to assess complexity of individual healthcare needs.[19 21] This metric provides lower prevalence estimates than MM and allows greater differentiation amongst older adults.[19] However, whether it enables more targeted patient care and health resource planning requires further investigation. To our knowledge, there have not been any published evaluations comparing the impact of MM and

CMM on older adult mortality in Australia. Hence, we conducted a large population-based data linkage study to: (i) compare the effect of MM and CMM on mortality among older adults aged 45 and above; and (ii) assess whether any observed effect on mortality varies by age group.

METHODS

Study design and population

We conducted a prospective cohort study of people aged 45 years and over from New South Wales (NSW), Australia enrolled in the 45 and Up Study with 8-year follow-up from recruitment. The 45 and Up Study is a large-scale population-based cohort study comprising 266,943 men and women aged 45 years and over. Detail of the study has been described elsewhere.[22] In brief, potential study participants aged 45 years or older in NSW were randomly sampled from the Medicare Australia enrolment database and invited to participate between 2006 and 2009. Participants consented to self-completing the baseline questionnaire and to long-term follow-up with linkage of survey data to other administrative health records. Data collected via baseline survey included socio-demographic and lifestyle characteristics, and self-reported chronic conditions. We excluded people from the study population who had completed their baseline data before 20 February as the death records were only available from that date.

Data linkage and outcome ascertainment

All deaths between 20 February 2006 and 30 September 2018 recorded in the Australian national deaths registry were linked to 45 and Up Study data by the NSW Centre for Health Record Linkage. Follow-up time for mortality was set at eight years as baseline data collection was completed in December 2009 and the latest available deaths registry data was from September 2018. All-cause mortality occurring within eight years of recruitment was our outcome of interest.

Multimorbidity and complex multimorbidity ascertainment

Self-reported chronic health conditions were ascertained from responses to two 45 and Up Study baseline survey questions: "Has a doctor ever told you that you have (name of condition)?" and "In the last month have you been treated for (name of condition)?". If the response was "Yes" for either question for a condition, we considered the person had the condition. These included cancer (all types), heart disease, diabetes, stroke, Parkinson's disease, depression, anxiety, asthma, allergic rhinitis, hypertension, thrombosis, and musculoskeletal conditions. Accordingly, participants were classified as having MM (two or more chronic conditions) and/or CMM (three or more chronic conditions affecting three or more body systems).[23] To define CMM, we first classified the 11 chronic conditions into nine groups according to the body system: cardiovascular, musculoskeletal, neurological, psychological, respiratory, skin, endocrine/metabolic, female genital, and male genital.[24] Conditions that occurred in different body parts (e.g. cancer at different sites) were grouped into one condition for the MM measure, but were classified into different body-systems depending on the sites.

Statistical analysis

Participant characteristics were compared for those with and without MM or CMM using chi-squared tests. We conducted a time-to-event analysis to measure impacts of MM and CMM on mortality. Follow-up time started at the date of baseline data collection and was censored at death or the date when participants completed 8-year follow-up, whichever came first. We generated Kaplan-Meir survival curves for people with and without MM or CMM and used log-rank tests for comparison. Death rate was calculated using person-time at-risk as the denominator. Crude and adjusted hazard ratios (HRs) with 95% confidence intervals (95%CIs) were estimated using univariate and multiple Cox proportional hazard models. The potential confounders were selected based on the following steps: first, we selected those variables for the base model which were found to be associated with multi-morbidity or complex multi-morbidity at $p<0.20$ using a chi-squared test; second, we applied the

change-in-estimate strategy using the "chest" package in R.[25 26] We then assessed potential effect modification for age groups, as there was a large variation in age at baseline, by adding an interaction term into the Cox proportional hazard model. If the interaction term was significant at $p<0.05$, we did a stratified analysis by age. We set 5% as the significance level for all statistical tests. We used R 3.6.3 software (R Foundation, Vienna, Austria) for data analysis and SAS 9.4 (SAS Institute, Cary, NC) for data management.

Patient and public involvement

Patients or public were not involved in design, management or reporting of our study.

RESULTS

The analytic cohort comprised 251,689 people aged 45 years and over (Figure 1). The percentage of the cohort assessed to have multi-morbidity was 44.1% (95%CI: 43.9-44.3) with the most frequent chronic conditions being cancer (34.7%), followed by hypertension (31.0%) and depression or anxiety (18.4%) (Table 1). The percentage of the cohort assessed to have complex multi-morbidity was 15.7% (95%CI: 15.5-15.8) and the cardiovascular system was the most prevalent body system (50.9%) followed by respiratory (22.0%) and psychological (18.4%).

Table 1: Percentage of self-reported chronic conditions among older adults aged 45 years and over by condition and by body system

	n	Prevalence (95% CI)
Morbidity		
Cancer[a]	87386	34.7 (34.5, 34.9)
Heart disease[b]	32690	13.0 (12.9, 13.1)
Diabetes	22575	9.0 (8.9, 9.1)
Parkinson's disease	1566	0.6 (0.6, 0.7)
Stroke	7893	3.1 (3.1, 3.2)
Depression or anxiety	46343	18.4 (18.3, 18. 6)
Asthma	31316	12.4 (12.3, 12.6)
Allergic rhinitis	34509	13.7 (13.6, 13.9)
Hypertension	78135	31.0 (30.9, 31.2)
Thrombosis	13834	5.5 (5.4, 5.6)

Musculoskeletal conditions[c]	29986	11.9 (11.8, 12.0)
Multimorbidity (MM, >=2 morbidities)	111084	44.1 (43.9, 44.3)
Body system morbidity: any conditions within these systems[d]		
Cardiovascular	128069	50. 9 (50.7, 51.1)
Musculoskeletal	35272	14.0 (13.9, 14.2)
Neurological	1566	0.6 (0.6, 0.7)
Psychological	46343	18.4 (18.3, 18. 6)
Respiratory	55279	22.0 (21.8, 22.1)
Skin	13811	5.5 (5.4, 5.6)
Endocrine/Metabolic	33533	13.3 (13.2, 13.5)
Female genital[e]	7300	2.9 (2.8, 3.0)
Male genital[f]	23850	9.5 (9.4, 9.6)
Complex multimorbidity (CMM, >=3 body system)	39478	15.7 (15.5, 15.8)

[a]Cancer includes melanoma, breast cancer (F), prostate cancer (M) and other cancer.
[b]Heart disease includes heart attack, angina or other heart disease.
[c]Musculoskeletal includes osteoarthritis, osteoporosis or low bone density.
[d]Body system morbidities- cardiovascular includes heart disease, high blood pressure, blood clot (thrombosis), heart attack or angina and other heart disease; musculoskeletal includes osteoarthritis, osteoporosis or low bone density; neurological includes Parkinson's disease; psychological includes depression or anxiety; respiratory includes asthma or allergic rhinitis; skin includes melanoma; endocrine/metabolic includes diabetes and thyroid problems; female genital includes breast cancer; male genital includes prostate cancer or enlarged prostate.
[e]Denominator for this estimate was total number of female participants.
[f]Denominator for this estimate was total number of male participants.

Participants baseline characteristics (see the supplementary material for detail descriptions) by morbidity status are presented in Table 2. All baseline characteristics except current smoking status were significantly ($p<0.001$) different between people with and without MM, while all baseline characteristics were significantly different between people with and without CMM. The proportion of the cohort categorised as having MM and CMM increased with increasing age, but the proportion decreased with increasing household income. People not working, self-reporting fair/poor quality of life or having high levels of psychological distress had significantly higher proportions of MM and CMM than those not in these groups.

Table 2: Percentage of multimorbidity (MM) and complex multimorbidity (CMM) by characteristics for the study participants

	N[a]	MM n (%)	p-value	CMM n (%)	p-value
Age at baseline					
45-59	116085	37374 (32.2)	-	10718 (9.2)	-
60-74	93060	46770 (50.3)	-	17587 (18.9)	-
75+	42544	26940 (63.3)	<0.001	9229 (26.3)	<0.001
Gender					
Male	117059	52750 (45.1)	-	17463 (14.9)	-
Female	134630	58334 (43.3)	<0.001	22015 (16.4)	<0.001
Highest education					
No school certificate or other qualification	29344	15328 (52.2)	-	6216 (21.2)	-
School or intermediate certificate	55196	25901 (46.9)	-	9532 (17.3)	-
Higher school or leaving certificate	24588	9976 (40.6)	-	3417 (13.9)	-
Trade or apprenticeship	28051	12806 (45.7)	-	4380 (15.6)	-
Certificate or diploma	52090	22522 (43.2)	-	7911 (15.2)	-
University degree or higher	58185	22581 (38.8)	<0.001	7246 (12.5)	<0.001
Speaks language other than English at home					
No	227541	102934 (45.2)	-	36354 (16.0)	-
Yes	24145	8149 (33.8)	<0.001	3124 (12.9)	<0.001
Born in Australia					
No	61166	22623 (37.0)	-	8165 (13.3)	-
Yes	188547	87495 (46.4)	<0.001	30924 (16.4)	<0.001
Speaks language other than English at home					
No	227541	102934 (45.2)	-	36354 (16.0)	-
Yes	24145	8149 (33.8)	<0.001	3124 (12.9)	<0.001
Household income					
<$20,000	49296	28472 (57.8)	-	12260 (24.9)	-
$20,000-39,999	43933	21581 (49.1)	-	8030 (18.3)	-
$40,000-69,999	44453	17613 (39.6)	-	5534 (12.4)	-
$70,000 or more	59794	20084 (33.6)	-	5072 (8.5)	-
Won't disclose	54213	23334 (43.0)	<0.001	8582 (15.8)	<0.001
Work status					
Not working	124277	69118 (55.6)	-	28029 (22.6)	-
Part time	47577	17175 (36.1)	-	5223 (11.0)	-

	N[a]	MM n (%)	p-value	CMM n (%)	p-value
Full time	75540	23093 (30.6)	<0.001	5600 (7.4)	<0.001
Current partner (married/de facto)					
No	62245	31637 (50.8)	-	12781 (20.5)	-
Yes	187853	78720 (41.9)	<0.001	26443 (14.1)	<0.001
Current smoker					
No	233130	103890 (44.6)	-	36883 (15.8)	-
Yes	18552	7192 (38.8)	<0.001	2595 (14.0)	<0.001
Adequate physical activity					
No	81815	39044 (47.7)	-	15333 (18.7)	-
Yes	169874	72040 (42.4)	<0.001	24145 (14.2)	<0.001
Alcohol consumption					
No	82068	39610 (48.3)	-	16347 (19.9)	-
Yes	164927	69308 (42.0)	<0.001	22229 (13.5)	<0.001
BMI category					
Under weight	26433	11326 (42.8)	-	3972 (15.0)	-
Normal weight	79040	30429 (38.5)	-	9653 (12.2)	-
Overweight	91879	40234 (43.8)	-	13684 (14.9)	-
Obese	54337	29095 (53.5)	<0.001	12169 (22.4)	<0.001
Self-reported good quality of life					
No	25379	17190 (67.7)	-	8912 (35.1)	-
Yes	212841	89079 (41.9)	-	28731 (13.5)	-
Missing	13469	4815 (35.7)	<0.001	1835 (13.6)	<0.001
Psychological distress					
Low	205402	84755 (41.3)	-	27573 (13.4)	-
High (22 or more)	18603	11239 (60.4)	-	5712 (30.7)	-
Missing	27684	15090 (54.5)	<0.001	6193 (22.4)	<0.001
Needing help with daily activity					
No	225634	96045 (42.6)	-	31823 (14.1)	-
Yes	13728	10269 (74.8)	-	5606 (40.8)	-
Missing	12327	4770 (38.7)	<0.001	2049 (16.6)	<0.001

[a]Missing value: Highest education (n=4235), speaks language other than English at home (n=3), born in Australia (n=1976), work status (n=4295), current partner (n=1591), current smoker (n=7), alcohol consumption (n=4694)

Survival probability for people with MM or CMM was significantly lower than for those without MM or CMM (p<0.001; Figure 2). Mortality was 2.5 times higher among people with MM compared to

those without (20.3 versus 8.3 deaths/1000 person-years; Table 3). When adjusted for confounding, mortality was 36% (HR: 1.36; 95% CI: 1.32-1.40) higher among people with MM compared to those without. Absolute difference in deaths/1000 person-years between people with and without MM increased as age increased: 2.3 for 45-59 years, 6.0 for 60-74 years and 12.4 for 75 years and over, respectively. However, impact of MM on mortality decreased as age increased: adjusted HRs (95%CI) were 1.59 (1.46, 1.73) for 45-59 years, 1.49 (1.41, 1.57) for 60-74 years and 1.15 (1.11, 1.19) for 75 years and over.

Table 3: Impact of multimorbidity (MM) on 8-year mortality (from recruitment)

	N	Person-year (py)	No of deaths	Death rate per 1000 py	Crude HR (95% CI)	Adj. HR[2] (95% CI)
Overall						
With no MM	140605	1093798	9071	8.3	1	1
With MM	111084	828231	16820	20.3	2.47 (2.4, 2.53)	1.36 (1.32, 1.40)
Age 45-59[1]						
With no MM	78711	625463	1219	1.9	1	1
With MM	37374	294385	1241	4.2	2.16 (2.00, 2.34)	1.59 (1.46, 1.73)
Age 60-74						
With no MM	46290	361559	2625	7.3	1	1
With MM	46770	357454	4757	13.3	1.84 (1.75, 1.93)	1.49 (1.41, 1.57)
Age 75+						
With no MM	15604	106775	5227	49.0	1	1
With MM	26940	176392	10822	61.4	1.27 (1.23, 1.31)	1.15 (1.11, 1.19)

[1]p-interaction <0.05, age vs MM status

[2]Adjusted for sex, current working status, needing help with daily activities and good quality of life

Mortality was 2.2 times higher among people with CMM compared to those without (25.3 versus 11.4 deaths/1000 person-years; Table 4). When adjusted for confounding, mortality was 22% (HR: 1.22; 95% CI: 1.18-1.25) higher among people with CMM compared to those without. Absolute difference in deaths/1000 person-years between people with and without CMM increased as age increased: 3.4 for 45-59 years, 6.3 for 60-74 years and 13.2 for 75 years and over, respectively. However, impact of

CMM on mortality decreased as age increased: adjusted HRs (95%CI) were 1.49 (1.33, 1.67) for 45-59 years, 1.29 (1.22, 1.36) for 60-74 years and 1.08 (1.04, 1.12) for 75 years and over.

