

# Understanding the Abrupt Effect of Spousal Bereavement on Mortality: an Application of Complex Dynamic Systems Theory

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## Research Article

**Keywords:** resilience, bereavement, complex systems, health, aging

**Posted Date:** September 9th, 2021

**DOI:** <https://doi.org/10.21203/rs.3.rs-871931/v1>

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**Version of Record:** A version of this preprint was published at BMC Geriatrics on April 8th, 2022. See the published version at <https://doi.org/10.1186/s12877-022-02992-x>.

# Abstract

## Background

The process of aging renders older people susceptible for adverse outcomes upon stress. Various indicators derived from complex systems theory have been proposed for quantifying resilience in living organisms, including humans. We investigated the ability of system-based indicators in capturing the dynamics of resilience in humans who suffer the adversity of spousal bereavement and tested their predictive power in mortality as a finite health transition.

## Methods

Using longitudinal register data on weekly healthcare consumption of all Danish citizens over the age of 65 from January 1st, 2011, throughout December 31st, 2016, we performed statistical comparisons of the indicators 'average', 'slope', 'mean squared error', and 'lag-1 autocorrelation' one year before and after spousal bereavement, stratified for age and sex. The relation between levels of these indicators before bereavement and mortality hazards thereafter was determined by time to event analysis and the added value for mortality prediction was estimated by the time dependent area under the receiver operating characteristic curve.

## Results

The study included 934,003 citizens of whom 51,890 experienced spousal bereavement and 2862 died in the first year thereafter. Values of all dynamic indicators were significantly higher with increasing age, in men compared to women, and except lag-1 autocorrelation, higher in the year after bereavement (all p-values < 0.001). All dynamic indicators before bereavement were positively related with mortality hazards thereafter (all p-values < 0.001). The area under the curve of the final model to predict mortality, including all relevant indicators, was 77.7% for males and it was 81.8% for females.

## Conclusions

It is concluded that healthcare consumption is increased, more volatile and accelerating with aging and in men compared to women. High values of these dynamic indicators before bereavement indicate loss of resilience as manifested by their predictive value to predict mortality when mourning after spousal loss.

## Background

Resilience as a term has been used in a variety of different fields to describe a certain system's ability to preserve specific characteristics or functions when being perturbed by different stressors (1). Originally developed within the physical sciences, insights from the theory of complex dynamical systems have been extrapolated to understand and predict failure of organisms in the life sciences (2–4). In human health, resilience to stressors can be interpreted as the potential of a person to bounce back into normal functioning after facing mental or physical disturbances (5–7). This adaptive capacity of humans

diminishes across time due to the process of aging, a phenomenon called frailty, describing the functional decline of various physiological systems rendering older people at an increased vulnerability to stressors (8).

A more formal application of complex dynamical systems theory to human aging has led to the development of indicators for quantifying and estimating resilience (9). According to theory some systems may exhibit a phenomenon called 'Critical Slowing Down' (CSD) during which the system recovers in a slower rate from disturbances (9–12). This decline of resilience can be manifested as the system approaches a tipping point transitioning from a stable steady state, e.g. health towards a contrasting one, e.g. disease (11, 13). By observing the fluctuations of a given continuous (physiologic) variable across time, various metric-based indicators, called Dynamical Indicators of Resilience (DIORs) or Early Warning Signals, can be computed for the purpose of estimating loss of resilience before a critical transition occurs (6, 14–18).

Bereavement, the loss of a loved one, is a disturbing life-event and linked with various psychological as well as physical complications, ranging from post-traumatic stress disorder and depression to impairment of immune system and increased mortality risk (19, 20). The impact of spousal bereavement has been observed to differ between males and females and increases upon aging (21, 22). It needs to be determined whether the aforementioned theory of complex dynamic systems can not only provide useful insights on how human resilience changes in response to various perturbations, such as bereavement, but also quantify the risk of approaching a tipping point, i.e., death, after being perturbed by the loss of a loved one, given the resilience status before the event happening.

The aim of this paper is to calculate various metric-based indicators, i.e., dynamic indicators of resilience to better understand the abrupt effect of spousal bereavement on mortality risk. To this end, we studied the association of spousal bereavement - as a standardized stressor - with dynamics of health status, as manifested in the healthcare consumption of Danish elderly over the age of 65. The idea is that healthcare consumption can serve as an indicator variable of a person's health and resilience. We first aim to analyse the behaviour of these indicators, before and after the stressor reflecting loss of resilience. Our second aim is to determine whether these indicators are predictors of failure by testing the hypothesis of them being associated with death, an ultimate 'tipping point' upon perturbation. The aforementioned would be fulfilled by observing significantly higher mortality in the groups of people with the highest levels of these indicators before the stressor.

