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The trajectory of functional decline over the last 4 months of life in a palliative care population: A prospective, consecutive cohort study.

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What is already known about the topic

- Functional decline can be anticipated for people with life limiting illnesses.
- Trajectories of functional decline differ in shapes and patterns.
- Understanding patterns of functional decline has implications for patient care and design of responsive health services.

What this paper adds

- This prospective study identifies two contemporary trajectories of functional decline for patients receiving specialist palliative care in the last 120 days of life.
- Precipitous deterioration in functional decline for cancers, solid organ failure and cardiovascular disease occurs as cohorts of patients approach an AKPS of 40.
- The pattern of functional decline for the neurological and dementias cohorts is flatter, showing a prolonged period of low function.

Implications for practice, theory or policy

- Study findings highlight that different types of care responses and resource allocation may be needed at different time points in different trajectories.
- This may require rapid mobilisation of carer support and modification of care plans preceding a precipitous functional decline (Trajectory 1).
- Extended periods of support to maintain patient function and support carers is required for those with a prolonged slow rate of functional decline (Trajectory 2).

Introduction

Decline in physical function can be anticipated in life-limiting illnesses. Understanding how and when the patients' function will change is critical in assisting patients receiving palliative care and their families meaningfully engage in decision making about their care. It will also enable better planning of health services. For patients, knowledge of functional decline can help them consider options regarding the place of care and how future care needs can be met best. Family members may find such information important in deciding when to take leave from work or in negotiating care arrangements and plans within the family. Better understanding the trajectories of functional decline will help health professionals provide

information to their patients to optimise their function and quality of life[1-4] as well as assist us design more responsive health services.[3, 5-9]

Trajectories of functional decline differ in shapes and patterns.[10] Four trajectories developed in the early 2000s continue to inform current economic and health service delivery: *Sudden death*: precipitous unexpected demise; *Cancer*: decline in the last 3 months after a variable plateau period; *Organ failure*: saw tooth pattern (chronic remitting and relapsing diseases) and *Other:* which includes 'unclassified' and 'dwindling'.[2, 9] However, as treatments change in late-stage disease and as co-morbidities are better managed, people live for longer, extending and potentially changing the disease trajectories of patients today.[5, 11-13] Trajectories of functional decline are therefore dynamic and need to be reviewed as clinical care evolves. Further, trajectories must be also relevant to diagnosis and the country in which care is provided when planning health service delivery around theoretical models of functional decline.[5, 13] There is an imperative for us to understand better current patterns of functional decline. This will inform the way we respond to care needs and health service and resource implications and will also provide a baseline to aid understanding of the effects of interventions to manage functional decline.

The aim of this study was to describe the trajectory of functional decline at the end-of-life in an Australian palliative care population, separated into diagnosis based cohorts. Of particular interest was the identification of time points associated with a significant change in the rate of functional decline.

Methods

Study design and setting

This was a consecutive cohort study of prospectively collected data using the Palliative Care Outcomes Collaboration (PCOC) longitudinal database. PCOC is a national program that collects voluntarily submitted clinical data from specialist palliative care services. These data are used for evaluating patient outcomes at a service level and benchmarking between services. PCOC has been approved by the Human Research Ethics Committee of the University of Wollongong (approval ID: HE06/045). Data collection was of routine clinical data de-identified and aggregated, and separate consent was not required. Using death as the anchor time point, data from the preceding four months were examined.

Participants and variables

This analysis included all patients with at least one recorded Australia-modified Karnofsky Performance Status (AKPS) score who died in the care of 115 palliative care services between 1st January 2013 – 31st December 2015. Data were integrated for patients cared for by multiple palliative care services in community and inpatient settings, using a statistical linkage key in combination with the patient's residential postcode. Patients are allocated to a PCOC diagnostic group based on the principal life limiting illness that necessitates a referral to palliative care. While many patients will have comorbidities and multimorbidity, this is not captured in PCOC data. Patients were grouped into five diagnostic cohorts: cancers; solid organ failure; neurological conditions; Alzheimer's Disease (AD) and other dementias (hereon known as dementias); cardiovascular disease; other and unknown. Cancer, solid organ failure and dementias[1] were selected based on cohorts frequently referred to in other trajectory studies.[2, 4, 14] There are some indications that those with neurological disorders and cardiac disease may have different care needs and a longer and more variable progress, making an investigation of the trajectories of these groups useful in

a large cohort sample.[15-17] Other and unknown were not included in the modelling due to the range of diagnoses and small numbers.