Table 4: Impact of complex multimorbidity (CMM) on 8-year mortality (from recruitment)

	N	Person-year (py)	No of deaths	Death rate per 1000 py	Crude HR (95% CI)	Adj. HR[2] (95% CI)
Overall						
With no CMM	212211	1632781	18571	11.4	1	1
With CMM	39478	289248	7320	25.3	2.24 (2.18, 2.30)	1.22 (1.18, 1.25)
Age 45-59[1]						
With no CMM	105367	835879	1973	2.4	1	1
With CMM	10718	83970	487	5.8	2.46 (2.23, 2.72)	1.49 (1.33, 1.67)
Age 60-74						
With no CMM	75473	585544	5328	9.1	1	1
With complex CMM	17587	133469	2054	15.4	1.70 (1.61, 1.79)	1.29 (1.22, 1.36)
Age 75+						
With no CMM	31371	211358	11270	53.4	1	1
With CMM	11173	71809	4779	66.6	1.26 (1.22, 1.31)	1.08 (1.04, 1.12)

[1]p-interaction <0.05, age vs CMM status

[2]Adjusted for sex, current working status, needing help with daily activities and good quality of life.

DISCUSSION

This is the first population-based analysis of the effect of CMM on mortality in Australia. MM and CMM were present in 44% and 16% of people within this cohort, respectively. During eight years of follow-up, mortality in MM and CMM sub-groups was at least twice that of those without MM and CMM; 20.3 versus 8.3 deaths/1000 person-years, and 25.3 versus 11.4 deaths/1000 person-years, respectively. Adjusted risk of all-cause mortality was 36% higher for people with MM and 22% higher for people with CMM, compared to people not in either group. When adjusted risk of all-cause mortality due to MM and CMM was stratified by age, risk was highest in the youngest age group (45-59 years) and decreased towards the oldest age group (75 years or more). In our analysis, MM was found to have a greater impact on mortality than CMM; and both MM and CMM had the greatest impact on all-cause mortality in the youngest age group (45-59 years).

Our prevalence estimate for MM depends on self-reported survey data for 11 chronic conditions and is comparable with other Australian and international studies.[6 27 28] Prevalence of MM in the Australian 2017-18 National Health Survey involving 10 self-reported chronic conditions was 47% which is similar to our estimate.[6] However, five out of 10 conditions were different to those available in the 45 and Up Study baseline survey. Another Australian study estimated 37.4% prevalence for MM and 8.7% prevalence for CMM using the 45 and Up Study baseline survey data, but unlike our analysis they did not include allergic rhinitis, thrombosis and musculoskeletal conditions and only included participants with consistent concession card holder status in the Pharmaceutical Benefits Scheme (PBS) dataset (n=90,352).[27] A cross-sectional Scottish study reported MM prevalence ranging between 39% for people aged 55-66 years and 76% for people aged 75 years and over(which is similar to our estimates), while other studies have reported much higher prevalence among older adults.[5]

Consistent with our study, a 2015 meta-analysis of 26 studies demonstrated greater mortality risk among older adults with MM compared to those without (HR: 1.44; 95% CI: 1.34-1.55).[14] More recently, the English Longitudinal Study of Aging reported a similar mortality risk associated with MM (HR: 1.27; 95% CI: 1.14-1.43).[29] However, other US and Scottish studies reported significantly greater effects of MM on mortality compared to our analysis.[15 16] Though several studies have evaluated the effect of MM on mortality, relatively few have evaluated the effect of CMM on mortality.[30 31] A Japanese population-based cohort study evaluating the effects of MM and CMM on mortality among adults aged 65 and over reported lower and similar effects for both MM and CMM compared to our study (HR: 1.07; 95% CI: 1.01-1.14 for MM and HR: 1.07; 95% CI: 0.99-1.16 for CMM). However, a Norwegian population-based cohort study found 22% higher mortality risk in those with CMM aged 60-69 years (RR: 1.22; 95% CI: 1.12-1.33).[31]

While all-cause mortality overall was higher in our study for the older age groups the relative effect sizes for mortality risk for both MM and CMM was higher in adults aged 45-59 years compared to the older age groups. A study using the UK Biobank (n= 502,640) found similar results and concluded that this may be because most interventions to date have been directed at middle aged populations.[32] They therefore highlighted the need for algorithms that could identify these younger people with multimorbidity to provide earlier more targeted care. This phenomenon may also be explained, in part, because early onset disease is often more aggressive and people are presenting later.[33 34] This again highlights the need for early diagnosis, treatment, and targeted care.

Risk of all-cause mortality associated with MM was found to be higher than mortality risk associated with CMM. This was unexpected given that CMM was proposed to be more specific in assessing the complexity of individual healthcare needs.[21] A possible reason for this finding is that our and other studies focused on prevalence of CMM and not the severity of illness.[23 35] For example, as Harrison et al identified, those with mild chronic conditions affecting three body systems, could have less healthcare needs than someone diagnosed with one severe chronic condition.[21] Also, the most prevalent MM and CMM combinations may not necessarily be the most severe. Another potential explanation for this finding could relate to cancer conditions being split and allocated by affected body system for CMM categorisation, rather than kept as a group. This meant those with cancer and other chronic conditions affecting less than three body systems were excluded from being categorised with CMM.

The finding MM was a better predictor of all-cause mortality risk than CMM suggests individuals with MM should be prioritised for intervention in clinical practice. That all-cause mortality risk was highest in the youngest age group (45-59 years) suggests tailored innovative healthcare interventions and better access to integrated care are needed for this age group. For example, the delivery of a nurse-led self-management program for COPD in the context of MM implemented in Australian general

practice.[36] A holistic approach is required for healthcare management of MM, involving shared decision-making and care coordination across all levels of the health system. Particularly cardiovascular, respiratory, and mental health conditions which were the most prevalent domains in our study. Though CMM was not a better predictor of mortality than MM in our analysis, this finding needs further exploration and confirmation. As suggested in another Australian study, CMM could be used to "examine the relationship between the number of diagnosed chronic conditions/body systems affected and overall severity of illness, complexity of care and health resource utilisation".[21]

The major strength of this study was our use of a large community-dwelling cohort of older adults which was not restricted only to those engaged with health services, thus providing a more realistic denominator. Recruitment of individuals across the age spectrum from 45 to 90 years to the 45 and Up Study at baseline enabled us to assess the impacts of MM and CMM on mortality across that age range. Also, to our knowledge, this is the first analysis to compare the effect of MM versus CMM on mortality. However, our study had limitations. Though the 45 and Up Study cohort has been shown to be representative of the population from which it is drawn, non-response at baseline may mean the cohort varies slightly from the broader population. Nevertheless, comparison of these rates over time and between subgroups is still valid. Another limitation was our analysis was restricted to the conditions listed in the baseline survey, though most important chronic conditions were included. An Australian study exploring the concordance between the 45 and Up Study baseline survey and administrative healthcare datasets, found that over 70% of individuals classified as having MM were identified from the baseline survey.[27] A systematic review has also found that self-report is a valid method for capturing MM.[37]

Further research exploring patterns of healthcare utilisation, such as uptake of primary care chronic disease management plans, between those with MM and CMM would provide better understanding of our findings. Survey data could be combined with other data sources (PBS, Medicare Benefits

Schedule, general practice clinic records and hospital administrative datasets) to assess whether our findings can be replicated when diverse data sources and a more extensive list of chronic conditions are used. Conducting research to explore how these associations may differ across health service regions in NSW, particularly between urban and rural settings, would also be beneficial. This would enable us to determine what works and does not work when managing those with MM across different settings.

Conclusion

MM and CMM were common in this large population-based cohort study of older adults in NSW, Australia. Mortality among people in MM and CMM sub-groups was high; with MM being a better predictor of all-cause mortality risk than CMM. All-cause mortality risk being highest in the youngest age group (45-59 years) is an important finding which indicates the need for tailored, person-centred integrated care interventions and better access to holistic healthcare for this age group.

Figure legends

Figure 1: Assembly of the analytic cohort

Figure 2: Kaplan-Meir curve- impact of multimorbidity (MM) and complex multimorbidity (CMM) on 8-year (from recruitment) mortality

Author's Contribution: All authors have substantially contributed to this manuscript and met the authorship criteria. AK, AT, SA, and MB conceived the study. All authors contributed to the design, analysis and interpreting the results. AK drafted, and all authors reviewed the manuscript. All authors read and approved the final manuscript.

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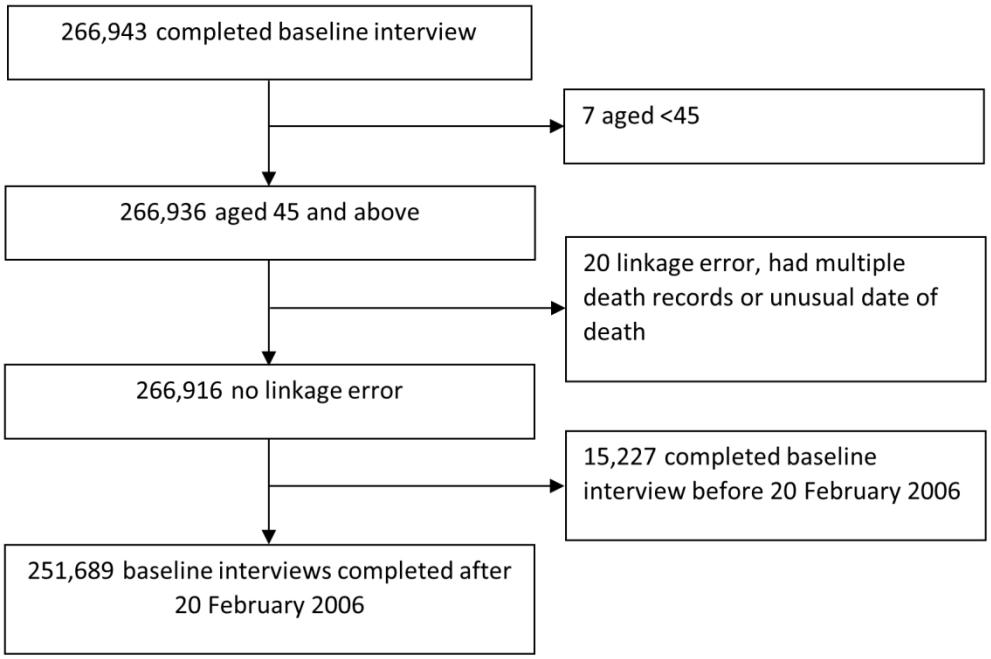
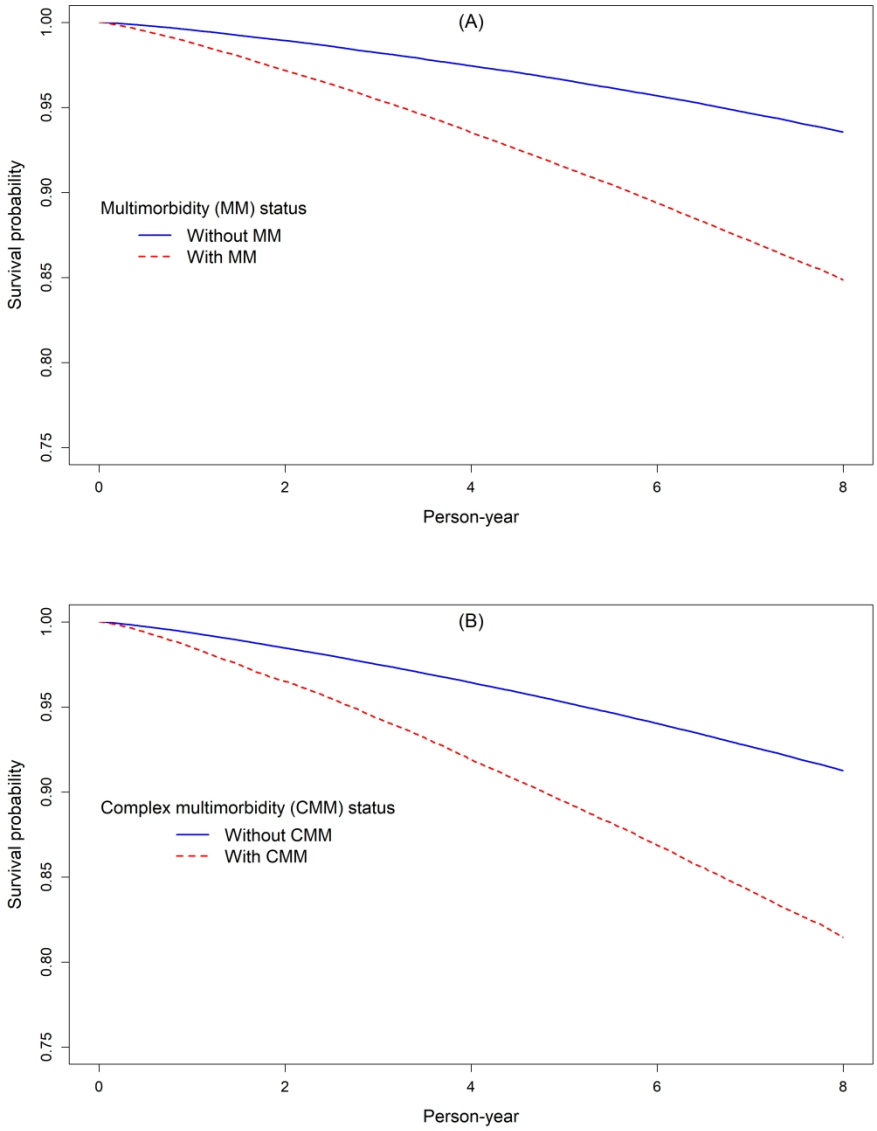


Assembly of the analytic cohort

145x99mm (300 x 300 DPI)



Kaplan-Meir curve- impact of multimorbidity (MM) and complex multimorbidity (CMM) on 8-year (from recruitment) mortality

299x399mm (300 x 300 DPI)

Supplementary Tables

Table S1: Characteristics variables, data sources and descriptions

Characteristics	Data source	Question	Categorisation for analysis
Demographic characteristics			
Age group	45 And Up Study Baseline	Self-reported age at baseline	45-59 years 60-74 75+
Gender	45 And Up Study Baseline	Self-reported sex	Male Female
Highest qualification	45 And Up Study Baseline	Self-reported highest level of educational qualification – categorised as	No school certificate or other qualification School or intermediate certificate Higher school or leaving certificate Trade or apprenticeship Certificate or diploma University degree or higher
Speaks a language other than English at home	45 And Up Study Baseline	Whether speaks a language other than English at home?	Yes: Speaks language other than English at home No: Speaks only English at home
Born in Australia	45 And Up Study Baseline	In which country where you born	No: Otherwise Yes: Born in Australia
Speaks language other than English at home	45 And Up Study Baseline	Do you speak a language other than English at home?	Yes No
Household income	45 And Up Study Baseline	Self-reported household income category	<$20,000 $20,000-39,999 $40,000-69,999 $70,000 or more Won't disclose
Work status	45 And Up Study Baseline	Working status at baseline	Not working Working part-time/full-time
Currently married/partnered	45 And Up Study Baseline	Current marital status: or not	Yes: currently married/partnered No: Not currently married/partnered
Health characteristics			
Current smoker	45 And Up Study Baseline	Smoking status at baseline	Yes: Currently smoking No: Non-smoker or ex-smoker
Adequate physical activity	45 And Up Study Baseline	Based on the amount of moderate and vigorous exercise reported: see AIHW definition	Yes: Adequate physical activity No: Inadequate physical activity
Alcohol consumption	45 And Up Study Baseline	Based on self-reported number of standard drinks each week, categorised as	zero low (1-14 drinks per week) high (>14 drinks per week)

Characteristics	Data source	Question	Categorisation for analysis
BMI	45 And Up Study Baseline	Calculation based on 2 questions: How tall are you without shoes? How much do you weigh?	Underweight: <18.5 Normal weight: 18.6-24.9 Overweight: 25.0-29.9 Obese: ≥30
Self-reported good quality of life	45 And Up Study Baseline	Based on self-rated quality of life question – classified as yes if responded as good; very good or excellent	Yes: Excellent, very good or good quality of life No: Fair or poor quality of life
Psychological distress-Index calculated based on 10 indicators	45 And Up Study Baseline	During the past 4 weeks about how often did you feel: Tired out for now good reason? Nervous? so nervous that nothing could calm you down? Hopeless? Restless or fidgety? So restless that you could not sit still? Depressed? That everything was an effort? So sad that nothing could cheer you up? Worthless?	1=None of the time 2=A little of the time 3=Some of the time 4=Most of the time 5=All the time Low= total score <22 High= total score >=22
Add Needing help with daily activity	45 And Up Study Baseline	Do you regularly need help with daily tasks because of long-term illness or disability	Yes No

The RECORD statement – checklist of items, extended from the STROBE statement, that should be reported in observational studies using routinely collected health data.