## Methods

### 2.1 Data Processing

Data were collected from national population registers of Statistics Denmark (<https://www.dst.dk>) containing information on the healthcare consumption of Danish Elderly over the age of 65, who had been resident in Denmark for at least 5 years before the date of death, from January 1st, 2011 to

December 31st, 2016 (23, 24). Healthcare consumption was divided into weekly measurements and was initially grouped into different kinds of costs, while being measured in thousands of Danish Kroner (1 unit = 1000 DKKR). Information on prescription drug, hospital (inpatient and outpatient), home care, residential care, and primary care costs was available and a new variable, aggregating all the types of healthcare costs, was constructed for each individual. Variables describing sex, date of birth, date of death and bereavement date (date when spouse died) were virtually complete.

## 2.2 Availability of Data & Materials

According to Danish law, scientific organizations can be authorized to work with data within Statistics Denmark and can provide access to individual scientists inside and outside of Denmark. Data are available via the Research Service Department at Statistics Denmark:

([www.dst.dk/da/TilSalg/Forskningservice](http://www.dst.dk/da/TilSalg/Forskningservice)) for researchers who meet the criteria for access to confidential data.

## 2.3 Definition of DIORs

We computed for each individual the average (AVERAGE) healthcare consumption one year before and after bereavement as an intuitive measure of health status. We also calculated several Dynamical Indicators Of Resilience (DIORs) or early warning signals, which are not measuring the healthcare consumption per se, but rather capture the individuals' dynamical changes in healthcare costs. Initial data exploration indicated that many individuals gradually increase their healthcare costs approximately linearly with time and hence we decided to compute the slope (SLOPE) of the average linear temporal increase of healthcare costs as an indicator of speed or magnitude at which the individual is drifting away from the intuitively 'healthy' status of zero healthcare costs (interpreted as being equivalent to zero healthcare needs). We also computed the mean squared error (MSE) of the time series of healthcare costs. Higher values of MSE could indicate slower recovery dynamics and hence increasing MSE for the individual is indicative of critical slowing down. We chose to include MSE instead of the standard deviation of the detrended time-series, since these metrics are both capturing the variability of the underlying phenomenon, with the former appearing to have a higher predictive value than the latter in the rest of the analysis (data not shown). Finally, we calculated the lag-1 autocorrelation measuring the correlation of subsequent moments (lagging by 1 unit of time) of a given time-series. High levels of lag-1 autocorrelation indicate an increased memory of measurements of a given system and are hence also indicative of critical slowing down. The overall idea behind the selection of the aforementioned DIORs is to capture changes in the functionality of human health, translating into changes in dynamic behavior, without being restricted to only investigate those indicators matched with the resilience paradigm of critical slowing down.

## 2.4 Data Analysis

Comparisons of the DIORs one year before and after the spousal bereavement were performed for the whole sample, but also stratified based on sex and various age categories. The distributions of the healthcare costs and the metrics describing them, were positively skewed and non-normally distributed.

Hence, we assessed the significance of the statistical differences in DIORs between the two bereavement periods via non-parametric two-tailed Wilcoxon signed-rank tests.

Comparison analysis of the DIORs one year before bereavement, between individuals who survived within one year after the bereavement event with those who did not, was performed to evaluate the hypothesis of these metrics signaling early loss of resilience. Statistically significant results were assessed with the use of two-tailed Mann-Whitney U tests.

We deployed quantile-median regression models (25) using each DIOR at a time as response (Y) variable and the age of the individuals as predictor (X), while adjusting for sex, to predict the change in the median of the DIORs in response to an increase in age. Therefore, we evaluated if those dynamic indicators follow the theory of aging, by observing the models' slope-coefficient, with older individuals becoming frailer, thus exhibiting higher DIORs values. It should be noted that the slopes of the median regression models are different from the SLOPE DIOR, with the former indicating the between-individuals variability and the latter the within-individual one. Sex-based statistical comparisons (two-tailed Mann-Whitney U tests), both pre- and post-bereavement, were furtherly performed to examine if loss of resilience, thus frailty, is more present in one of the sexes.

