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A multistate model of health transitions in older people: a secondary analysis of ASPREE clinical trial data

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JTN, JMT, AMT, and JJM contributed to study conceptualisation.

RLW, AMM, and JJM contributed to funding acquisition. JTN, LTPT, and RW accessed and verified the data. RLW, JDW, ABN, AMM, MEE, AMT, JJM, and SGO contributed to the investigation. LTPT, SGO, RW, and GP contributed to data curation. LTPT, RW, and GP contributed to the formal analysis. JTN, LTPT, EC, PRC, VQ, AMT, and JJM contributed to writing the original manuscript draft. MRN, CMR, RLW, SGO, RW, GP, JDW, JMT, ABN, AMM, and MEE contributed to reviewing and editing the manuscript. SGO contributed to project administration. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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Declaration of interests

We declare no competing interests.

Data sharing

With publication of this Article and upon request, individual deidentified participant data that underlie the reported results (text, tables, figures, and appendix), metadata, a data dictionary, and a copy of the clinical trial consent form will be made available. Requests for data access can be made via the ASPREE principal investigators (details can be found at www.ASPREE.org). Data will be made available to investigators whose proposed use has been approved by a review committee identified for this purpose. Access will be through a web-based data portal safe haven based at Monash University, Melbourne, VIC, Australia. The statistical analysis plan for the ASPREE trial has been published.³⁹

For the ASPREE study protocol see <https://aspree.org/>

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Summary

Background—Understanding the nature of transitions from a healthy state to chronic diseases and death is important for planning health-care system requirements and interventions. We aimed to quantify the trajectories of disease and disability in a population of healthy older people.

Methods—We conducted a secondary analysis of data from the ASPREE trial, which was done in 50 sites in Australia and the USA and recruited community-dwelling, healthy individuals who were aged 70 years or older (65 years for Black and Hispanic people in the USA) between March 10, 2010, and Dec 24, 2014. Participants were followed up with annual face-to-face visits, biennial assessments of cognitive function, and biannual visits for physical function until death or June 12, 2017, whichever occurred first. We used multistate models to examine transitions from a healthy state to first intermediate disease events (ie, cancer events, stroke events, cardiac events, and physical disability or dementia) and, ultimately, to death. We also examined the effects of age and sex on transition rates using Cox proportional hazards regression models.

Findings—19 114 participants with a median age of 74·0 years (IQR 71·6–77·7) were included in our analyses. During a median follow-up of 4·7 years (IQR 3·6–5·7), 1933 (10·1%) of 19 114 participants had an incident cancer event, 487 (2·5%) had an incident cardiac event, 398 (2·1%) had an incident stroke event, 924 (4·8%) developed persistent physical disability or dementia, and 1052 (5·5%) died. 15 398 (80·6%) individuals did not have any of these events during follow-up. The highest proportion of deaths followed incident cancer (501 [47·6%] of 1052) and 129 (12·3%) participants transitioned from disability or dementia to death. Among 12 postulated transitions, transitions from the intermediate states to death had much higher rates than transitions from a healthy state to death. The progression rates to death were 158 events per 1000 person-years (95% CI 144–172) from cancer, 112 events per 1000 person-years (86–145) from stroke, 88 events per 1000 person-years (68–111) from cardiac disease, 69 events per 1000 person-years (58–82) from disability or dementia, and four events per 1000 person-years (4–5) from a healthy state. Age was significantly associated with an accelerated rate for most transitions. Male sex (vs female sex) was significantly associated with an accelerate rate for five of 12 transitions.

Interpretation—We describe a multistate model in a healthy older population in whom the most common transition was from a healthy state to cancer. Our findings provide unique insights into the frequency of events, their transition rates, and the impact of age and sex. These results have implications for preventive health interventions and planning for appropriate levels of residential care in healthy ageing populations.

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Introduction

Mortality in middle-aged adults (eg, 45–65 years) has fallen sharply over the past 50 years in most high-income countries. This decrease has been driven primarily by a continuous decline in deaths from cardiovascular disease in this age group.¹ More than 80% of adults in these countries now survive beyond 70 years, often in relatively good health.² However, with

progression into the eighth and ninth decades of life, there are increasing rates of transition from good health to chronic disease and then to death, often with an intervening period of physical disability, cognitive disability, or both.

Although population ageing is occurring across most high-income countries, and increasingly also in low-income and middle-income countries, there is sparse knowledge about the health trajectories of older age groups. Rates of transition from one state to another are known to vary according to risk factors, such as age, sex, and social circumstances.^{3–5} Understanding the nature and rate of these transitions is important for planning health-care system requirements and interventions. Examples of disease transition modelling have been previously reported but have typically focused on discrete conditions, such as cardiovascular disease or cancer.^{6–8} However, with advancing age, health increasingly involves the development of chronic illnesses, which are associated with varying risks of disability and mortality, underscoring the need to identify the broader determinants of health impairment.