	Item No.	STROBE items	Location in manuscript where items are reported
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found	(a) Text document P1, P (b) Text document P2
Background rationale	2	Explain the scientific background and rationale for the investigation being reported	Text document P3-4
Objectives	3	State specific objectives, including any prespecified hypotheses	Text document P4
Study Design	4	Present key elements of study design early in the paper	Text document P4-5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Text document P4-5
Participants	6	*(a) Cohort study* - Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study* - Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study* - Give the eligibility criteria, and the sources and methods of selection of participants *(b) Cohort study* - For matched studies, give matching criteria and number of exposed and unexposed *Case-control study* - For matched studies, give matching criteria and the number of controls per case	(a) Text document P4
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.	Text document P5, and supplementary documen
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Text document P5
Bias	9	Describe any efforts to address potential sources of bias	Text document P6
Study size	10	Explain how the study size was arrived at	The study was based on extracting all available data for the study population. No sample size calculations were conducted. Figure 1.
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	Not applicable

Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) *Cohort study* - If applicable, explain how loss to follow-up was addressed *Case-control study* - If applicable, explain how matching of cases and controls was addressed *Cross-sectional study* - If applicable, describe analytical methods taking account of sampling strategy (e) Describe any sensitivity analyses	Text document P6
Data access and cleaning methods		..	
Linkage		..	Text document P5
Participants	13	(a) Report the numbers of individuals at each stage of the study (*e.g.*, numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed) (b) Give reasons for non-participation at each stage. (c) Consider use of a flow diagram	Text document P6 Text document Figure 1
Descriptive data	14	(a) Give characteristics of study participants (*e.g.*, demographic, clinical, social) and information on exposures and potential confounders (b) Indicate the number of participants with missing data for each variable of interest (c) *Cohort study* - summarise follow-up time (*e.g.*, average and total amount)	Text document Tables 1 & 2, P6, P10, P11 Tables 3 & 4
Outcome data	15	*Cohort study* - Report numbers of outcome events or summary measures over time *Case-control study* - Report numbers in each exposure category, or summary measures of exposure *Cross-sectional study* - Report numbers of outcome events or summary measures	Text document P10, P11, Tables 3 & 4
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Text document P10, P11, Tables 3 & 4
Other analyses	17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	Text document P10, P11, Tables 3 & 4
Key results	18	Summarise key results with reference to study objectives	Text document P11, P12

Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Text document P14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Text document P11-P14
Generalisability	21	Discuss the generalisability (external validity) of the study results	Text document P15
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Text document P16
Accessibility of protocol, raw data, and programming code			Text document P16

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Impact of multimorbidity and complex multimorbidity on mortality among older Australians aged 45 years and over: A large population-based record linkage study

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Impact of multimorbidity and complex multimorbidity on mortality among older Australians aged 45 years and over: A large population-based record linkage study

Alamgir Kabir,[1] An Tran,[1] Sameera Ansari,[2,3] Damian P Conway,[4,5] Margo Linn Barr[1]

[1]Centre for Primary Health Care and Equity, UNSW Sydney, NSW, Australia

[2]School of Population Health, UNSW Sydney, NSW, Australia

[3]Faculty of Health Sciences and Medicine, Bond University, QLD, Australia

[4]The Kirby Institute, UNSW Sydney, NSW, Australia

[5]Population and Community Health Directorate, South Eastern Sydney Local Health District, NSW, Australia

Corresponding author: Alamgir Kabir, Centre for Primary Health Care and Equity, Level 3, AGSM Building, UNSW Sydney NSW 2052 Australia, a.kabir@unsw.edu.au

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ABSTRACT

Objectives: Multimorbidity (MM; co-occurrence of two or more chronic health conditions) and complex multimorbidity (CMM; three or more chronic conditions affecting three or more different body systems) are used in the assessment of complex healthcare needs and their impact on health outcomes. However, little is known about the impacts of MM and CMM on mortality in an Australian population.

Design: Community-based prospective cohort study.

Setting: New South Wales, Australia.

Participants: People aged 45 years and over from New South Wales, Australia who completed the baseline survey of the 45 and Up Study.

Measures: Baseline survey data from the 45 and Up Study were linked with deaths registry data. Deaths occurred within eight years from the baseline survey date were the study outcome. Eleven self-reported chronic conditions (cancer, heart disease, diabetes, stroke, Parkinson's disease, depression/anxiety, asthma, allergic rhinitis, hypertension, thrombosis and musculoskeletal conditions) from the baseline survey were included in the MM classification. Chronic conditions were further classified into nine body system groups. Cox proportional hazard models were used to estimate adjusted and unadjusted 8-year mortality hazard ratios.

Results: Of 251,689 people (with 53% female and 54% aged ≥60 years) in the cohort, 111,084(44.1%) were classified as having MM and 39,478(15.7%) as having CMM. During 8-year follow up, there were 25,891 deaths. Cancer (34.7%) was the most prevalent chronic conditions and cardiovascular (50.9%) was the most affected body system with a chronic condition. MM and CMM were associated with a 37% (Adj.HR:1.36, 95%CI:1.32-1.40) and a 22% (Adj.HR:1.22, 95%CI:1.18-1.25) increased risk of death, respectively.

Conclusions: MM and CMM were common in older Australian adults; and MM was a better predictor of all-cause mortality risk than CMM. Higher mortality risk in those aged 45-59 years indicates tailored,

person-centred integrated care interventions and better access to holistic healthcare are needed for this age group.

Strengths and limitations of this study

- A large population-based prospective cohort study of people aged 45 years and over was used to evaluating the effect of multimorbidity and complex multimorbidity on 8-year mortality.
- Self-reported chronic health conditions were used to define multimorbidity and complex multimorbidity.
- Deaths registry data was probabilistically linked to the cohort data by the NSW Centre for Health Record Linkage for mortality surveillance.
- Though the study cohort has been shown to be generally representative of the population from which it is drawn, non-response at recruitment may mean the cohort varies slightly from the broader population.
- Our analysis was restricted to the conditions listed in the questionnaire, however this included all of the most important chronic conditions.

INTRODUCTION

Multimorbidity (MM), the co-occurrence of two or more chronic health conditions in an individual, is often used in the assessment of complex healthcare needs and their impact on health outcomes.[1] As life expectancy increases over time due to advances in healthcare and living standards, the burden of chronic conditions is increasing globally.[2] Consequently, the proportion of national healthcare expenditure spent caring for people with MM has increased substantially. For example, managing MM accounts for 71% of total US healthcare spending.[3] While overall prevalence of MM is 33% globally,[4] prevalence among those aged 65 years or more is estimated to be 55-98% in high-income countries.[5] In Australia, estimated prevalence of MM is 20% overall and 51% among those aged 65 years or more.[6]

MM is associated with increased risk of adverse mental and physical health outcomes,[7 8] and poor quality of life overall.[9 10] However, reported effects of MM on mortality in older adults are mixed: some studies report MM is associated with greater risk of mortality,[11-16] while others report no significant association.[17 18] A systematic review found an increased risk of mortality among those with MM, but noted the majority of studies were not population-based, had relatively small sample sizes and/or lacked internal validity.[14] Also, many studies reported the impact of MM on mortality among older adults overall without stratifying outcomes by age group. Though some Australian studies demonstrated an association between MM and mortality, these studies were not population-based and have limited generalisability.[19 20]

Some authors have proposed complex multimorbidity (CMM; co-occurrence of three or more chronic conditions affecting three or more different body systems) as an alternative and more specific metric to assess complexity of individual healthcare needs.[19 21] This metric provides lower prevalence estimates than MM and allows greater differentiation amongst older adults.[19] However, whether it enables more targeted patient care and health resource planning requires further investigation. To our knowledge, there have not been any published evaluations comparing the impact of MM and

CMM on older adult mortality in Australia. Hence, we conducted a large population-based data linkage study to: (i) compare the effect of MM and CMM on mortality among older adults aged 45 and above; and (ii) assess whether any observed effect on mortality varies by age group.

METHODS

Study design and population

We conducted a prospective cohort study of people aged 45 years and over from New South Wales (NSW), Australia enrolled in the Sax Institute's 45 and Up Study with 8-year follow-up from recruitment. People who completed the baseline survey questionnaire of the 45 and Up Study and who did not withdraw from the study were our study population. The 45 and Up Study is a large-scale population-based cohort study comprising 267,153 men and women aged 45 years and over. Detail of the study has been described elsewhere.[22] In brief, potential study participants aged 45 years or older in NSW were randomly sampled from the Services Australia (formerly the Australian Government Department of Human Services) Medicare enrolment database, which provides near complete coverage of the population and invited to participate between 2006 and 2009. However, people aged 80+ years from rural and remote areas were oversampled; about 18% of those invited participated and participants included about 11% of the NSW population aged 45 years and over. Participants consented to self-completing the baseline questionnaire and to long-term follow-up with linkage of survey data to other administrative health records. Data collected via baseline survey included socio-demographic and lifestyle characteristics, and self-reported chronic conditions. We excluded people from the study population who had completed their baseline data before 20 February 2006 as the death records were only available from that date.

Data linkage and outcome ascertainment

All deaths between 20 February 2006 and 30 September 2018 recorded in the NSW Registry of Births, Deaths and Marriages were probabilistically linked to 45 and Up Study data by the NSW Centre for Health Record Linkage. Follow-up time for mortality was set at eight years from baseline survey as baseline data collection was completed in December 2009 and the latest available deaths registry data was from September 2018. All-cause mortality occurring within eight years of recruitment was our outcome of interest.

Multimorbidity and complex multimorbidity ascertainment

Self-reported chronic health conditions were ascertained from responses to two 45 and Up Study baseline survey questions: "Has a doctor ever told you that you have (name of condition)?" and "In the last month have you been treated for (name of condition)?". If the response was "Yes" for either question for a condition, we considered the person had the condition. These included cancer (all types), heart disease, diabetes, stroke, Parkinson's disease, depression, anxiety, asthma, allergic rhinitis, hypertension, thrombosis, and musculoskeletal conditions. Accordingly, participants were classified as having MM (two or more chronic conditions at baseline) and/or CMM (three or more chronic conditions affecting three or more body systems at baseline; Table 1).[23] To define CMM, we first classified the 11 chronic conditions into nine groups according to the body system: cardiovascular, musculoskeletal, neurological, psychological, respiratory, skin, endocrine/metabolic, female genital, and male genital.[24] Conditions that occurred in different body parts (e.g. cancer at different sites) were grouped into one condition for the MM measure, but were classified into different body-systems depending on the sites.

Statistical analysis

Continuous variables were categorised and included one additional category for missing values if there are ≥5% missing values. Psychological distress was measured using the Kessler Psychological Distress Scale (K10) and categorised as low and moderate (<22) and high (≥22).[25] Participant characteristics were compared for those with and without MM or CMM using chi-squared tests. We conducted a

time-to-event analysis to measure impacts of MM and CMM on mortality. Follow-up time started at the date of baseline data collection and was censored at death or the date when participants completed 8-year follow-up, whichever came first. We generated Kaplan-Meier survival curves for people with and without MM or CMM and used log-rank tests for comparison. Death rate was calculated using person-time at-risk as the denominator. Crude and adjusted hazard ratios (HRs) with 95% confidence intervals (95%CIs) were estimated using univariate and multiple Cox proportional hazard models. The potential confounders were selected based on the following steps: first, we selected those variables for the base model which were found to be associated with multi-morbidity or complex multi-morbidity at $p<0.20$ using a chi-squared test; second, we applied the change-in-estimate strategy using the "chest" package in R.[26 27] We then assessed potential effect modification for age groups, as there was a large variation in age at baseline, by adding an interaction term into the Cox proportional hazard model. If the interaction term was significant at $p<0.05$, we did a stratified analysis by age. We set 5% as the significance level for all statistical tests. We used R 3.6.3 software (R Foundation, Vienna, Austria) for data analysis and SAS 9.4 (SAS Institute, Cary, NC) for data management.

Patient and public involvement

Patients or public were not involved in design, management or reporting of our study.

RESULTS

The analytic cohort comprised 251,689 people aged 45 years and over (Figure 1). The percentage of the cohort assessed to have multi-morbidity was 44.1% (95%CI: 43.9-44.3) with the most frequent chronic conditions being cancer (34.7%), followed by hypertension (31.0%) and depression or anxiety (18.4%) (Table 1). The percentage of the cohort assessed to have complex multi-morbidity was 15.7% (95%CI: 15.5-15.8) and the cardiovascular system was the most prevalent body system (50.9%) followed by respiratory (22.0%) and psychological (18.4%).