Functional status was measured using the Australia-modified Karnofsky Performance Status scale, an 11 point scale that reflects functional independence (100 – fully functional; 0 – dead). A person with an AKPS score of 40 would be in bed more than 50% of the time. People requiring considerable assistance with self-care and as well as frequent medical care would score an AKPS of 50. Those requiring minimal assistance with self-care on occasion would score an AKPS of 60.[18] Recommended frequency of AKPS assessments is daily or at each clinical contact (i.e. assessment frequency may vary according to the clinical setting e.g. inpatient, hospital consultation and community settings and access to the patient).[19] However, AKPS scores are only submitted to PCOC at change of Phase. Phases of care relate to the patient and are defined as 'stable', 'unstable', 'deteriorating', and 'terminal'. They have been found to be a reliable measure that can be used to plan responsive clinical care.[20]

Statistical methods

All data points were included and no data were imputed. Cohort characteristics were reported using descriptive statistics. All longitudinal analysis of trajectory of function were undertaken using a segmented (piece wise) regression. The variable of interest was change in AKPS score over time using the number of days before death as the longitudinal component. Segmented (piece wise) regression was used to identify time points prior to death associated with significant changes in the rate of functional decline (slope) at the group level in each diagnostic cohort.[21] Analysis examined the changes occurring on average to the trajectories of the five cohorts over time. An algorithm was written in R[22] using the 'segmented' package[21, 23] to compare models with between one and five change points. The

number of change points and resulting segmented regression model that best describes the trajectory of functional decline was determined using the Bayesian Information Criterion (BIC). Differences in trajectories for males / females and different age groups were investigated visually by employing Loess Smoothing.

Sensitivity analyses

There is no agreed national or international criteria for referral to specialist palliative care. As such, late referrals have the potential to influence the modelled trajectories. To investigate this, a sensitivity analysis was performed by rerunning the segmented regression model algorithm, after removing patients referred less than 14 days before death from the analysis.

Results

Data were collected from 55,954 patients cared for in hospices, hospitals and at home with 237,544 AKPS data points. The distribution of diagnoses (Table 1) and the characteristics of patients in each cohort (Table 2) demonstrated expected differences in age with the dementias cohort the oldest (mean 84.8, sd 8.7). It also had the highest proportion of females (60.4%) but the smallest number of observations (1,336 patients and 2,442 assessments). The cancers cohort had the largest number of observations (39,783 patients and 190,567 assessments), were the youngest (mean 71.6, sd 13.5) and a lower proportion of females (45.0%).

Table 1. Summary of diagnostic cohorts and related PCOC diagnoses.

Diagnostic cohort	PCOC diagnosis	Patients N=53,458	Assessments N=227,872
Cancers	Malignant – not further defined	517	2,150
	Bone and soft tissue cancer	564	2,679
	Breast cancer	2,769	14,178
	Central nervous system cancer	845	4,468
	Colorectal cancer	4,615	22,780

	Other Gastro-intestinal cancer	3,802	17,889
	Haematological cancer	2,496	9,672
	Head and neck cancer	2,234	10,370
	Lung cancer	8,830	42,448
	Pancreas cancer	2,685	12,848
	Prostate cancer	2,364	12,951
	Other urological cancer	1,726	8,390
	Gynaecological cancer	1,883	10,068
	Skin cancer	1,627	7,697
	Unknown primary cancer	1,185	4,804
	Other primary malignancy	1,641	7,175
	Total	***39,783***	***190,567***
	% of study	***74.4***	***83.6***
Solid organ failure	End stage kidney disease	1,306	3,922
	Respiratory failure	1,857	5,986
	End stage liver disease	500	1,468
	Multiple organ failure	375	645
	Total	***4,038***	***12,021***
	% of study	***7.6***	***5.3***
Neurological conditions	Stroke	1,069	1,869
	Motor Neurone Disease	344	1,729
	Other neurological disease	1,087	3,102
	Total	***2,500***	***6,700***
	% of study	***4.7***	***2.9***
Cardiovascular disease	Cardiovascular disease ***Total***	**2,369**	**6,584**
	% of study	***4.4***	***2.9***
Alzheimer's disease /Dementia	Alzheimer's dementia	504	954
	Other dementia	832	1,488
	Total	***1,336***	***2,442***
	% of study	***2.5***	***1.1***
Other	Non Malignant – not further defined	389	983
	HIV/AIDS	22	130
	Diabetes and its complications	60	211
	Sepsis	425	817
	Other non-malignancy	2,221	6,401
	Total	***3,117***	***8,542***
	% of study	***5.8***	***3.7***
Unknown	Unknown ***Total***	315	1,016
	% of study	***0.6***	***0.4***

Table 2. Characteristics of the five diagnostic cohorts.