Multistate models allow for the description and estimation of the risk of an individual transitioning from one health state to another.^{9–14} Several previous studies have developed limited multistate models applicable to ageing populations. The Leiden 85-plus study¹¹ investigated the risk of transitions between different states of disability in 597 older individuals (aged ≥85 years), and the Vitality 90+ study¹² evaluated predictors of disability and multimorbidity in older populations (aged ≥90 years). One study also discussed the relevance of multimorbidity for the transition to death in the Whitehall II cohort.¹⁴ However, the development of more all-encompassing models requires comprehensive ongoing data acquisition that is rarely available from cohort studies.

The ASPREE trial offers a unique, highly detailed data resource for the construction of a multistate model broadly applicable to a healthy older age group. ASPREE was a randomised controlled trial, which recruited community-dwelling, healthy, older adults who were free of clinically evident cardiovascular disease, dementia, or disability, with a high likelihood of 5-year survival. Participants were rigorously followed up with systematic ascertainment of the common diseases of ageing and regular assessment of cognitive function and physical disability.^{15–17} The extensive phenotyping of trial participants presents a unique opportunity to explore the full range of health state transition probabilities relevant to this age group. The aim of our study was to identify and quantify the trajectories of ageing from an initially healthy state to intermediate disease states, and, ultimately, to death.

Methods

Study design and participants

The ASPREE trial dataset and results have been previously described.^{15–18} Briefly, ASPREE was a randomised, double-blind, placebo-controlled, clinical trial comparing the effect of 100 mg/day of oral aspirin versus placebo on the primary endpoint of disability-free survival. Between March 10, 2010, and Dec 24, 2014, the trial recruited 19 114 community-dwelling, initially healthy individuals without a previous history of cardiovascular events, dementia, or major physical disabilities who were aged 70 years or older (≥65 years for

Black and Hispanic individuals in the USA) from 16 sites in Australia and 34 sites in the USA; the rationale for the lower age cutoff for minority ethnic individuals was based on the fact that, in the USA, they have a lower life expectancy than White people. At study entry, participants were required to be well functioning, defined as being cognitively unimpaired and able to perform the Katz activities of daily living with minimal difficulty.

Exclusion criteria were any previous cardiovascular diseases (eg, myocardial infarction, angina pectoris, coronary artery revascularisation, heart failure, stroke, or transient ischaemic attack), previously diagnosed atrial fibrillation, uncontrolled blood pressure ($\geq 180/105$ mmHg), a history of dementia (or a Modified Mini-Mental State Examination score of ≤ 7), or major difficulty or inability to perform any one of the six basic Katz activities of daily living. Although potential participants were not routinely excluded if they had a personal history of cancer, those with any serious illness with a life expectancy of less than 5 years (based on the judgement of their physician) or those with known active cancer were excluded; the 5-year timeframe was selected because it represented the duration of intervention.

All participants provided written informed consent. The ASPREE study was approved by local ethics committees and is registered on [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01038583) (NCT01038583) and the International Standard Randomised Controlled Trial Number Registry (ISRCTN83772183). The ASPREE study protocol is available online.

Procedures

Participants were followed up with annual face-to-face visits, biennial assessments of cognitive function, and biannual assessments for physical function, which alternated after the initial baseline assessment, as previously described.¹⁵ Follow-up was continued until death or June 12, 2017, whichever occurred first.¹⁹

For our analyses, the following incident events were used to define different health states: cardiac events (eg, myocardial infarction and hospitalisation for heart failure); stroke events (eg, haemorrhagic stroke, ischaemic stroke, ischaemic stroke with haemorrhagic transformation, sub-arachnoid haemorrhagic stroke, and stroke with undetermined origin); cancer events (any incident cancer diagnosis except non-melanoma skin cancer); persistent physical disability or dementia; and death. All these events were adjudicated by expert committees masked to treatment allocation and following standardised procedures. These events were selected because cancer, cardiac disease, dementia, and cerebrovascular disease are the major causes of disability-adjusted life-years lost among people older than 70 years and in the Australian population,²⁰ from which the majority of study participants were drawn. Disability-free survival, defined as survival free of persistent physical disability and dementia, was the prespecified primary endpoint of the trial, and cardiac events, stroke events, cancer events, persistent physical disability or dementia, and death were prespecified secondary outcomes.¹⁵

Physical disability was defined as having severe difficulty in performing, or an inability to perform, at least one of the six basic activities of daily living.¹⁹ Physical disability was considered to be persistent if it was reconfirmed 6 months after the initial assessment (ie,

activity remained impaired on reassessment). The definition of dementia was based on the criteria of the Diagnostic and Statistical Manual of Mental Disorders (version 4) and used an extensive screening and confirmation process.²¹ Information on death was collected from close contacts, physicians, public death notices, and by linkage to the Australian National Death Index and the US National Death Index.¹⁷ We combined physical disability and dementia in order for our analyses to be parsimonious and because they represent important reasons why individuals lose the ability to live independently.