Table 1: Percentage of self-reported chronic conditions among older adults aged 45 years and over by condition and by body system

	n	Prevalence (95% CI)
Morbidity		
Cancer[a]	87386	34.7 (34.5, 34.9)
Heart disease[b]	32690	13.0 (12.9, 13.1)
Diabetes	22575	9.0 (8.9, 9.1)
Parkinson's disease	1566	0.6 (0.6, 0.7)
Stroke	7893	3.1 (3.1, 3.2)
Depression or anxiety	46343	18.4 (18.3, 18. 6)
Asthma[c]	31316	12.4 (12.3, 12.6)
Allergic rhinitis[c]	34509	13.7 (13.6, 13.9)
Hypertension	78135	31.0 (30.9, 31.2)
Thrombosis	13834	5.5 (5.4, 5.6)
Musculoskeletal conditions[d]	29986	11.9 (11.8, 12.0)
Multimorbidity (MM, >=2 morbidities)	111084	44.1 (43.9, 44.3)
Body system morbidity: any conditions within these systems[e]		
Cardiovascular	128069	50. 9 (50.7, 51.1)
Musculoskeletal	35272	14.0 (13.9, 14.2)
Neurological	1566	0.6 (0.6, 0.7)
Psychological	46343	18.4 (18.3, 18. 6)
Respiratory	55279	22.0 (21.8, 22.1)
Skin	13811	5.5 (5.4, 5.6)
Endocrine/Metabolic	33533	13.3 (13.2, 13.5)
Female genital[f]	7300	2.9 (2.8, 3.0)
Male genital[g]	23850	9.5 (9.4, 9.6)
Complex multimorbidity (CMM, >=3 body system)	39478	15.7 (15.5, 15.8)

[a]Cancer includes melanoma, breast cancer (F), prostate cancer (M) and other cancer.
[b]Heart disease includes heart attack, angina or other heart disease.
[c]Asthma and allergic rhinitis were collected as aggregated for the first ~15% people, but they were separated for the remaining people.
[d]Musculoskeletal includes osteoarthritis, osteoporosis or low bone density.
[e]Body system morbidities- cardiovascular includes heart disease, high blood pressure, blood clot (thrombosis), heart attack or angina and other heart disease; musculoskeletal includes osteoarthritis, osteoporosis or low bone density; neurological includes Parkinson's disease; psychological includes depression or anxiety; respiratory includes asthma or allergic rhinitis; skin includes melanoma; endocrine/metabolic includes diabetes and thyroid problems; female genital includes breast cancer; male genital includes prostate cancer or enlarged prostate.
[f]Denominator for this estimate was total number of female participants.
[g]Denominator for this estimate was total number of male participants.

Participants baseline characteristics (see the supplementary material for detail descriptions) by morbidity status are presented in Table 2. All baseline characteristics except current smoking status were significantly ($p<0.001$) different between people with and without MM, while all baseline characteristics were significantly different between people with and without CMM. The proportion of the cohort categorised as having MM and CMM increased with increasing age, but the proportion decreased with increasing household income. People not working, self-reporting fair/poor quality of life or having high levels of psychological distress had significantly higher proportions of MM and CMM than those not in these groups.

Table 2: Percentage of multimorbidity (MM) and complex multimorbidity (CMM) by characteristics for the study participants

	N[a]	Multimorbidity (MM)		Complex multimorbidity (CMM)	
		With MM n (%)	Without MM n (%)	With CMM n (%)	Without CMM n (%)
Age at baseline					
45-59	116085	37374 (32.2)	78711 (67.8)	10718 (9.2)	105367 (90.8)
60-74	93060	46770 (50.3)	46290 (49.7)	17587 (18.9)	75473 (81.1)
75+	42544	26940 (63.3)	15604 (36.7)	9229 (26.3)	31371 (73.7)
Gender					
Male	117059	52750 (45.1)	64309 (54.9)	17463 (14.9)	99596 (85.1)
Female	134630	58334 (43.3)	76296 (56.7)	22015 (16.4)	112615 (83.6)
Highest education					
No school certificate or other qualification	29344	15328 (52.2)	14016 (47.8)	6216 (21.2)	23128 (78.8)
School, intermediate, higher school or leaving certificate	79784	35877 (45.0)	43907 (55.0)	12949 (16.2)	66835 (83.8)
Trade, apprenticeship, Certificate or diploma	80141	35328 (44.1)	44813 (55.9)	12291 (15.3)	67850 (84.7)
University degree or higher	58185	22581 (38.8)	35604 (61.2)	7246 (12.5)	50939 (87.5)
Speaks language other than English at home					
No	227541	102934 (45.2)	124607 (54.8)	36354 (16.0)	191187 (84.0)
Yes	24145	8149 (33.8)	15996 (66.2)	3124 (12.9)	21021 (87.1)
Born in Australia					

	N[a]	Multimorbidity (MM)		Complex multimorbidity (CMM)	
		With MM n (%)	Without MM n (%)	With CMM n (%)	Without CMM n (%)
No	61166	22623 (37.0)	38543 (63.0)	8165 (13.3)	53001 (86.7)
Yes	188547	87495 (46.4)	101052 (53.6)	30924 (16.4)	157623 (83.6)
Household income					
<$20,000	49296	28472 (57.8)	20824 (42.2)	12260 (24.9)	37036 (75.1)
$20,000-39,999	43933	21581 (49.1)	22352 (50.9)	8030 (18.3)	35903 (81.7)
$40,000-69,999	44453	17613 (39.6)	26840 (60.4)	5534 (12.4)	38919 (87.6)
$70,000 or more	59794	20084 (33.6)	39710 (66.4)	5072 (8.5)	54722 (91.5)
Won't disclose	54213	23334 (43.0)	30879 (57.0)	8582 (15.8)	45631 (84.2)
Work status					
Not working	124277	69118 (55.6)	55159 (44.4)	28029 (22.6)	96248 (77.4)
Part time	47577	17175 (36.1)	30402 (63.9)	5223 (11.0)	42354 (89.0)
Full time	75540	23093 (30.6)	52447 (69.4)	5600 (7.4)	69940 (92.6)
Current partner (married/de facto)					
No	62245	31637 (50.8)	30608 (49.2)	12781 (20.5)	49464 (79.5)
Yes	187853	78720 (41.9)	109133 (58.1)	26443 (14.1)	161410 (85.9)
Current smoker					
No	233130	103890 (44.6)	129240 (55.4)	36883 (15.8)	196247 (84.2)
Yes	18552	7192 (38.8)	11360 (61.2)	2595 (14.0)	15957 (86.0)
Adequate physical activity[b]					
No	81815	39044 (47.7)	42771 (52.3)	15333 (18.7)	66482 (81.3)
Yes	169874	72040 (42.4)	97834 (57.6)	24145 (14.2)	145729 (85.8)
Alcohol consumption					
No	82068	39610 (48.3)	42458 (51.7)	16347 (19.9)	65721 (80.1)
Yes	164927	69308 (42.0)	95619 (58.0)	22229 (13.5)	142698 (86.5)
BMI category					
Under weight	26433	11326 (42.8)	15107 (57.2)	3972 (15.0)	22461 (85.0)
Normal weight	79040	30429 (38.5)	48611 (61.5)	9653 (12.2)	69387 (87.8)
Overweight	91879	40234 (43.8)	51645 (56.2)	13684 (14.9)	78195 (85.1)
Obese	54337	29095 (53.5)	25242 (46.5)	12169 (22.4)	42168 (77.6)
Self-reported good quality of life[c]					
No	25379	17190 (67.7)	8189 (32.3)	8912 (35.1)	16467 (64.9)
Yes	212841	89079 (41.9)	123762 (58.1)	28731 (13.5)	184110 (86.5)
Missing	13469	4815 (35.7)	8654 (64.3)	1835 (13.6)	11634 (86.4)
Psychological distress[d]					

	N[a]	Multimorbidity (MM)		Complex multimorbidity (CMM)	
		With MM n (%)	Without MM n (%)	With CMM n (%)	Without CMM n (%)
Low or Moderate	205402	84755 (41.3)	120647 (58.7)	27573 (13.4)	177829 (86.6)
High (22 or more)	18603	11239 (60.4)	7364 (39.6)	5712 (30.7)	12891 (69.3)
Missing	27684	15090 (54.5)	12594 (45.5)	6193 (22.4)	21491 (77.6)
Needing help with daily activity					
No	225634	96045 (42.6)	129589 (57.4)	31823 (14.1)	193811 (85.9)
Yes	13728	10269 (74.8)	3459 (25.2)	5606 (40.8)	8122 (59.2)
Missing	12327	4770 (38.7)	7557 (61.3)	2049 (16.6)	10278 (83.4)

[a]Missing value: Highest education (n=4235), speaks language other than English at home (n=3), born in Australia (n=1976), work status (n=4295), current partner (n=1591), current smoker (n=7), alcohol consumption (n=4694)
[b]Adequate physical activity was defined based on the amount of time spent on moderate and vigorous exercise in the last week of survey.
[c]Self-reported good quality of life was defined if people reported their quality of life was good, very good or excellent in response to the self-rated quality of life question.
[d]Psychological distress was categorised based on the K10 score that ranges between 10 and 50.

Survival probability for people with MM or CMM was significantly lower than for those without MM or CMM (p<0.001; Figure 2). Mortality was 2.5 times higher among people with MM compared to those without (20.3 versus 8.3 deaths/1000 person-years; Table 3). When adjusted for confounding, mortality was 36% (HR: 1.36; 95% CI: 1.32-1.40) higher among people with MM compared to those without. Absolute difference in deaths/1000 person-years between people with and without MM increased as age increased: 2.3 for 45-59 years, 6.0 for 60-74 years and 12.4 for 75 years and over, respectively. However, impact of MM on mortality decreased as age increased: adjusted HRs (95%CI) were 1.59 (1.46, 1.73) for 45-59 years, 1.49 (1.41, 1.57) for 60-74 years and 1.15 (1.11, 1.19) for 75 years and over.

Table 3: Impact of multimorbidity (MM) on 8-year mortality (from recruitment)

	N	Person-year (py)	No of deaths	Death rate per 1000 py	Crude HR (95% CI)	Adj. HR[2] (95% CI)
Overall						
With no MM	140605	1093798	9071	8.3	1	1
With MM	111084	828231	16820	20.3	2.47 (2.4, 2.53)	1.36 (1.32, 1.40)
Age 45-59[1]						

With no MM	78711	625463	1219	1.9	1	1
With MM	37374	294385	1241	4.2	2.16 (2.00, 2.34)	1.59 (1.46, 1.73)
Age 60-74						
With no MM	46290	361559	2625	7.3	1	1
With MM	46770	357454	4757	13.3	1.84 (1.75, 1.93)	1.49 (1.41, 1.57)
Age 75+						
With no MM	15604	106775	5227	49.0	1	1
With MM	26940	176392	10822	61.4	1.27 (1.23, 1.31)	1.15 (1.11, 1.19)

[1]p-interaction <0.05, age vs MM status

[2]Adjusted for sex, current working status, needing help with daily activities and good quality of life

Mortality was 2.2 times higher among people with CMM compared to those without (25.3 versus 11.4 deaths/1000 person-years; Table 4). When adjusted for confounding, mortality was 22% (HR: 1.22; 95% CI: 1.18-1.25) higher among people with CMM compared to those without. Absolute difference in deaths/1000 person-years between people with and without CMM increased as age increased: 3.4 for 45-59 years, 6.3 for 60-74 years and 13.2 for 75 years and over, respectively. However, impact of CMM on mortality decreased as age increased: adjusted HRs (95%CI) were 1.49 (1.33, 1.67) for 45-59 years, 1.29 (1.22, 1.36) for 60-74 years and 1.08 (1.04, 1.12) for 75 years and over.

Table 4: Impact of complex multimorbidity (CMM) on 8-year mortality (from recruitment)

	N	Person-year (py)	No of deaths	Death rate per 1000 py	Crude HR (95% CI)	Adj. HR[2] (95% CI)
Overall						
With no CMM	212211	1632781	18571	11.4	1	1
With CMM	39478	289248	7320	25.3	2.24 (2.18, 2.30)	1.22 (1.18, 1.25)
Age 45-59[1]						
With no CMM	105367	835879	1973	2.4	1	1
With CMM	10718	83970	487	5.8	2.46 (2.23, 2.72)	1.49 (1.33, 1.67)
Age 60-74						
With no CMM	75473	585544	5328	9.1	1	1
With complex CMM	17587	133469	2054	15.4	1.70 (1.61, 1.79)	1.29 (1.22, 1.36)
Age 75+						
With no CMM	31371	211358	11270	53.4	1	1
With CMM	11173	71809	4779	66.6	1.26 (1.22, 1.31)	1.08 (1.04, 1.12)

[1]p-interaction <0.05, age vs CMM status

[2]Adjusted for sex, current working status, needing help with daily activities and good quality of life.

DISCUSSION

This is the first population-based analysis of the effect of CMM on mortality in Australia. MM and CMM were present in 44.1% and 15.7% of people within this cohort, respectively. During eight years of follow-up, mortality in MM and CMM sub-groups was at least twice that of those without MM and CMM; 20.3 versus 8.3 deaths/1000 person-years, and 25.3 versus 11.4 deaths/1000 person-years, respectively. Adjusted risk of all-cause mortality was 36% higher for people with MM and 22% higher for people with CMM, compared to people not in either group. When adjusted risk of all-cause mortality due to MM and CMM was stratified by age, risk was highest in the youngest age group (45-59 years) and decreased towards the oldest age group (75 years or more). In our analysis, MM was found to have a greater impact on mortality than CMM; and both MM and CMM had the greatest impact on all-cause mortality in the youngest age group (45-59 years).

Our prevalence estimate for MM depends on self-reported survey data for 11 chronic conditions and is comparable with other Australian and international studies.[6 28 29] Prevalence of MM in the Australian 2017-18 National Health Survey involving 10 self-reported chronic conditions was 47% which is similar to our estimate.[6] However, five out of 10 conditions were different to those available in the 45 and Up Study baseline survey. Another Australian study estimated 37.4% prevalence for MM and 8.7% prevalence for CMM using the 45 and Up Study baseline survey data, but unlike our analysis they did not include allergic rhinitis, thrombosis and musculoskeletal conditions and only included participants with consistent concession card holder status in the Pharmaceutical Benefits Scheme (PBS) dataset (n=90,352).[28] A cross-sectional Scottish study reported MM prevalence ranging between 39% for people aged 55-66 years and 76% for people aged 75 years and over (which is similar to our estimates), while other studies have reported much higher prevalence among older adults.[5]

Several international studies have reported that MM and CMM are associated with a greater risk of mortality, but the effect size in most of the previous studies may not be directly comparable to our study because of the number and type of chronic conditions, different study designs, varying follow up time, and study population of different age groups.[14-16 30-32] Consistent with our study, a 2015 meta-analysis of 26 studies demonstrated greater mortality risk among older adults aged ≥65 years of age with MM compared to those without (HR: 1.44; 95% CI: 1.34-1.55).[14] More recently, the English Longitudinal Study of Aging reported lower mortality risk associated with MM (HR: 1.27; 95% CI: 1.14-1.43) among 9171 people aged ≥50 years, which may be related to a relatively older population (90% were aged ≥60 years) who were at a greater risk of mortality.[30] However, other US and Scottish studies reported significantly greater effects of MM on mortality compared to our analysis.[15 16] The Scottish study involved younger people (≥18 years of age), and considered severe conditions to be those needing hospitalisation, while the US study had different classes of multimorbidity. Though several studies have evaluated the effect of MM on mortality, relatively few have evaluated the effect of CMM on mortality.[31 32] A Japanese population-based cohort study evaluating the effects of MM and CMM on mortality among adults aged 65 and over reported lower and similar effects for both MM and CMM compared to our study (HR: 1.07; 95% CI: 1.01-1.14 for MM and HR: 1.07; 95% CI: 0.99-1.16 for CMM). However, a Norwegian population-based cohort study found 22% higher mortality risk in those with CMM aged 60-69 years (RR: 1.22; 95% CI: 1.12-1.33).[32]

While all-cause mortality overall was higher in our study for the older age groups the relative effect sizes for mortality risk for both MM and CMM was higher in adults aged 45-59 years compared to the older age groups. A study using the UK Biobank (n= 502,640) found similar results and concluded that this may be because most interventions to date have been directed at middle aged populations.[33] They therefore highlighted the need for algorithms that could identify these younger people with multimorbidity to provide earlier more targeted care. This phenomenon may also be explained, in

part, because early onset disease is often more aggressive and people are presenting later.[34 35] This again highlights the need for early diagnosis, treatment, and targeted care.