	Cancer (N = 39,783)	Solid organ failure (N = 4,038)	Neurological conditions (N = 2,500)	Cardiovascular disease (N = 2,369)	Alzheimer's & Dementia (N = 1,336)	Entire cohort (N = 53,458)
Female (%)	45.0	43.3	54.1	49.5	60.4	46.5
Born in Australia (%)	64.9	63.8	63.7	62.7	59.0	64.5
English speaking (%)	90.7	88.5	87.6	88.3	85.9	90.1
Age at death						
Mean	71.6	77.6	77.5	83.2	84.8	73.7
SD	13.5	12.4	14.5	10.8	8.7	13.9
Median	73	80	81	86	86	76
Range	0 - 109	0 - 110	0 - 104	0 - 104	35 - 107	0 - 110
Place of death (%)						
Hospital	71.0	72.9	71.3	67.2	38.6	71.0
Home	19.7	17.3	12.6	18.1	16.2	19.7
Residential aged care	6.8	7.6	13.4	12.2	44.5	6.8
Community, not specified	2.4	2.2	2.7	1.9	0.7	2.4

Trajectory patterns

The stacked bar charts in the left hand panel of Figure 1 show the distribution of AKPS scores each week prior to death. They demonstrate that function declines for all cohorts as patients get closer to death. The functional levels of the 'Alzheimer's Disease and other dementia' group is lower than cancer in the weeks before death with AKPS scores of 10 and 20 common in 10+ weeks from death. Cancers have the highest proportion of 60 - 100 AKPS scores.

Rate of functional decline and final change points

Table 3 summarises the results of the segmented regression models. The right hand panel of Figure 1 plots the segmented regression lines and the average daily AKPS scores for each of the 120 days prior to death. In the cancers cohort, the segmented regression algorithm found that a four change point model best described the trajectory of functional decline at the group level. At 120 days prior to death, the modelled average AKPS was 55.6. Function is declining for the entire period, with significant changes in function at 43.2, 15.8, 8.0 and 3.3 days prior to death (change points in the model). The most rapid decline in function occurs during the last three days of life, with a decrease in AKPS of 3.82 on average each day. At 3.3 days prior to death, the mean AKPS is 28.9 which decreases to a mean AKPS of 16.3 on the day that the patient died). Similar patterns were seen in the other four cohorts, with the rate of functional decline increasing at each of the identified change points. Of note, the cancers, solid organ failure and cardiovascular cohorts started from a higher AKPS four months preceding death. Decline in function is gradual, accelerating more rapidly the closer the patient

gets to death. By contrast, the neurological and dementias cohorts demonstrated the slowest rate of functional decline and had a lower AKPS at 4 months (< 40) preceding death.

Variability in trajectory means

Results from the sensitivity analyses are included in Table 3. Models with the same number of change points at similar times prior to death were obtained for the cancers and neurological conditions cohorts. The algorithm found that a simpler model with a single change point provided the best fit in the decline in average daily AKPS for the dementias and cardiovascular disease cohorts. The sensitivity analysis shows a more gradual decline for the final slopes of the models, however, the change points are also further away from death.

Results from the Loess Smoothing used to investigate differences between age groups and between males and females are included in Figure 2. [Insert Figure 2]. The results do not vary greatly for age or sex as the trajectories in each plot are similar.

Table 3. Results of the segmented regression models and sensitivity analyses for each of the five cohorts.

	Estimate (standard error)				
	Cancers	Solid organ failure	Cardiovascular disease	Alzheimer's & dementia	Neurological conditions
Full model					
N	138,711	9,575	5,373	2,227	5,095
Model coefficients					
Change point (days)[a]					
4 (further from death)	43.2 (1.292)	-	-	-	-
3	15.8 (0.492)	-	-	-	-
2	8.0 (0.335)	11.3 (0.460)	15.0 (1.135)	22.8 (2.699)	53.6 (6.0)
1 (closer to death)	3.3 (0.098)	2.7 (0.331)	4.7 (0.405)	4.5 (0.775)	13.9 (0.905)
Rate of functional decline (slope)[b]					
5 (further from death)	0.08 (0.010)	-	-	-	-
4	0.26 (0.050)	-	-	-	-
3	0.78 (0.079)	0.12 (0.093)	0.10 (0.103)	0.05 (0.080)	0.00 (0.040)
2	1.56 (0.092)	1.52 (0.287)	0.86 (0.206)	0.55 (0.249)	0.21 (0.062)
1 (closer to death)	3.85 (0.069)	3.44 (0.287)	2.77 (0.178)	1.65 (0..237)	1.07 (0.053)
Average AKPS at death (intercept)[c]	16.30 (0.125)	15.62 (0.362)	15.71 (0.382)	13.87 (0.541)	14.39 (0.276)
Sensitivity analysis[d]					
N	104,135	4,779	2,468	730	2,346
Model coefficients					
Change points[a]					