Statistical analysis

Overall, the ASPREE trial did not show that aspirin had a significant influence on the primary outcome and therefore we combined the aspirin-treated and placebo groups for the current analyses.¹⁵ We postulated a semi-Markov, six-state model with 12 transitions to capture possible major health conditions of a participant over time (figure 1). Specifically, all participants began in the initial healthy state at baseline, which was defined as the timepoint of study entry. When a first event occurred, participants could move from their current state to one of the intermediate states (ie, incident cancer, incident cardiac disease, incident stroke, or physical disability or dementia) or to death as the final absorbing state. Importantly, due to the small number of events and to keep the model graspable, we did not consider all possible transitions between intermediate states. As previous cancer diagnoses might have impacted our findings, we also did post-hoc sensitivity analyses excluding participants with a history of cancer at study entry.

To quantify the effect of baseline risk factors (ie, age and sex) on transition rates, we used Cox proportional hazards regression for each transition separately. We assumed that each transition was associated with a separate baseline hazard and that covariate effects differed for each transition. In all models, a clock-forward approach was used in which each transition was modelled by use of a single time scale: time since entering the initial state.²² Due to the large number of tests, all formal comparisons for covariate effects were considered exploratory.

To estimate the expected duration of a particular health condition, we calculated the probabilities of entering each state and the mean state occupation times (at the end of the 5-year follow-up) for four basic demographic profiles: male and aged 75 years, female and aged 75 years, male and aged 85 years, and female and aged 85 years. These two age values were chosen because 75.0 years (SD 4.5) was the mean age of the cohort, and 85 years was additionally included to illustrate the effect of ageing. All analyses were done by use of R (version 4.0) and the *mstate* package for the multistate models.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

19 114 participants with a median age of 74.0 years (IQR 71.6–77.7) were included (table 1; appendix p 2). Among them, 56.4% were female, 10.7% had diabetes, 74.3% had

hypertension, and 19.2% had a history of cancer at baseline (table 1). During the median follow-up time of 4.7 years (IQR 3.6–5.7), 1933 (10.1%) participants had an incident cancer event, 487 (2.5%) had an incident cardiac event, and 398 (2.1%) had an incident stroke event (table 2). Furthermore, 924 (4.8%) participants developed persistent physical disability or dementia and 1052 (5.5%) died (table 2). 15 398 (80.6%) individuals did not have any of these events during follow-up. 296 (1.5%) participants were lost to follow-up and 237 (1.2%) withdrew consent (appendix p 2). Of all 19 114 participants at risk of transitioning from a healthy state, 1849 (9.7%) transitioned to cancer, 425 (2.2%) transitioned to cardiac events, 328 (1.7%) transitioned to stroke events, and 819 (4.3%) transitioned to disability or dementia as their first intermediate state, and 295 (1.5%) transitioned directly to death (figure 1).

Of the 1849 participants who had incident cancer as their first event, 51 (2.8%) progressed to disability or dementia, 501 (27.1%) progressed to death, and 1297 (70.1%) remained in the cancer state (figure 1). In total, 924 participants entered the disability or dementia state, in which 795 (86.0%) remained and 129 (14.0%) subsequently died. Despite the focus on first events, the model captured 96% of all observed cancer events, 88% of cardiac events, 82% of stroke events, 100% of physical disability or dementia events, and 100% of deaths in the study. We observed similar findings for transition rates in a post-hoc sensitivity analysis in which we excluded participants with a history of cancer (appendix p 3). Because participants can develop events in a different order to that in the multistate model we developed, the number of events captured by our model is not necessarily 100%.

Among 12 postulated transitions, transitions from the intermediate states (cancer, cardiac disease, stroke, or physical disability or dementia) to death had much higher rates than that from a healthy state to death (figure 1; appendix pp 4, 6). The progression rates to death were 158 events per 1000 person-years (95% CI 144–172) from cancer, 112 events per 1000 person-years (86–145) from stroke, 88 events per 1000 person-years (68–111) from cardiac disease, 69 events per 1000 person-years (58–82) from disability or dementia, and 4 events per 1000 person-years (4–5) from a healthy state (figure 1; appendix p 6).

Among transitions to the disability or dementia state, transition from stroke had the highest rate (55 events per 1000 person-years, 95% CI 37–79), followed by transition from cardiac disease (32 events per 1000 person-years, 21–48), cancer (16 events per 1000 person years, 12–21), and a healthy state (11 events per 1000 person-years, 10–12; figure 1). When stratified by sex and age, men (*vs* women) and participants aged 75 years or older (*vs* <75 years) had an accelerated rate of transition to death from most of the intermediate adverse health conditions (appendix p 5). For example, the rate of transition to death from cancer in participants aged 75 years or older (223 events per 1000 person-years) was double that in participants younger than 75 years (110 events per 1000 person-years; appendix p 5). Compared with women, male participants had a higher rate of transition from disability or dementia to death (94 events per 1000 person-years *vs* 49 events per 1000 person-years; appendix p 5).