Risk of all-cause mortality associated with MM was found to be higher than mortality risk associated with CMM. This was unexpected given that CMM was proposed to be more specific in assessing the complexity of individual healthcare needs.[21] A possible reason for this finding is that our and other studies focused on prevalence of CMM and not the severity of illness.[23 36] For example, as Harrison et al identified, those with mild chronic conditions affecting three body systems, could have less healthcare needs than someone diagnosed with one severe chronic condition.[21] Also, the most prevalent MM and CMM combinations may not necessarily be the most severe. Another potential explanation for this finding could relate to cancer conditions being split and allocated by affected body system for CMM categorisation, rather than kept as a group. This meant those with cancer and other chronic conditions affecting less than three body systems were excluded from being categorised with CMM.

The finding MM was a better predictor of all-cause mortality risk than CMM suggests individuals with MM should be prioritised for intervention in clinical practice. That all-cause mortality risk was highest in the youngest age group (45-59 years) suggests tailored innovative healthcare interventions and better access to integrated care are needed for this age group. For example, the delivery of a nurse-led self-management program for COPD in the context of MM implemented in Australian general practice.[37] A holistic approach is required for healthcare management of MM, involving shared decision-making and care coordination across all levels of the health system. Particularly cardiovascular, respiratory, and mental health conditions which were the most prevalent domains in our study. Though CMM was not a better predictor of mortality than MM in our analysis, this finding needs further exploration and confirmation. As suggested in another Australian study, CMM could be

used to "examine the relationship between the number of diagnosed chronic conditions/body systems affected and overall severity of illness, complexity of care and health resource utilisation".[21]

The major strength of this study was our use of a large community-dwelling cohort of older adults which was not restricted only to those engaged with health services, thus providing a more realistic denominator. Recruitment of individuals across the age spectrum from 45 to 90 years to the 45 and Up Study at baseline enabled us to assess the impacts of MM and CMM on mortality across that age range. Also, to our knowledge, this is the first analysis to compare the effect of MM versus CMM on mortality.

Our study had several limitations. Though the 45 and Up Study cohort has been shown to be generally representative of the population from which it is drawn, non-response at baseline may mean the cohort varies slightly from the broader population. However, studies with relatively low response rates provide similar estimates to the studies with higher response rate.[38] There were some other important confounding variables, such as functional disability that we were unable to adjust for, and thus residual confounding is possible. Self-reported chronic conditions were considered without any clinical diagnosis, so misclassification might occur. We defined CMM based on patients' self-reported chronic conditions in the 45 and Up Study and used the ICPC-2 classification of disease, so it was not possible to classify the 11 chronic conditions reported in our study according to the exact body system, as in the clinically-coded and single disease-focussed International Classification of Diseases (ICD-10).
For example, treatment of cancer can affect the whole body, taking into account the side effects of anti-cancer drugs and radiotherapy, therefore lung cancer (though not reported separately in our study) would have the potential to affect the body in more ways than can be categorised as a respiratory disease. Another limitation was, we considered only those chronic conditions, which were listed in the baseline survey, but some other important chronic conditions, such as dyslipidemia, chronic kidney disease, blood disorders, and rheumatic diseases which also increase the risk of

mortality were not included in this study. As a result, the effect of MM or CMM might be underestimated due to non-differential misclassification bias. However, an Australian study exploring the concordance between the 45 and Up Study baseline survey and administrative healthcare datasets, found that over 70% of individuals classified as having MM were identified from the baseline survey.[28] A systematic review has also found that self-report is a valid method for capturing MM.[39] There might have some losses to follow up in our study cohort due to overseas or inter-state migration, but the estimated migration rate in 2011 in NSW population was ~3% which has unlikely to have any impact. [40]

Further research exploring patterns of healthcare utilisation, such as uptake of primary care chronic disease management plans, between those with MM and CMM would provide better understanding of our findings. Survey data could be combined with other data sources (PBS, Medicare Benefits Schedule, general practice clinic records and hospital administrative datasets) to assess whether our findings can be replicated when diverse data sources and a more extensive list of chronic conditions are used. Conducting research to explore how these associations may differ across health service regions in NSW, particularly between urban and rural settings, would also be beneficial. This would enable us to determine what works and does not work when managing those with MM across different settings.

Conclusion

MM and CMM were common in this large population-based cohort study of older adults in NSW, Australia. Mortality among people in MM and CMM sub-groups was high; with MM being a better predictor of all-cause mortality risk than CMM. However, further research is required with additional data on chronic conditions to confirm that MM is a better predictor for mortality than CMM. All-cause mortality risk being highest in the youngest age group (45-59 years) is an important finding which

indicates the need for tailored, person-centred integrated care interventions and better access to holistic healthcare for this age group.

Figure legends

Figure 1: Assembly of the analytic cohort

Figure 2: Kaplan-Meier curve- impact of multimorbidity (MM) and complex multimorbidity (CMM) on 8-year (from recruitment) mortality

Author's Contribution: All authors have substantially contributed to this manuscript and met the authorship criteria. AK, AT, SA, and MB conceived the study. AK, AT, SA, DPC, and MB contributed to the design, analysis and interpreting the results. AK drafted the manuscript and coordinated its revision, and all authors critically reviewed the manuscript. All authors read and approved the final version of the manuscript.

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Data availability statement: Data that support the findings of this study are available from the Sax Institute, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. The data are however available from the authors upon reasonable request and with permission of the Sax Institute.

Patient consent for publication: Not applicable.

Ethics approval: Ethical Approval was granted for this research project by the NSW Population and Health Services Research Ethics Committee (Ref # 2016/06/642) and from the University of NSW Human Research Ethics Committee for the 45 and Up Study overall.

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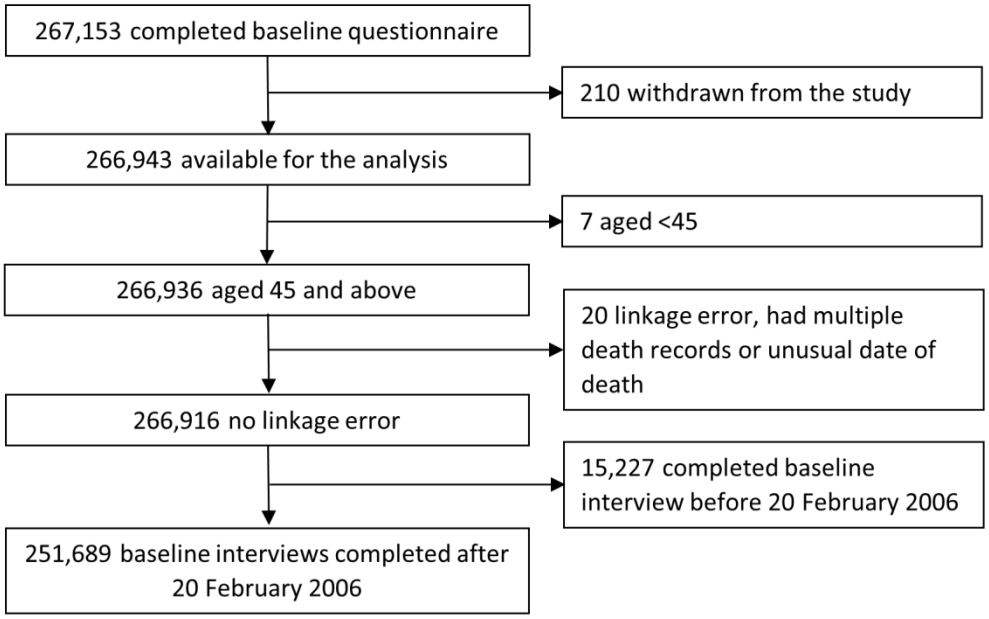
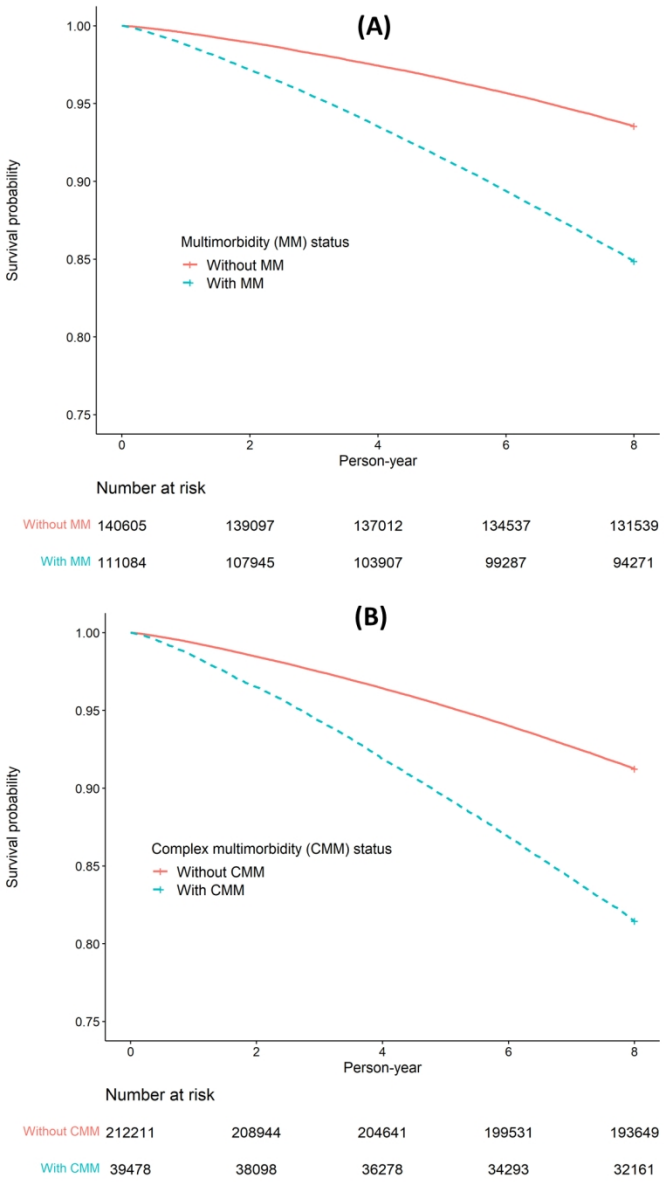


Assembly of the analytic cohort

145x99mm (300 x 300 DPI)



Kaplan-Meier curve- impact of multimorbidity (MM) and complex multimorbidity (CMM) on 8-year (from recruitment) mortality

99x180mm (300 x 300 DPI)

Supplementary Tables

Table S1: Characteristics variables, data sources and descriptions

Characteristics	Data source	Question	Categorisation for analysis
Demographic characteristics			
Age group	45 And Up Study Baseline	Self-reported age at baseline	45-59 years 60-74 75+
Gender	45 And Up Study Baseline	Self-reported sex	Male Female
Highest qualification	45 And Up Study Baseline	Self-reported highest level of educational qualification – categorised as	No school certificate or other qualification School or intermediate certificate Higher school or leaving certificate Trade or apprenticeship Certificate or diploma University degree or higher
Speaks a language other than English at home	45 And Up Study Baseline	Whether speaks a language other than English at home?	Yes: Speaks language other than English at home No: Speaks only English at home
Born in Australia	45 And Up Study Baseline	In which country where you born	No: Otherwise Yes: Born in Australia
Speaks language other than English at home	45 And Up Study Baseline	Do you speak a language other than English at home?	Yes No
Household income	45 And Up Study Baseline	Self-reported household income category	<$20,000 $20,000-39,999 $40,000-69,999 $70,000 or more Won't disclose
Work status	45 And Up Study Baseline	Working status at baseline	Not working Working part-time/full-time
Currently married/partnered	45 And Up Study Baseline	Current marital status: or not	Yes: currently married/partnered No: Not currently married/partnered
Health characteristics			
Current smoker	45 And Up Study Baseline	Smoking status at baseline	Yes: Currently smoking No: Non-smoker or ex-smoker
Adequate physical activity	45 And Up Study Baseline	Based on the amount of moderate and vigorous exercise reported: see AIHW definition	Yes: Adequate physical activity No: Inadequate physical activity
Alcohol consumption	45 And Up Study Baseline	Based on self-reported number of standard drinks each week, categorised as	zero low (1-14 drinks per week) high (>14 drinks per week)

Characteristics	Data source	Question	Categorisation for analysis
BMI	45 And Up Study Baseline	Calculation based on 2 questions: How tall are you without shoes? How much do you weigh?	Underweight: <18.5 Normal weight: 18.6-24.9 Overweight: 25.0-29.9 Obese: ≥30
Self-reported good quality of life	45 And Up Study Baseline	Based on self-rated quality of life question – classified as yes if responded as good; very good or excellent	Yes: Excellent, very good or good quality of life No: Fair or poor quality of life
Psychological distress-Index calculated based on 10 indicators	45 And Up Study Baseline	During the past 4 weeks about how often did you feel: Tired out for now good reason? Nervous? so nervous that nothing could calm you down? Hopeless? Restless or fidgety? So restless that you could not sit still? Depressed? That everything was an effort? So sad that nothing could cheer you up? Worthless?	1=None of the time 2=A little of the time 3=Some of the time 4=Most of the time 5=All the time Low= total score <22 High= total score >=22
Add Needing help with daily activity	45 And Up Study Baseline	Do you regularly need help with daily tasks because of long-term illness or disability	Yes No

The RECORD statement – checklist of items, extended from the STROBE statement, that should be reported in observational studies using routinely collected health data.