4 (further from death)	46.8 (1.659)	-	-	-	-
3	18.4 (0.424)	-	-	-	-
2	7.6 (0.287)	18.3 (1.915)	-	-	59.8 (8.213)
1 (closer to death)	2.5 (0.162)	6.1 (0.628)	8.5 (0.565)	19.9 (2.181)	12.6 (1.558)
Rate of functional decline (slope)[b]					
5 (further from death)	0.08 (0.011)	-	-	-	-
4	0.23 (0.031)	-	-	-	-
3	0.78 (0.083)	0.11 (0.113)	-	-	-0.01 (0.046)
2	1.85 (0.169)	0.57 (0.219)	0.11 (0.184)	0.07 (0.094)	0.17 (0.123)
1 (closer to death)	3.80 (0.151)	2.34 (0.188)	2.18 (0.184)	0.74 (0.091)	0.96 (0.120)
Average AKPS at death (intercept)[c]	15.98 (0.201)	18.44 (0.595)	17.83 (0.740)	16.23 (0.940)	17.68 (0.713)

[a] The change points describe the number of days prior to death where there is a significant change in the rate of functional decline.
[b] The model slope is rate of functional decline (i.e. the decrease in average AKPS for each day closer to death). Slope 1 indicates the rate of rate of functional decline in the period just prior to death (the far right on Figure 1).
[c] The model intercept is the average AKPS on the day that the patient died.
[d] The sensitivity analysis describes the results obtained after re-running the algorithm with late referrals (last 14 days) removed from the analysis.

Discussion

The largest trajectory study of its kind internationally, this prospective cohort study sought to map the shape and pattern of functional decline trajectories at the end-of-life by diagnosis in an Australian palliative care population.

Significance of the findings

This study identifies two simplified trajectories of functional decline for five pre-identified patient cohorts in the last four months of life, based on the mean AKPS scores 120 days out from death; *Trajectory 1*: Cancer, solid organ failure and cardiovascular disease and *Trajectory 2*: Dementias and neurological conditions. This study builds on previous findings that identify a rapid decline in function in the last month of life for a range of diagnostic cohorts such as cancer, solid organ failure and frailty.[1,2,13,14,24] These prospectively collected data mirror some longer prospective[2,24] and retrospective[1,25] trajectory studies for cancer, organ failure,[2,13,14] and frailty/dementia.[2,12,14] Data show there are rapid periods of decline in the last 14 – 22 days of life for all diagnostic cohorts, with the average AKPS score dropping by 15 – 26 points.

Study findings also codify the tipping points in the slope or rate of functional decline that enable family and health professionals to plan care more proactively for end stage care.[26-28] Precipitous deterioration in functional decline for cancers, solid organ failure and cardiovascular disease (Trajectory 1) occurs once cohorts of patients approach an AKPS of 40. A threshold of an AKPS of 40 indicates the need for a rapid increase in caregiver support, particularly for people living in the community and modification of care plans as patients move towards the terminal phase of care.[19]

The pattern of functional decline of the neurological and dementias cohorts (Trajectory 2) is flatter, showing a prolonged period of low function. The trajectory for the dementia

group is consistent with an earlier study which found higher rates of cognitive decline correlated with earlier functional decline, and higher and prolonged rates of functional impairment for the frail elderly with cognitive decline.[3] This has important ramifications for resource allocation and is particularly important when planning supports for community-dwelling patients and their caregivers as prolonged low AKPS scores indicate substantial care is required for an extended time.[29]

Recognition that different diseases have different trajectories and decline points highlights the need for potentially different approaches to patient, carer and family support. When functional decline is prolonged for patients who choose to die at home, we need to consider how to maintain or enhance patient function and caregiver health at this time.[29,30] It may indicate the need for increased allied health care to support patients and carers manage the ramifications of functional decline for this sustained period of functional dependency. The starting AKPS scores (mean of 37.2 dementias and 55.7 for cancers) demonstrate the intensity of support and care needs of this whole cohort at 120 days preceding death. Support prior to this time is also indicated given correlations between cognitive and functional decline.[3]

Understanding patterns of functional decline can inform the planning and delivery of responsive health care to those we cannot cure but sustain with medical and health interventions.[6,28] However, as with earlier trajectory studies that continue to inform development of health care services nearly 20 years after their publication,[1,2] these trajectories need to be considered within a changing health care context. As we gather a more sophisticated understanding of the interplay of clinical interventions on life expectancy, quality of life and functional decline, the shapes of the trajectories may well change. All of these considerations will influence the design, availability and funding of care and service delivery in the future.