The detailed effects of age and sex on transition rates are presented in figure 2 and the appendix (p 7). Increasing age was strongly associated with all transitions, except for

stroke to disability or dementia. Specifically, a 5-year increase in age doubled the risk of transitioning to death from a healthy state (hazard ratio [HR] 1.99, 95% CI 1.80–2.20; appendix p 7). A 5-year increase in age also increased the risk of developing disability or dementia among participants with cardiac diseases (HR 1.97, 95% CI 1.39–2.79) and the risk of dying after a stroke (HR 1.88, 1.52–2.34). Compared with men, women were half as likely to develop incident cardiac disease, transition from previous cancer to disability or dementia, and transition from previous disability or dementia to death (appendix p 7).

For 75-year-old participants, the probabilities of death at 5 years were 7.03% for men and 4.13% for women (figure 3A, B; appendix p 8), which were considerably lower than those for 85-year-old men (21.91%) and women (13.51%; figure 3C, D; appendix p 8). The probability of being in the disability or dementia state at 5 years was also higher for 85-year-old participants (11.90% for men and 12.70% for women) than for 75-year-old participants (4.75% for men and 4.52% for women). By contrast, the probability of remaining in the healthy state at 5 years was higher in 75-year-old participants (73.91% for men and 82.00% for women) than in 85-year-old participants (52.58% for men and 63.93% for women). Within the same age group, women were more likely to remain in the healthy state and less likely to die than were men (appendix p 8).

Expected years of life spent in each state during 5 years of follow-up are presented in the appendix (p 9) for the four demographic profiles. If participants were healthy at age 75 years, the expected total life remaining was 4.87 years for men and 4.93 years for women, with a longer time spent in the healthy state for women (4.60 years) than for men (4.40 years). Compared with participants who were healthy at age 75 years, participants who were healthy at age 85 years had a shorter expected remaining time spent in the healthy state (3.89 years for men and 4.20 years for women). Participants aged 85 years were also estimated to spend a longer time in the disability or dementia state than were participants aged 75 years (0.27 years for men and women vs 0.09 years for men and women).

Discussion

In this Article, we describe the transition rates from a healthy, well functioning state to intermediate disease states or death during a median of 4.7 years of follow-up among participants recruited to the ASPREE trial. The development of persistent physical disability or dementia were prespecified outcomes of the ASPREE trial, which together were regarded as a surrogate for a loss of independence.

In our analyses, we report four salient findings. First, most individuals (80.6%) remained in a healthy state during follow-up, reflecting the relatively healthy status of the participants entering the study. Second, cancer dominated as the most common reason for leaving the healthy state, with a rate of incident cancer per 1000 person-years more than double that of cardiac disease, stroke, disability or dementia, or death. In previous analyses using data from the ASPREE trial, prostate, colorectal, and breast cancers were the most common incident cancers.²³ We found that transition to death after a diagnosis of cancer was also substantially higher than after a diagnosis of incident stroke, cardiac disease, or disability or dementia. However, the strict screening procedures at baseline (eg, excluding people with a history of

cardiovascular events) probably led to a lower-than-expected rate of cardiovascular events. Third, only 105 (11.4%) of 924 participants who developed persistent physical disability or dementia did so following the intermediate health states of stroke, cardiac disease, or cancer. Not surprisingly, the transition rate to disability or dementia was substantially greater after stroke than after cardiac disease or cancer.^{24,25} Finally, increasing age was strongly associated with increased risk for almost all transitions. Transition rates across states remained proportionally similar among participants aged 75 years or older and among those younger than 75 years, but absolute rates were higher among participants 75 years or older than among participants younger than 75 years. Furthermore, most transitions occurred at a substantially lower rate in women than in men.

The application of this modelling approach was possible because of the detailed outcome data (eg, on cancer) collected in the contemporary ASPREE trial. This dataset provided the opportunity to observe a large population of relatively healthy participants screened for the presence of previous cardiac disease events, cognitive impairment, and other potentially life-limiting conditions. Most importantly, in accordance with trial procedures, participants were continuously followed up until death or the end of follow-up, regardless of intervening events, making the dataset valuable for multistate modelling.