	Item No.	STROBE items	Location in manuscript where items are reported
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found	(a) Text document P1, P (b) Text document P2
Background rationale	2	Explain the scientific background and rationale for the investigation being reported	Text document P3-4
Objectives	3	State specific objectives, including any prespecified hypotheses	Text document P4
Study Design	4	Present key elements of study design early in the paper	Text document P4-5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Text document P4-5
Participants	6	*(a) Cohort study* - Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study* - Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study* - Give the eligibility criteria, and the sources and methods of selection of participants *(b) Cohort study* - For matched studies, give matching criteria and number of exposed and unexposed *Case-control study* - For matched studies, give matching criteria and the number of controls per case	(a) Text document P4
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.	Text document P5, and supplementary documen
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Text document P5
Bias	9	Describe any efforts to address potential sources of bias	Text document P6
Study size	10	Explain how the study size was arrived at	The study was based on extracting all available data for the study population. No sample size calculations were conducted. Figure 1.
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	Not applicable

Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) *Cohort study* - If applicable, explain how loss to follow-up was addressed *Case-control study* - If applicable, explain how matching of cases and controls was addressed *Cross-sectional study* - If applicable, describe analytical methods taking account of sampling strategy (e) Describe any sensitivity analyses	Text document P6
Data access and cleaning methods		..	
Linkage		..	Text document P5
Participants	13	(a) Report the numbers of individuals at each stage of the study (*e.g.*, numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed) (b) Give reasons for non-participation at each stage. (c) Consider use of a flow diagram	Text document P6 Text document Figure 1
Descriptive data	14	(a) Give characteristics of study participants (*e.g.*, demographic, clinical, social) and information on exposures and potential confounders (b) Indicate the number of participants with missing data for each variable of interest (c) *Cohort study* - summarise follow-up time (*e.g.*, average and total amount)	Text document Tables 1 & 2, P6, P10, P11 Tables 3 & 4
Outcome data	15	*Cohort study* - Report numbers of outcome events or summary measures over time *Case-control study* - Report numbers in each exposure category, or summary measures of exposure *Cross-sectional study* - Report numbers of outcome events or summary measures	Text document P10, P11, Tables 3 & 4
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Text document P10, P11, Tables 3 & 4
Other analyses	17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	Text document P10, P11, Tables 3 & 4
Key results	18	Summarise key results with reference to study objectives	Text document P11, P12

Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Text document P14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Text document P11-P14
Generalisability	21	Discuss the generalisability (external validity) of the study results	Text document P15
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Text document P16
Accessibility of protocol, raw data, and programming code			Text document P16

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Impact of multimorbidity and complex multimorbidity on mortality among older Australians aged 45 years and over: A large population-based record linkage study

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Impact of multimorbidity and complex multimorbidity on mortality among older Australians aged 45 years and over: A large population-based record linkage study

Alamgir Kabir,[1] An Tran,[1] Sameera Ansari,[2,3] Damian P Conway,[4,5] Margo Linn Barr[1]

[1]Centre for Primary Health Care and Equity, UNSW Sydney, NSW, Australia

[2]School of Population Health, UNSW Sydney, NSW, Australia

[3]Faculty of Health Sciences and Medicine, Bond University, QLD, Australia

[4]The Kirby Institute, UNSW Sydney, NSW, Australia

[5]Population and Community Health Directorate, South Eastern Sydney Local Health District, NSW, Australia

Corresponding author: Alamgir Kabir, Centre for Primary Health Care and Equity, Level 3, AGSM Building, UNSW Sydney NSW 2052 Australia, a.kabir@unsw.edu.au

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ABSTRACT

Objectives: Multimorbidity (MM; co-occurrence of two or more chronic conditions) and complex multimorbidity (CMM; three or more chronic conditions affecting three or more different body systems) are used in the assessment of complex healthcare needs and their impact on health outcomes. However, little is known about the impacts of MM and CMM on mortality in Australia.

Design: Community-based prospective cohort study.

Setting: New South Wales, Australia.

Participants: People aged 45 years and over who completed the baseline survey of the 45 and Up Study.

Measures: Baseline survey data from the 45 and Up Study were linked with deaths registry data. Deaths occurred within eight years from the baseline survey date were the study outcome. Eleven self-reported chronic conditions (cancer, heart disease, diabetes, stroke, Parkinson's disease, depression/anxiety, asthma, allergic rhinitis, hypertension, thrombosis and musculoskeletal conditions) from the baseline survey were included in the MM and CMM classification. Cox proportional hazard models were used to estimate adjusted and unadjusted 8-year mortality hazard ratios.

Results: Of 251,689 people (53% female and 54% aged ≥60 years) in the cohort, 111,084(44.1%) were classified as having MM and 39,478(15.7%) as having CMM. During the 8-year follow-up, there were 25,891 deaths. Cancer (34.7%) was the most prevalent chronic conditions and cardiovascular (50.9%) was the most affected body system with a chronic condition. MM and CMM were associated with a 37% (Adj.HR: 1.36, 95%CI:1.32-1.40) and a 22% (Adj.HR: 1.22, 95%CI: 1.18-1.25) increased risk of death, respectively. The relative impact of MM and CMM on mortality decreased as age increased.

Conclusions: MM and CMM were common in older Australian adults; MM was a better predictor of all-cause mortality risk than CMM. Higher mortality risk in those aged 45-59 years indicates tailored, person-centred integrated care interventions and better access to holistic healthcare are needed for this age group.

Strengths and limitations of this study

- A large population-based prospective cohort study of people aged 45 years and over was used to evaluate the effect of multimorbidity and complex multimorbidity on 8-year mortality.
- Self-reported chronic health conditions were used to define multimorbidity and complex multimorbidity.
- Deaths registry data was probabilistically linked to the cohort data by the NSW Centre for Health Record Linkage for mortality surveillance.
- Though the study cohort has been shown to be generally representative of the population from which it is drawn, non-response at recruitment may mean the cohort varies slightly from the broader population.
- Our analysis was restricted to the conditions listed in the 45 and Up Study baseline survey questionnaire, however this included all of the most important chronic conditions.

INTRODUCTION

Multimorbidity (MM), the co-occurrence of two or more chronic health conditions in an individual, is often used in the assessment of complex healthcare needs and their impact on health outcomes.[1] As life expectancy increases over time due to advances in healthcare and living standards, the burden of chronic conditions is increasing globally.[2] Consequently, the proportion of national healthcare expenditure spent caring for people with MM has increased substantially. For example, managing MM accounts for 71% of total US healthcare spending.[3] While overall prevalence of MM is 33% globally,[4] prevalence among those aged 65 years or more is estimated to be 55-98% in high-income countries.[5] In Australia, estimated prevalence of MM is 20% overall and 51% among those aged 65 years or more.[6]

MM is associated with increased risk of adverse mental and physical health outcomes,[7 8] and poor quality of life overall.[9 10] However, reported effects of MM on mortality in older adults are mixed: some studies report MM is associated with greater risk of mortality,[11-16] while others report no significant association.[17 18] A systematic review found an increased risk of mortality among those with MM, but noted the majority of studies were not population-based, had relatively small sample sizes and/or lacked internal validity.[14] Also, many studies reported the impact of MM on mortality among older adults overall without stratifying outcomes by age group. Though some Australian studies demonstrated an association between MM and mortality, these studies were not population-based and have limited generalisability.[19 20]

Some authors have proposed complex multimorbidity (CMM; co-occurrence of three or more chronic conditions affecting three or more different body systems) as an alternative and more specific metric to assess complexity of individual healthcare needs.[19 21] This metric provides lower prevalence estimates than MM and allows greater differentiation amongst older adults.[19] However, whether it enables more targeted patient care and health resource planning requires further investigation. To our knowledge, there have not been any published evaluations comparing the impact of MM and

CMM on older adult mortality in Australia. Hence, we conducted a large population-based data linkage study to: (i) compare the effect of MM and CMM on mortality among older adults aged 45 and above; and (ii) assess whether any observed effect on mortality varies by age group.

METHODS

Study design and population

We conducted a prospective cohort study of people aged 45 years and over from New South Wales (NSW), Australia enrolled in the Sax Institute's 45 and Up Study with 8-year follow-up from recruitment. People who completed the baseline survey questionnaire of the 45 and Up Study and who did not withdraw from the study were our study population. The 45 and Up Study is a large-scale population-based cohort study comprising 267,153 men and women aged 45 years and over. Detail of the study has been described elsewhere.[22] In brief, potential study participants aged 45 years or older in NSW were randomly sampled from the Services Australia (formerly the Australian Government Department of Human Services) Medicare enrolment database, which provides near complete coverage of the population and invited to participate between 2006 and 2009. However, people aged 80+ years from rural and remote areas were oversampled; about 18% of those invited participated and participants included about 11% of the NSW population aged 45 years and over. Participants consented to self-completing the baseline questionnaire and to long-term follow-up with linkage of survey data to other administrative health records. Data collected via baseline survey included socio-demographic and lifestyle characteristics, and self-reported chronic conditions. We excluded people from the study population who had completed their baseline data before 20 February 2006 as the death records were only available from that date.

Data linkage and outcome ascertainment

All deaths between 20 February 2006 and 30 September 2018 recorded in the NSW Registry of Births, Deaths and Marriages were probabilistically linked to 45 and Up Study data by the NSW Centre for Health Record Linkage. Follow-up time for mortality was set at eight years from baseline survey as baseline data collection was completed in December 2009 and the latest available deaths registry data was from September 2018. All-cause mortality occurring within eight years of recruitment was our outcome of interest.

Multimorbidity and complex multimorbidity ascertainment

Self-reported chronic health conditions were ascertained from responses to two 45 and Up Study baseline survey questions: "Has a doctor ever told you that you have (name of condition)?" and "In the last month have you been treated for (name of condition)?". If the response was "Yes" for either question for a condition, we considered the person had the condition. These included cancer (all types), heart disease, diabetes, stroke, Parkinson's disease, depression, anxiety, asthma, allergic rhinitis, hypertension, thrombosis, and musculoskeletal conditions. Accordingly, participants were classified as having MM (two or more chronic conditions at baseline) and/or CMM (three or more chronic conditions affecting three or more body systems at baseline; Table 1).[23] To define CMM, we first classified the 11 chronic conditions into nine groups according to the body system: cardiovascular, musculoskeletal, neurological, psychological, respiratory, skin, endocrine/metabolic, female genital, and male genital.[24] Conditions that occurred in different body parts (e.g. cancer at different sites) were grouped into one condition for the MM measure, but were classified into different body-systems depending on the sites.

Statistical analysis

Continuous variables were categorised and included one additional category for missing values if there are ≥5% missing values. Psychological distress was measured using the Kessler Psychological Distress Scale (K10) and categorised as low and moderate (<22) and high (≥22).[25] Participant characteristics were compared for those with and without MM or CMM using chi-squared tests. We conducted a

time-to-event analysis to measure impacts of MM and CMM on mortality. Follow-up time started at the date of baseline data collection and was censored at death or the date when participants completed 8-year follow-up, whichever came first. We generated Kaplan-Meier survival curves for people with and without MM or CMM and used log-rank tests for comparison. Death rate was calculated using person-time at-risk as the denominator. Crude and adjusted hazard ratios (HRs) with 95% confidence intervals (95%CIs) were estimated using univariate and multiple Cox proportional hazard models. The potential confounders were selected based on the following steps: first, we selected those variables for the base model which were found to be associated with multi-morbidity or complex multi-morbidity at $p<0.20$ using a chi-squared test; second, we applied the change-in-estimate strategy using the "chest" package in R.[26 27] We then assessed potential effect modification for age groups, as there was a large variation in age at baseline, by adding an interaction term into the Cox proportional hazard model. If the interaction term was significant at $p<0.05$, we did a stratified analysis by age. We set 5% as the significance level for all statistical tests. We used R 3.6.3 software (R Foundation, Vienna, Austria) for data analysis and SAS 9.4 (SAS Institute, Cary, NC) for data management.

Patient and public involvement

Patients or public were not involved in design, management or reporting of our study.

RESULTS

The analytic cohort comprised 251,689 people aged 45 years and over (Figure 1). The percentage of the cohort assessed to have multi-morbidity was 44.1% (95%CI: 43.9-44.3) with the most frequent chronic conditions being cancer (34.7%), followed by hypertension (31.0%) and depression or anxiety (18.4%) (Table 1). The percentage of the cohort assessed to have complex multi-morbidity was 15.7% (95%CI: 15.5-15.8) and the cardiovascular system was the most prevalent body system (50.9%) followed by respiratory (22.0%) and psychological (18.4%).

Table 1: Percentage of self-reported chronic conditions among older adults aged 45 years and over by condition and by body system

	n	Prevalence (95% CI)
Morbidity		
Cancer[a]	87386	34.7 (34.5, 34.9)
Heart disease[b]	32690	13.0 (12.9, 13.1)
Diabetes	22575	9.0 (8.9, 9.1)
Parkinson's disease	1566	0.6 (0.6, 0.7)
Stroke	7893	3.1 (3.1, 3.2)
Depression or anxiety	46343	18.4 (18.3, 18. 6)
Asthma[c]	31316	12.4 (12.3, 12.6)
Allergic rhinitis[c]	34509	13.7 (13.6, 13.9)
Hypertension	78135	31.0 (30.9, 31.2)
Thrombosis	13834	5.5 (5.4, 5.6)
Musculoskeletal conditions[d]	29986	11.9 (11.8, 12.0)
Multimorbidity (MM, >=2 morbidities)	111084	44.1 (43.9, 44.3)
Body system morbidity: any conditions within these systems[e]		
Cardiovascular	128069	50. 9 (50.7, 51.1)
Musculoskeletal	35272	14.0 (13.9, 14.2)
Neurological	1566	0.6 (0.6, 0.7)
Psychological	46343	18.4 (18.3, 18. 6)
Respiratory	55279	22.0 (21.8, 22.1)
Skin	13811	5.5 (5.4, 5.6)
Endocrine/Metabolic	33533	13.3 (13.2, 13.5)
Female genital[f]	7300	2.9 (2.8, 3.0)
Male genital[g]	23850	9.5 (9.4, 9.6)
Complex multimorbidity (CMM, >=3 body system)	39478	15.7 (15.5, 15.8)

[a]Cancer includes melanoma, breast cancer (F), prostate cancer (M) and other cancer.
[b]Heart disease includes heart attack, angina or other heart disease.
[c]Asthma and allergic rhinitis were collected as aggregated for the first ~15% people, but they were separated for the remaining people.
[d]Musculoskeletal includes osteoarthritis, osteoporosis or low bone density.
[e]Body system morbidities- cardiovascular includes heart disease, high blood pressure, blood clot (thrombosis), heart attack or angina and other heart disease; musculoskeletal includes osteoarthritis, osteoporosis or low bone density; neurological includes Parkinson's disease; psychological includes depression or anxiety; respiratory includes asthma or allergic rhinitis; skin includes melanoma; endocrine/metabolic includes diabetes and thyroid problems; female genital includes breast cancer; male genital includes prostate cancer or enlarged prostate.
[f]Denominator for this estimate was total number of female participants.
[g]Denominator for this estimate was total number of male participants.