Strengths and limitations

A strength of the present study is that it utilised prospective, point-of-care data collection in contrast to other studies that employed a retrospective approach.[1,3,12,25,31] Earlier trajectory studies relied on less rigorous methods to map functional decline such as retrospective proxy recall[1,25] and the use of non-standardised assessments.[1-3,11,25] This study employed the AKPS, a standardised assessment tool to record functional status[18] and data were drawn from an Australian longitudinal palliative care database, PCOC. More recent trajectory studies have employed standardised measures to assess end of life functional change over time.[5,12,13,24] This will allow for comparison of trajectories across diagnoses and countries. As noted this is the largest trajectory study of its kind. Earlier trajectory study cohorts range in size from < 100,[5,13,31] <1000,[3,11,14] < 5000[1,2,25] to <11,000.[12,24] While a prospective, point-of-care data collection was employed in this study, data was examined retrospectively from date of death. Therefore, results must be considered in this light. They inform our understanding about shapes of trajectories and offer considerations for service planning but should not be used prescriptively to make decisions about individual patient care.

Several factors may have influenced the shape of the two simplified trajectories. Approximately 80% of patients of all patients who receive specialist palliative care and 12.4% of all Australian deaths, including sudden deaths were captured in PCOC data sets in 2016.[32] Only those people referred to palliative care and likely to have advanced disease were included in this dataset. As there are no universal criteria for referral to palliative care, people with life limiting illnesses who are not referred to palliative care are not included. Those with non-malignant disease such as Alzheimer's Disease or Motor Neurone Disease (MND) are more likely to be referred when the disease is significantly advanced so may have presented with an initial lower AKPS. Approximately one third of the Australian population

are living in residential aged care at the time of their death.[33] Numbers of women in residential aged care in Australia exceed those of men (two thirds:one third) as they tend to live longer.[34] This longevity is also associated with higher care needs. The lower AKPS scores of women with dementia at 120 days may reflect that they are already receiving support through residential aged care and are only likely to be referred at a lower functional level. It is likely that people with chronic neurological conditions such as MND will be linked with other health care supports at diagnosis which may delay or replace referral to palliative care. The precipitous decline of the cancers, solid organ failure and cardiovascular disease may in part be due to higher starting AKPS scores preceding death, therefore opportunity to fall further. Differences in cohort sizes, both the number of patients and occasions of assessment, may be also be responsible for variability in the trajectory means. Disease process and sampling times are not independent. Assessment occasions may be dependent on disease process such as symptom exacerbations. This may have led to higher numbers of AKPS assessments for the cancer cohort and lower assessment numbers for the slower progressing diseases such as dementia and MND. Further, they were not collected systematically at predetermined times, rather at changes in 'phase of care' as described in methods as care is delivered.

A key finding for clinical practice is the tipping point of an AKPS approaching 40 for cancers, solid organ failure and cardiovascular disease. This is significant if functional decline is used as a prognostic indicator as it will inform and enable responsive service provision. This tipping point gives a targeted window of time when health clinicians, patients and families can prepare for the precipitous period of decline. It is important to note however, that this is not the only time in disease trajectory that requires targeted interventions and care. A second key finding is the flatter trajectory for people with dementias and neurological diseases. It identifies the significant ongoing functional care needs that extend

for several months preceding the rapid decline.[15] Recent studies suggest that specialist palliative care interventions can reduce hospitalisations and support patients to die at home.[28, 35]

Supporting functional and end-of-life needs of burgeoning numbers of an ageing and frail population living in the community with multiple physical and cognitive comorbidities requires a targeted approach to care and care interventions. While details about multimorbidity are not captured in PCOC data, examination of the impact of increased symptom burden and care needs associated with the number and combinations of morbidities is an important area for future research given the prevalence of comorbidity and multimorbidity in palliative care populations.