Our analyses have important implications. Most individuals remained in a healthy state, albeit during a moderate timeframe of approximately 5 years. The average life remaining for people aged 65 years is 18.2 years for men and 20.8 years for women in the USA and 20.0 years for men and 22.7 years for women in Australia.²⁶ These projections include those who already have chronic disease and those who are healthy, underscoring the possible gains from effective prevention. Prevention might be at an individual level through engagement with health-care professionals or at a population-wide level to diminish the impact of risk factors that are often shared between different diseases and that might be targeted by common evidence-based interventions. One specific aspect of disease prevention is targeted cancer screening in older people. Cancer screening is somewhat controversial, and the relatively high incidence of cancer observed in our analyses highlights the importance of this debate.^{27,28}

Our findings are also relevant for health economics and planning. Approximately 1.3 million individuals are currently in residential care in the USA, most of whom have a physical or mental disability.²⁹ Delaying the onset of chronic disease offers the greatest economic benefit, both within and outside of health systems (cross-health system benefit).³⁰ In 2020, the Decade of Healthy Ageing collaboration was introduced by WHO to stimulate improvements in the lives of older individuals.³¹ An improved understanding of ageing and the prevention of transition from an initially healthy state to chronic disease, loss of independence, and death is becoming increasingly important for those formulating health policy and strategies.

Many countries are facing rapidly ageing populations with reduced independence due to acute and chronic diseases, leading to increased demand for health services and high costs for treatment and residential care.³² Epidemiological modelling based on accurate information regarding time spent in various health states will assist in prioritising preventive

interventions and guiding resource allocation. Such modelling could, for example, be used to estimate the required resources for residential care if local public health data with sufficient detail were available. In the future, more detailed modelling could also consider a broader range of illnesses and health states and account for other changes (eg, in secular disease patterns and the ethnic mix of a population). Ultimately, approaches to improve the lives of older people, particularly those geared towards prevention, will be most effective if a longer-term perspective is applied.

Several previous observational studies have used multistate models to estimate the risk of recurrent events in patients with chronic conditions, such as cancer, diabetes, or heart failure.^{9,33–36} For example, the Leiden 85-plus study¹¹ investigated the risk of transitions between different states of disability in 597 older Dutch individuals (aged 85 years) and found depression, chronic diseases, and cognitive impairment to be the most relevant predictors of deterioration of specific health conditions. The Newcastle 85+ study³⁷ reported sex-specific differences in predictors for disability and death and the Vitality 90+ study¹² evaluated predictors for disability and multimorbidity in older individuals (aged 90 years). In the Whitehall II study,³⁸ the investigators used multistate modelling to assess risk factors for different cardiovascular diseases states. However, none of these studies had detailed access to information about participants' transitions from health, to chronic illness, to disability or dementia, and to death. This information was available in a study of 754 community-dwelling participants aged 70 years or older in the USA, from which the investigators developed a multistate model to evaluate different states of disability and the transition to death.¹³ The authors reported a high frequency of transitions between states and highlighted the relevance of frailty. However, no data on intermediate health states were collected. By contrast to these previous studies, the ASPREE trial provides several unique aspects that makes it highly suitable for multistate analyses. For instance, at study entry, all participants were screened to confirm their healthy status. Furthermore, the trial protocol ensured a continuous follow-up and the collection of multiple, adjudicated outcome events and measures of cognitive function.

Our study has some limitations. First, our analyses were based on a dataset with strict trial inclusion criteria and a healthy volunteer bias. Thus, our results are not fully representative of a typical population of older individuals, a substantial proportion of which is usually already affected by chronic disease, disability, or dementia. However, our results are likely to reflect the later life course of the substantial proportion of individuals who enter older age in a relatively healthy state, free of overt cardiovascular disease, physical disability, or considerable cognitive impairment. Such representation is important because the incidence of cardiovascular disease has substantially decreased with time in high-income countries.²⁵ Second, we developed a simplified model that did not include all possible interstate transitions, reverse transitions, or cause-specific mortality. However, our decision to simplify the model was based on the fact that transition models with additional states can become very complex and difficult to interpret, partly because of the smaller numbers that arise when stratifying events by a larger number of states. We also included both acute and chronic health conditions, and combined physical disability and dementia. Although these simplifications might not be appropriate in predictive modelling or clinical decision making, we aimed instead to describe an overview of trajectories leading to the end of independent

living. We also did not include other potential factors in our analyses, such as social determinants, multimorbidity, or ethnicity, which might have affected transitions. Third, we acknowledge that 19.2% of ASPREE participants had a history of cancer, which could have influenced the incidence of cancer during follow-up. However, at baseline, all participants were required to have an estimated life expectancy of at least 5 years and only 113 (5.8%) of 1933 incident cancer diagnoses were a recurrence of a cancer diagnosed before entry to ASPREE.²³ Finally, our results were derived from populations in two high-income countries with high health-care standards. Australia also has a universal health-care system for people aged 75 years or older, whereas the Medicare programme in the USA (a federal agency that administers health-care services) varies in its health-care coverage.