Participants baseline characteristics (see the supplementary material for detail descriptions) by morbidity status are presented in Table 2. All baseline characteristics except current smoking status were significantly ($p<0.001$) different between people with and without MM, while all baseline characteristics were significantly different between people with and without CMM. The proportion of the cohort categorised as having MM and CMM increased with increasing age, but the proportion decreased with increasing household income. People not working, self-reporting fair/poor quality of life or having high levels of psychological distress had significantly higher proportions of MM and CMM than those not in these groups.

Table 2: Percentage of multimorbidity (MM) and complex multimorbidity (CMM) by characteristics for the study participants

	N[a]	Multimorbidity (MM)		Complex multimorbidity (CMM)	
		With MM n (%)	Without MM n (%)	With CMM n (%)	Without CMM n (%)
Age at baseline					
45-59	116085	37374 (32.2)	78711 (67.8)	10718 (9.2)	105367 (90.8)
60-74	93060	46770 (50.3)	46290 (49.7)	17587 (18.9)	75473 (81.1)
75+	42544	26940 (63.3)	15604 (36.7)	9229 (26.3)	31371 (73.7)
Gender					
Male	117059	52750 (45.1)	64309 (54.9)	17463 (14.9)	99596 (85.1)
Female	134630	58334 (43.3)	76296 (56.7)	22015 (16.4)	112615 (83.6)
Highest education					
No school certificate or other qualification	29344	15328 (52.2)	14016 (47.8)	6216 (21.2)	23128 (78.8)
School, intermediate, higher school or leaving certificate	79784	35877 (45.0)	43907 (55.0)	12949 (16.2)	66835 (83.8)
Trade, apprenticeship, Certificate or diploma	80141	35328 (44.1)	44813 (55.9)	12291 (15.3)	67850 (84.7)
University degree or higher	58185	22581 (38.8)	35604 (61.2)	7246 (12.5)	50939 (87.5)
Speaks language other than English at home					
No	227541	102934 (45.2)	124607 (54.8)	36354 (16.0)	191187 (84.0)
Yes	24145	8149 (33.8)	15996 (66.2)	3124 (12.9)	21021 (87.1)
Born in Australia					
No	61166	22623 (37.0)	38543 (63.0)	8165 (13.3)	53001 (86.7)
Yes	188547	87495 (46.4)	101052 (53.6)	30924 (16.4)	157623 (83.6)
Household income					
<$20,000	49296	28472 (57.8)	20824 (42.2)	12260 (24.9)	37036 (75.1)
$20,000-39,999	43933	21581 (49.1)	22352 (50.9)	8030 (18.3)	35903 (81.7)
$40,000-69,999	44453	17613 (39.6)	26840 (60.4)	5534 (12.4)	38919 (87.6)

	N[a]	Multimorbidity (MM)		Complex multimorbidity (CMM)	
		With MM n (%)	Without MM n (%)	With CMM n (%)	Without CMM n (%)
$70,000 or more	59794	20084 (33.6)	39710 (66.4)	5072 (8.5)	54722 (91.5)
Won't disclose	54213	23334 (43.0)	30879 (57.0)	8582 (15.8)	45631 (84.2)
Work status					
Not working	124277	69118 (55.6)	55159 (44.4)	28029 (22.6)	96248 (77.4)
Part time	47577	17175 (36.1)	30402 (63.9)	5223 (11.0)	42354 (89.0)
Full time	75540	23093 (30.6)	52447 (69.4)	5600 (7.4)	69940 (92.6)
Current partner (married/de facto)					
No	62245	31637 (50.8)	30608 (49.2)	12781 (20.5)	49464 (79.5)
Yes	187853	78720 (41.9)	109133 (58.1)	26443 (14.1)	161410 (85.9)
Current smoker					
No	233130	103890 (44.6)	129240 (55.4)	36883 (15.8)	196247 (84.2)
Yes	18552	7192 (38.8)	11360 (61.2)	2595 (14.0)	15957 (86.0)
Adequate physical activity[b]					
No	81815	39044 (47.7)	42771 (52.3)	15333 (18.7)	66482 (81.3)
Yes	169874	72040 (42.4)	97834 (57.6)	24145 (14.2)	145729 (85.8)
Alcohol consumption					
No	82068	39610 (48.3)	42458 (51.7)	16347 (19.9)	65721 (80.1)
Yes	164927	69308 (42.0)	95619 (58.0)	22229 (13.5)	142698 (86.5)
BMI category					
Under weight	26433	11326 (42.8)	15107 (57.2)	3972 (15.0)	22461 (85.0)
Normal weight	79040	30429 (38.5)	48611 (61.5)	9653 (12.2)	69387 (87.8)
Overweight	91879	40234 (43.8)	51645 (56.2)	13684 (14.9)	78195 (85.1)
Obese	54337	29095 (53.5)	25242 (46.5)	12169 (22.4)	42168 (77.6)
Self-reported good quality of life[c]					
No	25379	17190 (67.7)	8189 (32.3)	8912 (35.1)	16467 (64.9)
Yes	212841	89079 (41.9)	123762 (58.1)	28731 (13.5)	184110 (86.5)
Missing	13469	4815 (35.7)	8654 (64.3)	1835 (13.6)	11634 (86.4)
Psychological distress[d]					
Low or Moderate	205402	84755 (41.3)	120647 (58.7)	27573 (13.4)	177829 (86.6)
High (22 or more)	18603	11239 (60.4)	7364 (39.6)	5712 (30.7)	12891 (69.3)
Missing	27684	15090 (54.5)	12594 (45.5)	6193 (22.4)	21491 (77.6)
Needing help with daily activity					
No	225634	96045 (42.6)	129589 (57.4)	31823 (14.1)	193811 (85.9)
Yes	13728	10269 (74.8)	3459 (25.2)	5606 (40.8)	8122 (59.2)
Missing	12327	4770 (38.7)	7557 (61.3)	2049 (16.6)	10278 (83.4)

[a]Missing value: Highest education (n=4235), speaks language other than English at home (n=3), born in Australia (n=1976), work status (n=4295), current partner (n=1591), current smoker (n=7), alcohol consumption (n=4694)

[b]Adequate physical activity was defined based on the amount of time spent on moderate and vigorous exercise in the last week of survey.

[c]Self-reported good quality of life was defined if people reported their quality of life was good, very good or excellent in response to the self-rated quality of life question.

[d]Psychological distress was categorised based on the K10 score that ranges between 10 and 50.

Survival probability for people with MM or CMM was significantly lower than for those without MM or CMM (p<0.001; Figure 2). Mortality was 2.5 times higher among people with MM compared to those without (20.3 versus 8.3 deaths/1000 person-years; Table 3). When adjusted for confounding, mortality was 36% (HR: 1.36; 95% CI: 1.32-1.40) higher among people with MM compared to those without. Absolute difference in deaths/1000 person-years between people with and without MM increased as age increased: 2.3 for 45-59 years, 6.0 for 60-74 years and 12.4 for 75 years and over, respectively. However, impact of MM on mortality decreased as age increased: adjusted HRs (95%CI) were 1.59 (1.46, 1.73) for 45-59 years, 1.49 (1.41, 1.57) for 60-74 years and 1.15 (1.11, 1.19) for 75 years and over.

Table 3: Impact of multimorbidity (MM) on 8-year mortality (from recruitment)

	N	Person-year (py)	No of deaths	Death rate per 1000 py	Crude HR (95% CI)	Adj. HR[2] (95% CI)
Overall						
With no MM	140605	1093798	9071	8.3	1	1
With MM	111084	828231	16820	20.3	2.47 (2.4, 2.53)	1.36 (1.32, 1.40)
Age 45-59[1]						
With no MM	78711	625463	1219	1.9	1	1
With MM	37374	294385	1241	4.2	2.16 (2.00, 2.34)	1.59 (1.46, 1.73)
Age 60-74						
With no MM	46290	361559	2625	7.3	1	1
With MM	46770	357454	4757	13.3	1.84 (1.75, 1.93)	1.49 (1.41, 1.57)
Age 75+						
With no MM	15604	106775	5227	49.0	1	1
With MM	26940	176392	10822	61.4	1.27 (1.23, 1.31)	1.15 (1.11, 1.19)

[1]p-interaction <0.05, age vs MM status

[2]Adjusted for sex, current working status, needing help with daily activities and good quality of life

Mortality was 2.2 times higher among people with CMM compared to those without (25.3 versus 11.4 deaths/1000 person-years; Table 4). When adjusted for confounding, mortality was 22% (HR: 1.22; 95% CI: 1.18-1.25) higher among people with CMM compared to those without. Absolute difference in deaths/1000 person-years between people with and without CMM increased as age increased: 3.4 for 45-59 years, 6.3 for 60-74 years and 13.2 for 75 years and over, respectively. However, impact of CMM on mortality decreased as age increased: adjusted HRs (95%CI) were 1.49 (1.33, 1.67) for 45-59 years, 1.29 (1.22, 1.36) for 60-74 years and 1.08 (1.04, 1.12) for 75 years and over.

Table 4: Impact of complex multimorbidity (CMM) on 8-year mortality (from recruitment)

	N	Person-year (py)	No of deaths	Death rate per 1000 py	Crude HR (95% CI)	Adj. HR[2] (95% CI)
Overall						
With no CMM	212211	1632781	18571	11.4	1	1
With CMM	39478	289248	7320	25.3	2.24 (2.18, 2.30)	1.22 (1.18, 1.25)
Age 45-59[1]						
With no CMM	105367	835879	1973	2.4	1	1
With CMM	10718	83970	487	5.8	2.46 (2.23, 2.72)	1.49 (1.33, 1.67)
Age 60-74						
With no CMM	75473	585544	5328	9.1	1	1
With complex CMM	17587	133469	2054	15.4	1.70 (1.61, 1.79)	1.29 (1.22, 1.36)
Age 75+						
With no CMM	31371	211358	11270	53.4	1	1
With CMM	11173	71809	4779	66.6	1.26 (1.22, 1.31)	1.08 (1.04, 1.12)

[1]p-interaction <0.05, age vs CMM status

[2]Adjusted for sex, current working status, needing help with daily activities and good quality of life.

DISCUSSION

This is the first population-based analysis of the effect of CMM on mortality in Australia. MM and CMM were present in 44.1% and 15.7% of people within this cohort, respectively. During eight years of follow-up, mortality in MM and CMM sub-groups was at least twice that of those without MM and CMM; 20.3 versus 8.3 deaths/1000 person-years, and 25.3 versus 11.4 deaths/1000 person-years, respectively. Adjusted risk of all-cause mortality was 36% higher for people with MM and 22% higher for people with CMM, compared to people not in either group. When adjusted risk of all-cause mortality due to MM and CMM was stratified by age, risk was highest in the youngest age group (45-59 years) and decreased towards the oldest age group (75 years or more). In our analysis, MM was found to have a greater impact on mortality than CMM; and both MM and CMM had the greatest impact on all-cause mortality in the youngest age group (45-59 years).

Our prevalence estimate for MM depends on self-reported survey data for 11 chronic conditions and is comparable with other Australian and international studies.[6 28 29] Prevalence of MM in the Australian 2017-18 National Health Survey involving 10 self-reported chronic conditions was 47% which is similar to our estimate.[6] However, five out of 10 conditions were different to those available in the 45 and Up Study baseline survey. Another Australian study estimated 37.4% prevalence for MM and 8.7% prevalence for CMM using the 45 and Up Study baseline survey data, but unlike our analysis they did not include allergic rhinitis, thrombosis and musculoskeletal conditions and only included participants with consistent concession card holder status in the Pharmaceutical Benefits Scheme (PBS) dataset (n=90,352).[28] A cross-sectional Scottish study reported MM prevalence ranging between 39% for people aged 55-66 years and 76% for people aged 75 years and over (which is similar to our estimates), while other studies have reported much higher prevalence among older adults.[5]

Several international studies have reported that MM and CMM are associated with a greater risk of mortality, but the effect size in most of the previous studies may not be directly comparable to our study because of the number and type of chronic conditions, different study designs, varying follow up time, and study population of different age groups.[14-16 30-32] Consistent with our study, a 2015 meta-analysis of 26 studies demonstrated greater mortality risk among older adults aged ≥65 years of age with MM compared to those without (HR: 1.44; 95% CI: 1.34-1.55).[14] More recently, the English Longitudinal Study of Aging reported lower mortality risk associated with MM (HR: 1.27; 95% CI: 1.14-1.43) among 9171 people aged ≥50 years, which may be related to a relatively older population (90% were aged ≥60 years) who were at a greater risk of mortality.[30] However, other US and Scottish studies reported significantly greater effects of MM on mortality compared to our analysis.[15 16] The Scottish study involved younger people (≥18 years of age), and considered severe conditions to be those needing hospitalisation, while the US study had different classes of multimorbidity. Though several studies have evaluated the effect of MM on mortality, relatively few have evaluated the effect of CMM on mortality.[31 32] A Japanese population-based cohort study evaluating the effects of MM and CMM

on mortality among adults aged 65 and over reported lower and similar effects for both MM and CMM compared to our study (HR: 1.07; 95% CI: 1.01-1.14 for MM and HR: 1.07; 95% CI: 0.99-1.16 for CMM). However, a Norwegian population-based cohort study found 22% higher mortality risk in those with CMM aged 60-69 years (RR: 1.22; 95% CI: 1.12-1.33).[32]

While all-cause mortality overall was higher in our study for the older age groups the relative effect sizes for mortality risk for both MM and CMM was higher in adults aged 45-59 years compared to the older age groups. A study using the UK Biobank (n= 502,640) found similar results and concluded that this may be because most interventions to date have been directed at middle aged populations.[33] They therefore highlighted the need for algorithms that could identify these younger people with multimorbidity to provide earlier more targeted care. This phenomenon may also be explained, in part, because early onset disease is often more aggressive and people are presenting later.[34 35] This again highlights the need for early diagnosis, treatment, and targeted care.

Risk of all-cause mortality associated with MM was found to be higher than mortality risk associated with CMM. This was unexpected given that CMM was proposed to be more specific in assessing the complexity of individual healthcare needs.[21] A possible reason for this finding is that our and other studies focused on prevalence of CMM and not the severity of illness.[23 36] For example, as Harrison et al identified, those with mild chronic conditions affecting three body systems, could have less healthcare needs than someone diagnosed with one severe chronic condition.[21] Also, the most prevalent MM and CMM combinations may not necessarily be the most severe. Another potential explanation for this finding could relate to cancer conditions being split and allocated by affected body system for CMM categorisation, rather than kept as a group. This meant those with cancer and other chronic conditions affecting less than three body systems were excluded from being categorised with CMM.