Conclusion

This paper provides an update and examination of contemporary trajectories of functional decline by diagnosis for patients receiving specialist palliative care. It identifies two trajectories of functional decline and significant changes in slope or rate of functional decline for five pre-identified patient cohorts. It confirms the cancer trajectory, suggesting a sustained level of function and a relatively rapid decline to death. It identifies a tipping point of an AKPS approaching 40 approximately two weeks before death for cancer, solid organ failure cardiovascular disease cohorts which precedes a precipitous decline. This presents an opportunity for planning a timely and considered response to patient's precipitous decline and imminent death. It also identifies an extended low level of function with a more gradual decline for dementia and neurological cohorts. This suggests patient and caregivers may require additional supports to manage functional decline earlier in the disease trajectory. Study findings highlight that different types of care responses may be needed at different time points for different trajectories. This speaks to the importance of understanding the

care needs of different cohorts and the need for policy response to inform appropriate health care resource allocation.

Declarations

Authors' contributions

DM, JT and DC designed the study with contribution from all authors. SA and AC performed the statistical analysis. DM and all authors contributed to critical interpretation of the results and development of the manuscript. All authors read and approved the final version.

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Declaration of competing interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation, no financial relationships with any organisations that might have an interest in the submitted work; no other relationships or activities that could appear to have influenced the submitted work.

Ethics approval

The Palliative Care Outcomes Collaboration has received ethics approval from the Human Research Ethics Committee of the University of Wollongong (Approval ID: HE06/045).

Availability of data and materials

Data can be made available to bona fide researchers.