In conclusion, we have described transitions to intermediate health states and to death in an initially healthy, older population. These findings have potential implications for preventive cancer screening and planning for residential care in healthier ageing populations. The application of a multistate model provides unique insights into the frequency of events, their transition rates, and the impact of age and sex.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Research in context

Evidence before this study

Because life expectancy is progressively increasing in many countries, there is a corresponding need to understand the risk of individuals transitioning from healthy states to chronic disease states and death. We searched PubMed without language restrictions for population-based studies published between database inception and May 9, 2021, that evaluated transitions between different health states using the search terms “multi-state model”, “transitions”, “trajectories”, and “population health”. We found seven studies that used multistate models to estimate trajectories between different health conditions, but, due to sparse data, these models did not fully cover the transition from health to chronic disease and death.

Added value of this study

We describe the trajectories of ageing in a population of healthy, older people and show that the most common transition was from health to cancer, which affected 10.1% of participants. Disability or dementia, a surrogate of loss of independence, occurred in 4.8% of participants, but only 12.3% of deaths were preceded by disability or dementia. Importantly, 80.6% of participants remained healthy. We also examined the effects of age and sex on transition rates. Age was significantly associated with an accelerated rate for most transitions. Male sex (*vs* female sex) was significantly associated with an accelerated rate for five of 12 transitions.

Implications of all the available evidence

Our findings provide important evidence relevant for residential care requirements and underscore the possible gains from effective prevention strategies in ageing populations. Prevention might be at an individual level through engagement with health-care professionals or at a population-wide level (eg, via screening) to diminish the impact of risk factors that are often shared between different diseases and that might be targeted by common evidence-based interventions.

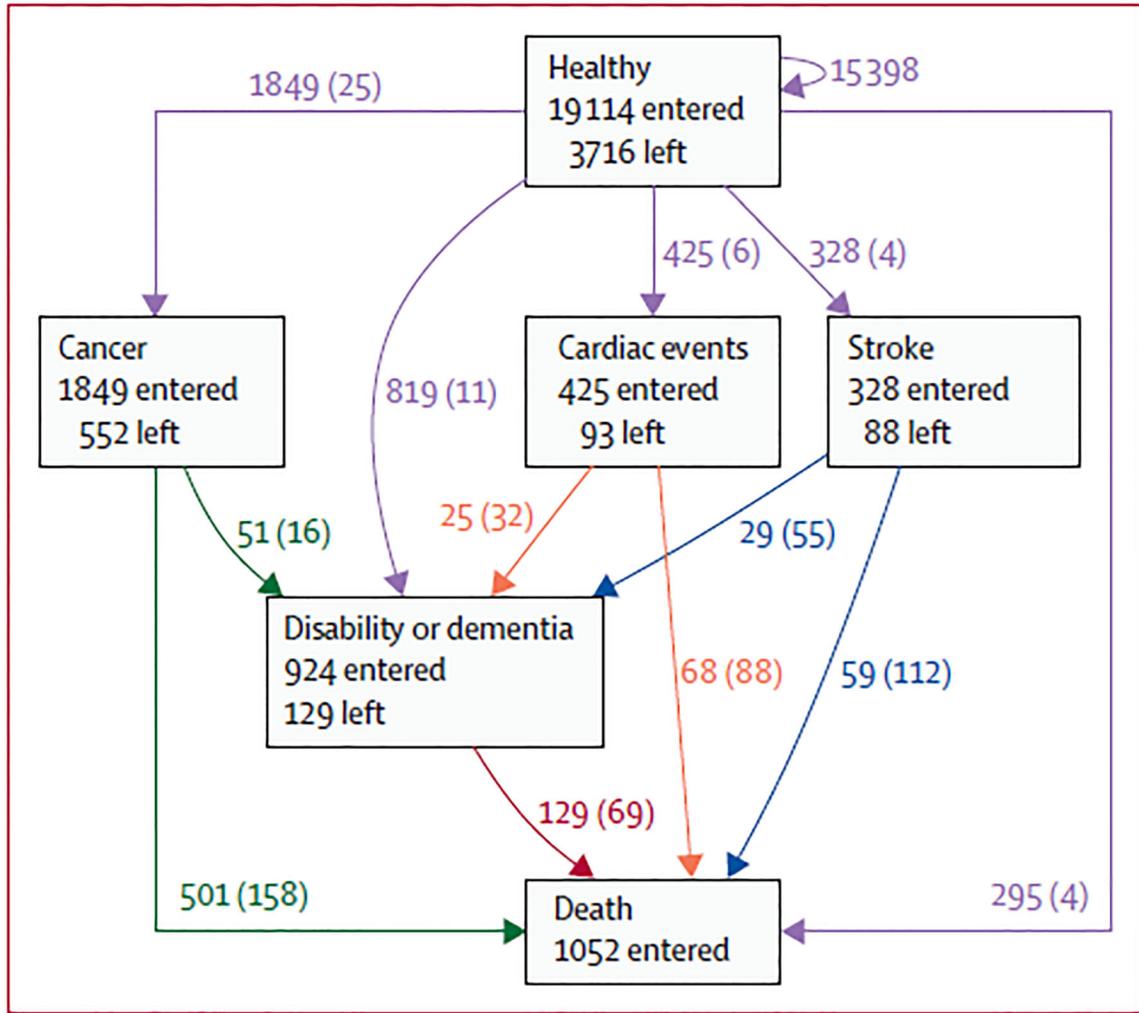


Figure 1: Transitions from a healthy state to intermediate adverse health states and death for all participants