The finding MM was a better predictor of all-cause mortality risk than CMM suggests individuals with MM should be prioritised for intervention in clinical practice. That all-cause mortality risk was highest in the youngest age group (45-59 years) suggests tailored innovative healthcare interventions and better access to integrated care are needed for this age group. For example, the delivery of a nurse-led self-management program for COPD in the context of MM implemented in Australian general practice.[37] A holistic approach is required for healthcare management of MM, involving shared decision-making and care coordination across all levels of the health system. Particularly cardiovascular, respiratory, and mental health conditions which were the most prevalent domains in our study. Though CMM was not a better predictor of mortality than MM in our analysis, this finding needs further exploration and confirmation. As suggested in another Australian study, CMM could be used to "examine the relationship between the number of diagnosed chronic conditions/body systems affected and overall severity of illness, complexity of care and health resource utilisation".[21]

The major strength of this study was our use of a large community-dwelling cohort of older adults which was not restricted only to those engaged with health services, thus providing a more realistic denominator. Recruitment of individuals across the age spectrum from 45 to 90 years to the 45 and Up Study at baseline enabled us to assess the impacts of MM and CMM on mortality across that age range. Also, to our knowledge, this is the first analysis to compare the effect of MM versus CMM on mortality.

Our study had several limitations. Though the 45 and Up Study cohort has been shown to be generally representative of the population from which it is drawn, non-response at baseline may mean the cohort varies slightly from the broader population. However, studies with relatively low response rates provide similar estimates to the studies with higher response rate.[38] There were some other important confounding variables, such as functional disability that we were unable to adjust for, and thus residual confounding is possible. Self-reported chronic conditions were considered without any clinical

diagnosis, so misclassification might occur. We defined CMM based on patients' self-reported chronic conditions in the 45 and Up Study and used the ICPC-2 classification of disease, so it was not possible to classify the 11 chronic conditions reported in our study according to the exact body system, as in the clinically-coded and single disease-focussed International Classification of Diseases (ICD-10).

For example, treatment of cancer can affect the whole body, taking into account the side effects of anti-cancer drugs and radiotherapy, therefore lung cancer (though not reported separately in our study) would have the potential to affect the body in more ways than can be categorised as a respiratory disease. Another limitation was, we considered only those chronic conditions, which were listed in the baseline survey, but some other important chronic conditions, such as dyslipidemia, chronic kidney disease, blood disorders, and rheumatic diseases which also increase the risk of mortality were not included in this study. As a result, the effect of MM or CMM might be underestimated due to non-differential misclassification bias. However, an Australian study exploring the concordance between the 45 and Up Study baseline survey and administrative healthcare datasets, found that over 70% of individuals classified as having MM were identified from the baseline survey.[28] A systematic review has also found that self-report is a valid method for capturing MM.[39] There might have some losses to follow up in our study cohort due to overseas or inter-state migration, but the estimated migration rate in 2011 in NSW population was ~3% which has unlikely to have any impact. [40]

Further research exploring patterns of healthcare utilisation, such as uptake of primary care chronic disease management plans, between those with MM and CMM would provide better understanding of our findings. Survey data could be combined with other data sources (PBS, Medicare Benefits Schedule, general practice clinic records and hospital administrative datasets) to assess whether our findings can be replicated when diverse data sources and a more extensive list of chronic conditions are used. Conducting research to explore how these associations may differ across health service regions in NSW, particularly between urban and rural settings, would also be beneficial. This would

enable us to determine what works and does not work when managing those with MM across different settings.

Conclusion

MM and CMM were common in this large population-based cohort study of older adults in NSW, Australia. Mortality among people in MM and CMM sub-groups was high; with MM being a better predictor of all-cause mortality risk than CMM. However, further research is required with additional data on chronic conditions to confirm that MM is a better predictor for mortality than CMM. All-cause mortality risk being highest in the youngest age group (45-59 years) is an important finding which indicates the need for tailored, person-centred integrated care interventions and better access to holistic healthcare for this age group.

Figure legends

Figure 1: Assembly of the analytic cohort

Figure 2: Kaplan-Meier curve- impact of multimorbidity (MM) and complex multimorbidity (CMM) on 8-year (from recruitment) mortality

Author's Contribution: All authors have substantially contributed to this manuscript and met the authorship criteria. AK, AT, SA, and MB conceived the study. AK, AT, SA, DPC, and MB contributed to the design, analysis and interpreting the results. AK drafted the manuscript and coordinated its revision, and all authors critically reviewed the manuscript. All authors read and approved the final version of the manuscript.

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Data availability statement: Data that support the findings of this study are available from the Sax Institute, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. The data are however available from the authors upon reasonable request and with permission of the Sax Institute.

Patient consent for publication: Not applicable.

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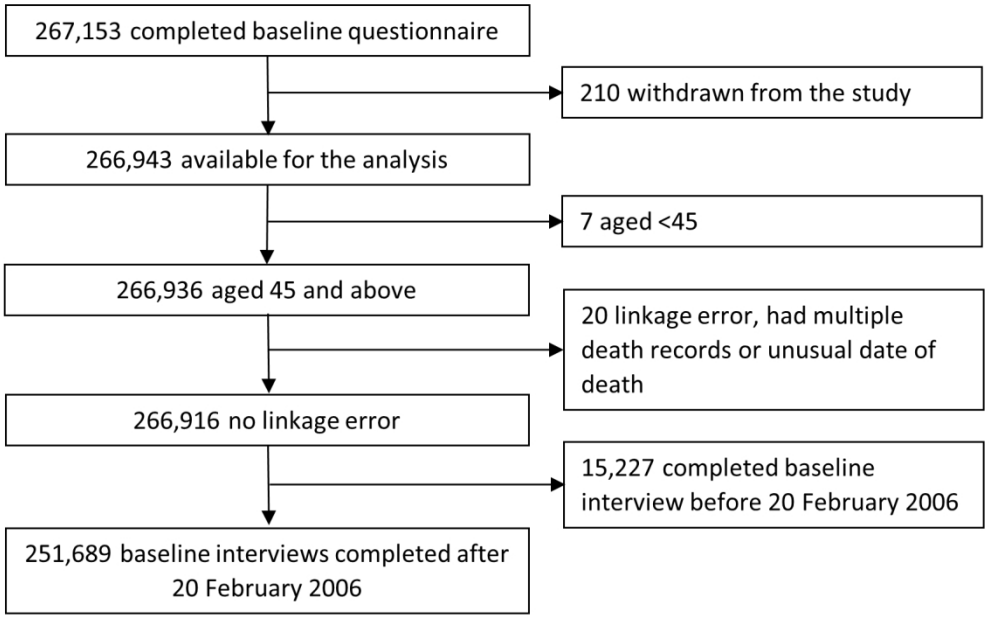

Figure 1: Assembly of the analytic cohort

145x99mm (300 x 300 DPI)

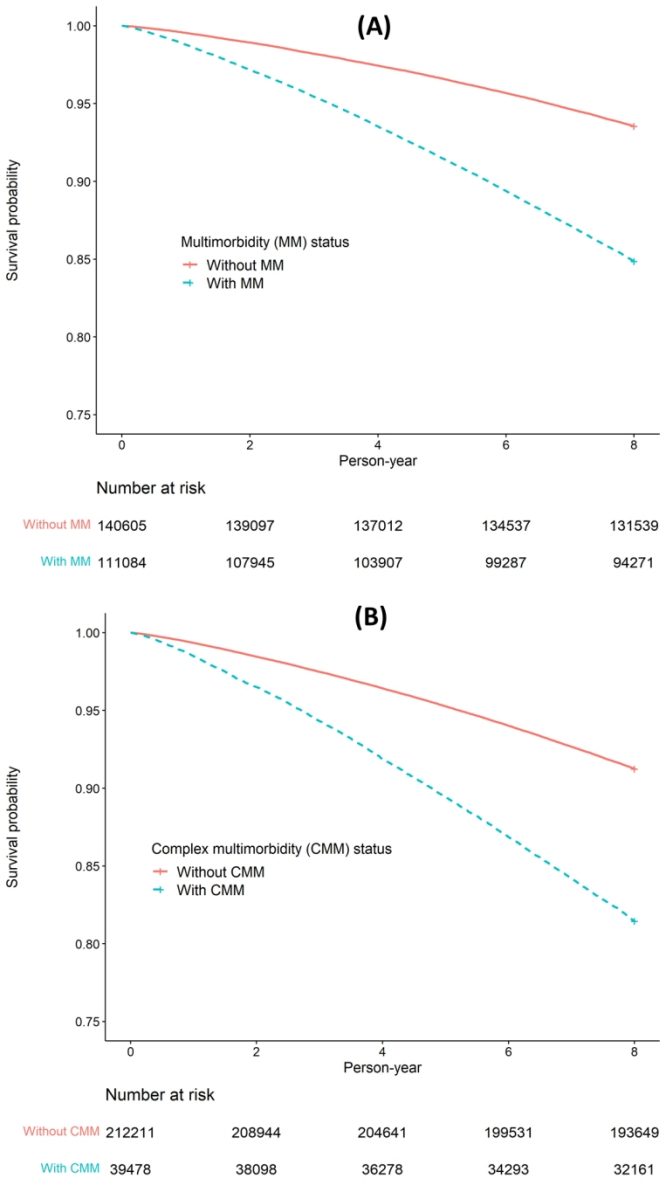

Figure 2: Kaplan-Meier curve- impact of multimorbidity (MM) and complex multimorbidity (CMM) on 8-year (from recruitment) mortality

99x180mm (300 x 300 DPI)

Supplementary Tables

Table S1: Characteristics variables, data sources and descriptions

Characteristics	Data source	Question	Categorisation for analysis
Demographic characteristics			
Age group	45 And Up Study Baseline	Self-reported age at baseline	45-59 years 60-74 75+
Gender	45 And Up Study Baseline	Self-reported sex	Male Female
Highest qualification	45 And Up Study Baseline	Self-reported highest level of educational qualification – categorised as	No school certificate or other qualification School or intermediate certificate Higher school or leaving certificate Trade or apprenticeship Certificate or diploma University degree or higher
Speaks a language other than English at home	45 And Up Study Baseline	Whether speaks a language other than English at home?	Yes: Speaks language other than English at home No: Speaks only English at home
Born in Australia	45 And Up Study Baseline	In which country where you born	No: Otherwise Yes: Born in Australia
Speaks language other than English at home	45 And Up Study Baseline	Do you speak a language other than English at home?	Yes No
Household income	45 And Up Study Baseline	Self-reported household income category	<$20,000 $20,000-39,999 $40,000-69,999 $70,000 or more Won't disclose
Work status	45 And Up Study Baseline	Working status at baseline	Not working Working part-time/full-time
Currently married/partnered	45 And Up Study Baseline	Current marital status: or not	Yes: currently married/partnered No: Not currently married/partnered
Health characteristics			
Current smoker	45 And Up Study Baseline	Smoking status at baseline	Yes: Currently smoking No: Non-smoker or ex-smoker
Adequate physical activity	45 And Up Study Baseline	Based on the amount of moderate and vigorous exercise reported: see AIHW definition	Yes: Adequate physical activity No: Inadequate physical activity
Alcohol consumption	45 And Up Study Baseline	Based on self-reported number of standard drinks each week, categorised as	zero low (1-14 drinks per week) high (>14 drinks per week)

Characteristics	Data source	Question	Categorisation for analysis
BMI	45 And Up Study Baseline	Calculation based on 2 questions: How tall are you without shoes? How much do you weigh?	Underweight: <18.5 Normal weight: 18.6-24.9 Overweight: 25.0-29.9 Obese: ≥30
Self-reported good quality of life	45 And Up Study Baseline	Based on self-rated quality of life question – classified as yes if responded as good; very good or excellent	Yes: Excellent, very good or good quality of life No: Fair or poor quality of life
Psychological distress-Index calculated based on 10 indicators	45 And Up Study Baseline	During the past 4 weeks about how often did you feel: Tired out for now good reason? Nervous? so nervous that nothing could calm you down? Hopeless? Restless or fidgety? So restless that you could not sit still? Depressed? That everything was an effort? So sad that nothing could cheer you up? Worthless?	1=None of the time 2=A little of the time 3=Some of the time 4=Most of the time 5=All the time Low= total score <22 High= total score >=22
Add Needing help with daily activity	45 And Up Study Baseline	Do you regularly need help with daily tasks because of long-term illness or disability	Yes No

The RECORD statement – checklist of items, extended from the STROBE statement, that should be reported in observational studies using routinely collected health data.

	Item No.	STROBE items	Location in manuscript where items are reported
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found	(a) Text document P1, P (b) Text document P2
Background rationale	2	Explain the scientific background and rationale for the investigation being reported	Text document P3-4
Objectives	3	State specific objectives, including any prespecified hypotheses	Text document P4
Study Design	4	Present key elements of study design early in the paper	Text document P4-5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Text document P4-5
Participants	6	*(a) Cohort study* - Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study* - Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study* - Give the eligibility criteria, and the sources and methods of selection of participants *(b) Cohort study* - For matched studies, give matching criteria and number of exposed and unexposed *Case-control study* - For matched studies, give matching criteria and the number of controls per case	(a) Text document P4
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.	Text document P5, and supplementary documen
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Text document P5
Bias	9	Describe any efforts to address potential sources of bias	Text document P6
Study size	10	Explain how the study size was arrived at	The study was based on extracting all available data for the study population. No sample size calculations were conducted. Figure 1.
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	Not applicable

Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) *Cohort study* - If applicable, explain how loss to follow-up was addressed *Case-control study* - If applicable, explain how matching of cases and controls was addressed *Cross-sectional study* - If applicable, describe analytical methods taking account of sampling strategy (e) Describe any sensitivity analyses	Text document P6
Data access and cleaning methods		..	
Linkage		..	Text document P5
Participants	13	(a) Report the numbers of individuals at each stage of the study (*e.g.*, numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed) (b) Give reasons for non-participation at each stage. (c) Consider use of a flow diagram	Text document P6 Text document Figure 1
Descriptive data	14	(a) Give characteristics of study participants (*e.g.*, demographic, clinical, social) and information on exposures and potential confounders (b) Indicate the number of participants with missing data for each variable of interest (c) *Cohort study* - summarise follow-up time (*e.g.*, average and total amount)	Text document Tables 1 & 2, P6, P10, P11 Tables 3 & 4
Outcome data	15	*Cohort study* - Report numbers of outcome events or summary measures over time *Case-control study* - Report numbers in each exposure category, or summary measures of exposure *Cross-sectional study* - Report numbers of outcome events or summary measures	Text document P10, P11, Tables 3 & 4
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Text document P10, P11, Tables 3 & 4
Other analyses	17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	Text document P10, P11, Tables 3 & 4
Key results	18	Summarise key results with reference to study objectives	Text document P11, P12

Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Text document P14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Text document P11-P14
Generalisability	21	Discuss the generalisability (external validity) of the study results	Text document P15
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Text document P16
Accessibility of protocol, raw data, and programming code			Text document P16