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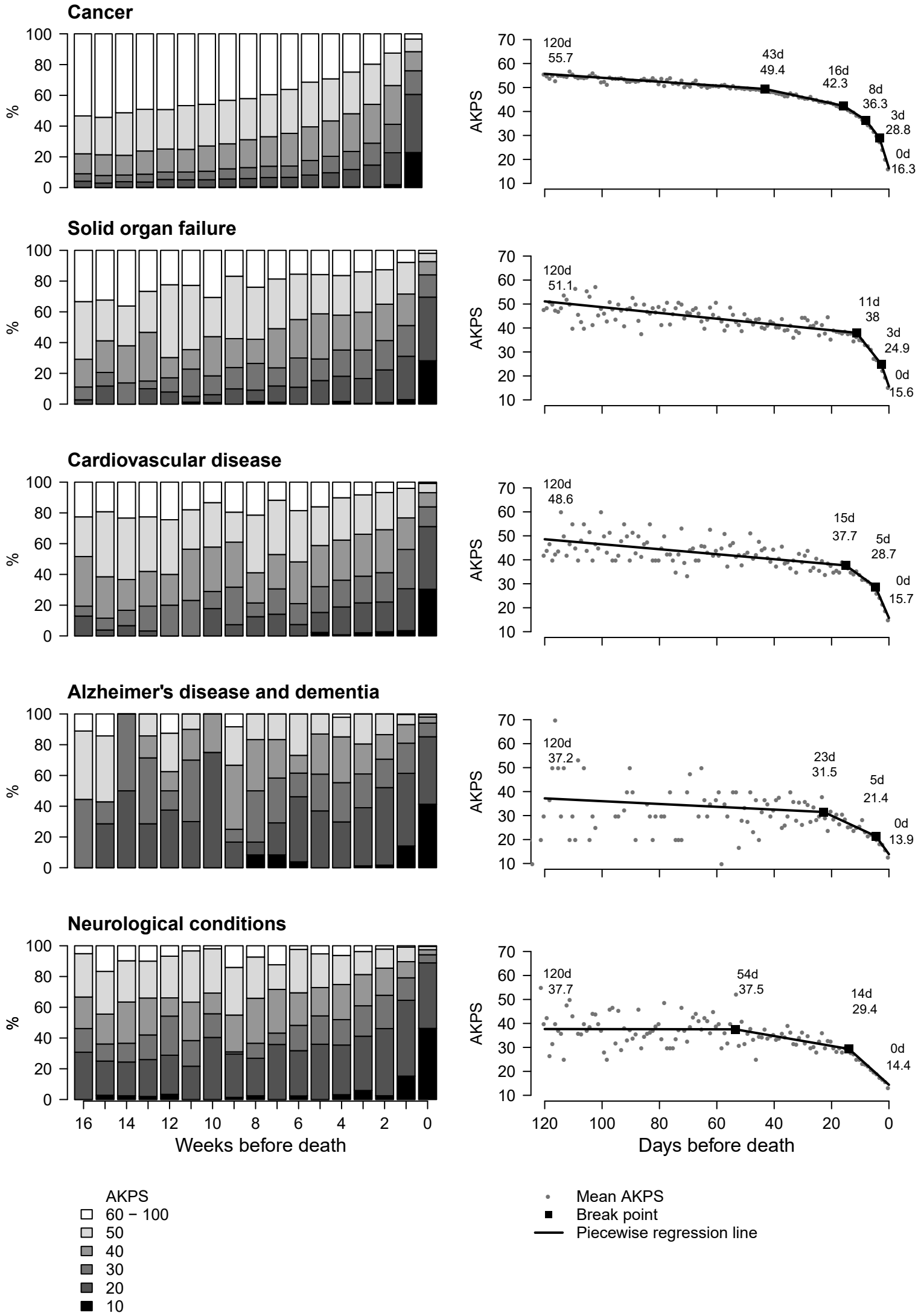
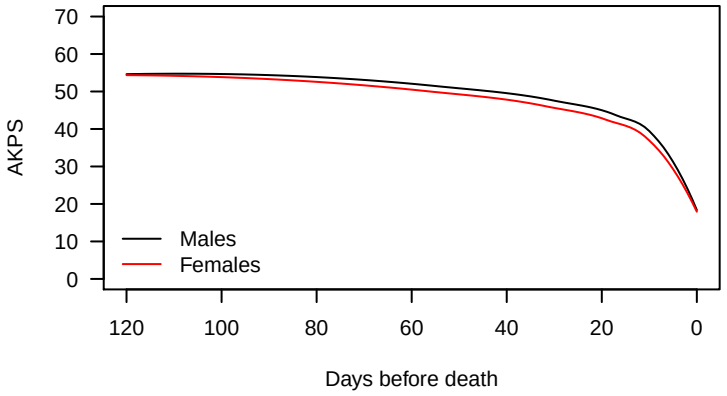
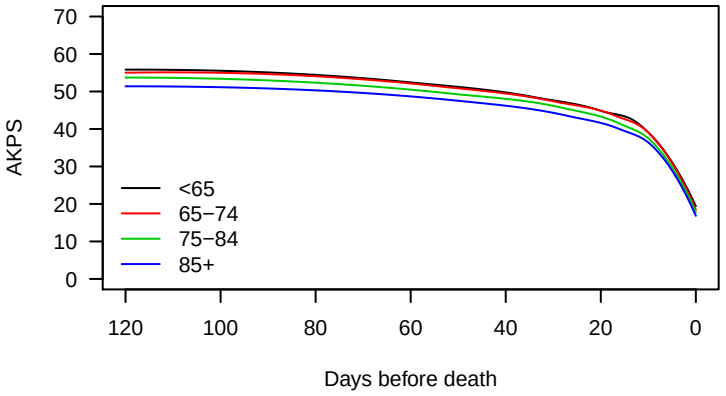
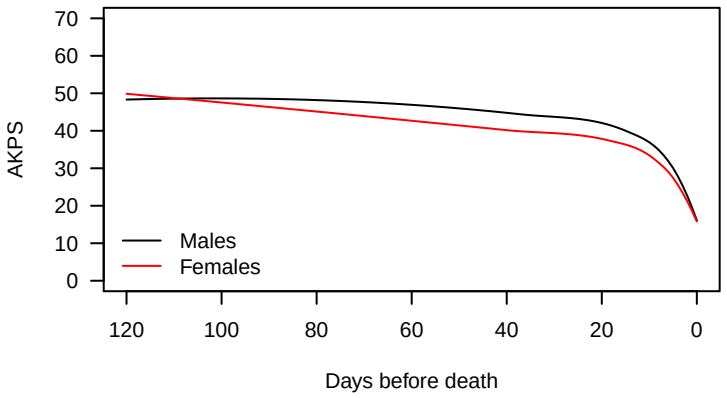

Cancer
Solid organ failure
Cardiovascular disease
Alzheimer's disease and dementia
Neurological conditions
%
AKPS
120d
55.7
43d
49.4
16d
42.3
8d
36.3
3d
28.8
0d
16.3
120d
51.1
11d
38
3d
24.9
0d
15.6
120d
48.6
15d
37.7
5d
28.7
0d
15.7
120d
37.2
23d
31.5
5d
21.4
0d
13.9
120d
37.7
54d
37.5
14d
29.4
0d
14.4
Weeks before death
Days before death
AKPS
60 − 100
50
40
30
20
10
Mean AKPS
Break point
Piecewise regression line