Data along the arrows represent the number of transitions (incidence per 1000 person-years). Entering indicates the number of participants entering each state and leaving indicates the number of participants leaving each state at the end of follow-up. Transitions between states are indicated by arrows.

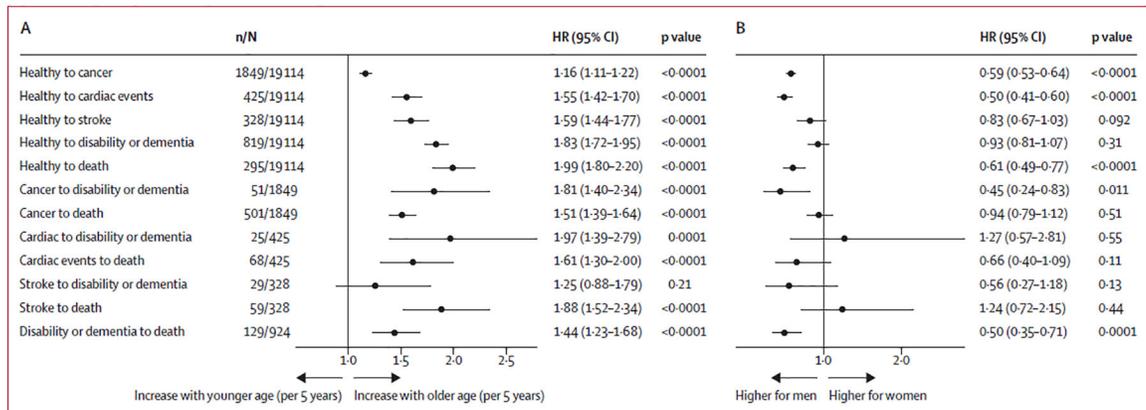


Figure 2: Forest plots of the association of age and sex with transition rates in the multistate model

(A) Age (per 5 years). (B) Sex (women vs men). Dots represent HR estimates and grey bars represent 95% CIs. Analyses were done by fitting separate Cox proportional hazard models on each transition in the multistate model. HR=hazard ratio.

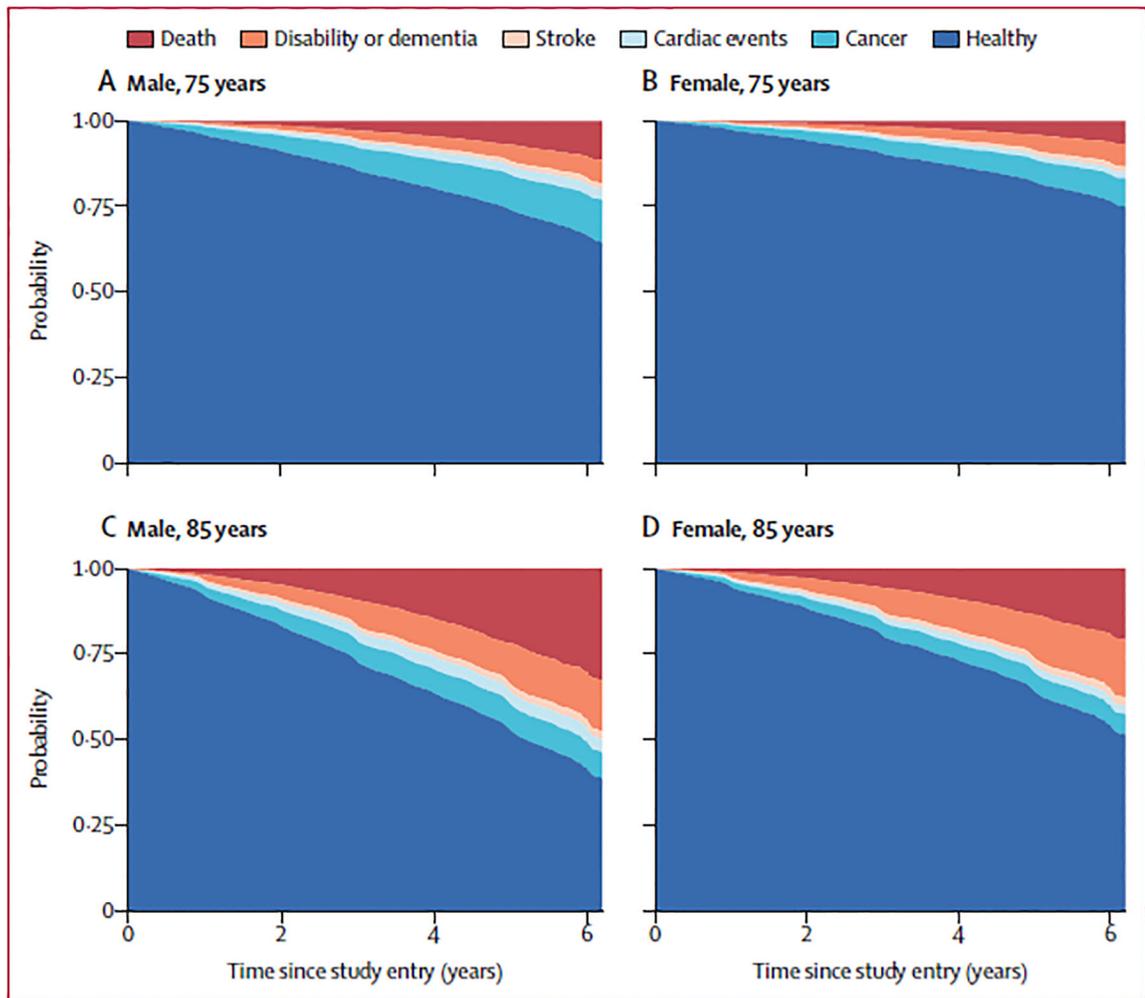


Figure 3: Stacked predicted state occupancy probabilities with time
 (A) 75-year-old man. (B) 75-year-old woman. (C) 85-year-old man. (D) 85-year-old woman.

Table 1:

Baseline characteristics

Participants (n=19 114)	
Age	
Median, years	74.0 (71.6–77.7)
65–74 years	9569 (50.1%)
75–84 years	8555 (44.8%)
85 years	990 (5.2%)
Sex	
Female	10 782 (56.4%)
Male	8332 (43.6%)
Country	
Australia	16 703 (87.4%)
USA	2411 (12.6%)
Education	
<9 years of education	3002/19 113 (15.7%)
9–11 years of education	5634/19 113 (29.5%)
12 years of education	2319/19 113 (12.1%)
13–15 years of education	3255/19 113 (17.0%)
16 years of education	1766/19 113 (9.2%)
17–21 years of education	3137/19 113 (16.4%)
Living situation	
At home alone	6251 (32.7%)
At home with family, friends, or spouse	12 780 (66.9%)
In a residential home	83 (0.4%)
Body-mass index [*] , kg/m ²	27.5 (24.9–30.7)
Smoking	
Former or never smoker	18 379 (96.2%)
Current smoker	735 (3.8%)
Diabetes	2045 (10.7%)
Hypertension	14 195 (74.3%)
Previous history of cancer	3660/19 035 (19.2%)
HDL concentration [†] , mmol/L	1.5 (1.3–1.8)
Non-HDL concentration [‡] , mmol/L	3.6 (3.0–4.3)
Systolic blood pressure, mmHg	139 (127–151)
Diastolic blood pressure, mmHg	77 (70–84)
Gait speed [§] , m/s	1.0 (0.9–1.2)
Grip strength , kg	25 (20–34)
Lipid-lowering agents	5987 (31.3%)
Antihypertensive agents	10 062 (52.6%)

Data are median (IQR), n (%), or n/N (%).

* Data for 19 025 participants.

† Data for 18 668 participants.

‡ Data for 18 666 participants.

§ Data for 19 018 participants.

¶ Data for 18 828 participants.

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Table 2:

All incident events during follow-up

	Participants (n=19 114)
Death	1052 (5.5%)
Disability or dementia	924 (4.8%)
Cardiac events	487 (2.5%)
Hospitalisation for heart failure	149/487 (30.6%)
Myocardial infarction	338/487 (69.4%)
Stroke events	398 (2.1%)
Haemorrhagic stroke	73/398 (18.3%)
Ischaemic stroke	301/398 (75.6%)
Ischaemic stroke with haemorrhagic transformation	9/398 (2.3%)
Stroke type uncertain	2/398 (0.5%)
Sub-arachnoid haemorrhagic stroke	13/398 (3.3%)
Cancer events	1933 (10.1%)
Prostate	375/1933 (19.4%)
Colon or rectum	267/1933 (13.8%)
Breast	246/1933 (12.7%)
Melanoma	190/1933 (9.8%)
Blood (leukaemia, myeloma, or lymphoma)	187/1933 (9.7%)
Lung	156/1933 (8.1%)
Others	512/1933 (26.5%)

Data are n (%) or n/N (%). Numbers are counts of individuals with each event, so represent first events of a particular type.

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