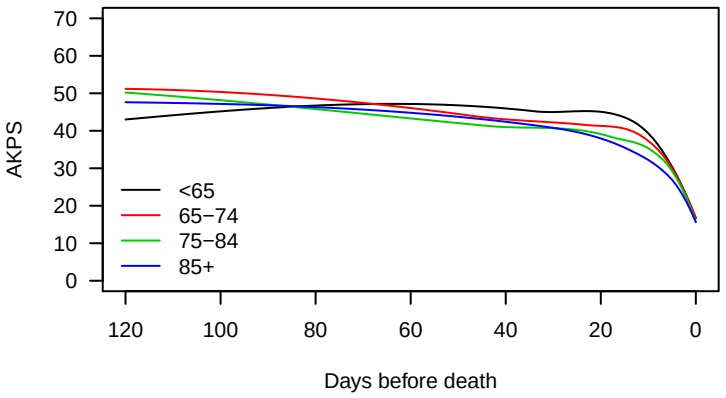
Cancer



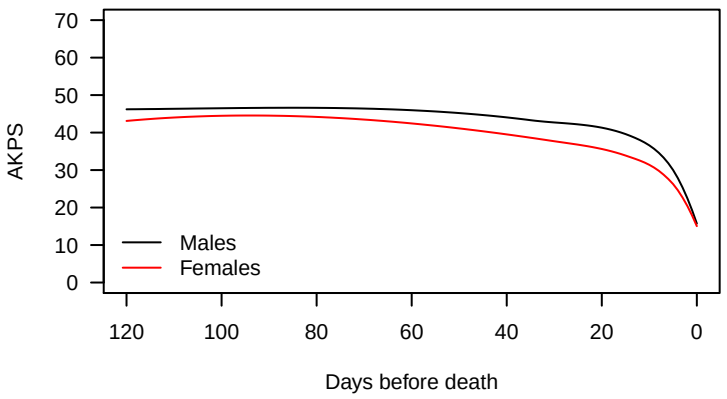


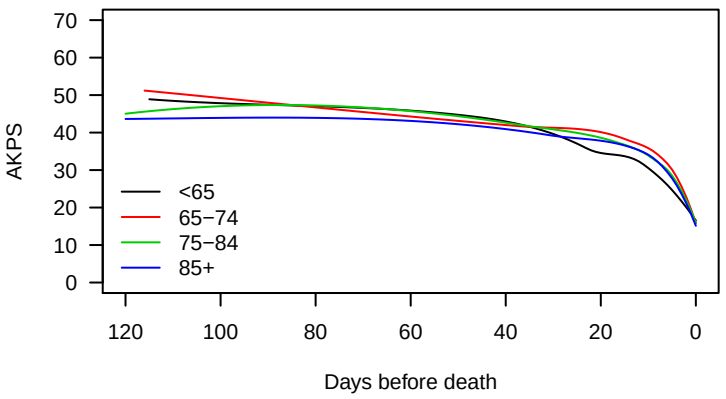
Solid organ failure



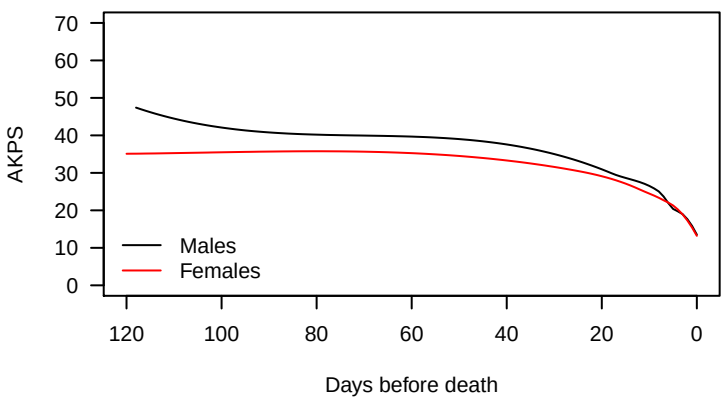


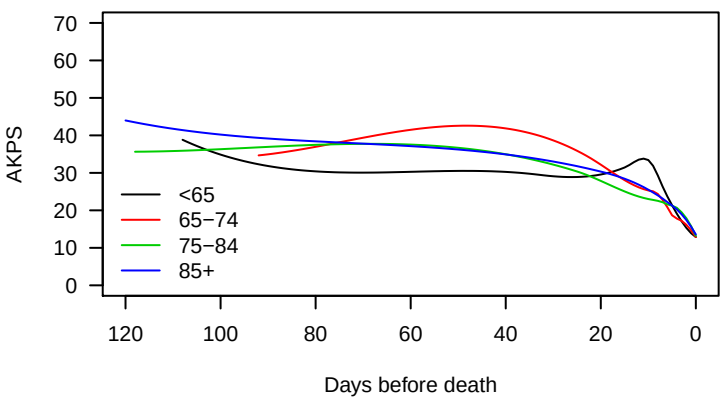
Cardiovascular disease





Dementia





Neurological conditions