To investigate if extreme DIORs of healthcare expenditures before bereavement are predictive of death after the stressor, we performed a time to event (mortality) analysis using Kaplan-Meier survival estimates and Cox regression stratified on sex, with a follow-up period up to one year after the bereavement with the outcome being death from any cause. Each DIOR was categorized into tertiles, with the reference category being the bottom tertile for each respective DIOR. Autocorrelation for those individuals with constantly zero healthcare costs across the follow-up could not be computed and were classified in the bottom tertile of the respective metric as this corresponds to our intuitive expectation that persons with zero healthcare costs are more resilient than persons with varying healthcare costs. We note that some individuals may have healthcare trajectories with many consecutive zeros (i.e., zero healthcare expenses for an extended time-period) leading to high autocorrelation measures, and that for these cases lag-1 autocorrelation is not an appropriate indicator of critical slowing down, as the observed "memory" in the data is not due to a slowing down per se, but rather due to lack of signal. This issue may lead to some noise in the intended use of the lag-1 autocorrelation measure (the intention being that high autocorrelation corresponds to slowing down phenomena indicating higher frailty), and we anticipate that this may cause decrease in the significance of statistical associations between the lag-1 autocorrelation and dependent variables.

To assess the added value of DIORs in the discrimination ability of a Cox regression model including only age to predict one-year mortality after spousal bereavement, we calculated the time-dependent area under the one-year receiver-operating-characteristic curve (AUC) (26–28). Estimation of prediction error was performed using the leave-one-out-bootstrap method, on 50 bootstrap (drawn with replacement) samples (29). Within a 1-year timespan, the AUC is the probability of an individual receiving a higher mortality risk,

given that he/she died within that year, compared to an individual who survived in the same period. All the analyses were conducted using R version 4.0.3 (30).

## Results

### 3.1 Population statistics

The general population consisted of 934,003 Danish citizens, with their age ranging from 65 to 105 years old. Weekly healthcare expenditures for each individual were available from January 1st, 2011, to December 31st, 2016. For the purposes of calculating their respective DIORs one year before and after bereavement, our analysis was restricted to 51,890 individuals who experienced a spousal bereavement within the 2012–2015 time period (5.55 % of the initial sample). The final sample consisted of 17,813 males (34.3%) and 34,077 females (65.7%) with their median age (interquartile range) at start of the study being 76 (11) and 74 (10) years respectively. An illustration of the sample processing is depicted in Fig. 1.

The population average healthcare costs were investigated by a stratified-on sex analysis for the weekly average expenditures and residual time-series and portrayed in Fig. 2. Increasing trends are observed on the weekly average, manifesting the effect of aging in healthcare costs. Both the weekly average costs and residuals are increased after bereavement, a pattern that can be also observed in the sex and age stratified analysis (see Additional File 1; Supplementary Figs. 1 & 2)

### 3.2 DIORs Across Bereavement States

A comparison of the dynamical indicators of resilience (DIORs) pre- and post-bereavement is listed in Table 1. The average of healthcare expenditures (DKK \* 1000) post-bereavement (median (IQR) = 0.299 (1.377)) was significantly higher ( $p$ -value < 0.001) than pre-bereavement (median (IQR) = 0.208 (0.697)). A comparison of slope and MSE of healthcare costs pre- and post-bereavement followed a similar pattern. Lag-1 autocorrelation of linearly detrended healthcare costs exhibited a different behaviour than the rest of the metrics, that being not significantly different ( $p$ -value = 0.065) after bereavement (median (IQR) = 0.019 (0.378)) when compared with before (median (IQR) = 0.017 (0.391)).

Table 1  
Median (IQR) of DIORs one year before and after spousal bereavement in subgroups

<b>Group</b>	<b>DIORs</b>	<b>Pre Bereavement</b>	<b>Post Bereavement</b>	<b>P-value of difference in pairs</b>
All (N = 51,890)	Average	0.208 (0.697)	0.299 (1.377)	< 0.001
	Slope	0.007 (7)	0.200 (10)	< 0.001
	Mean Squared Error	0.522 (4.237)	0.715 (6.864)	< 0.001
	Autocorrelation	0.017 (0.391)	0.019 (0.378)	0.065
Males (N = 17,813)	Average	0.234 (0.875)	0.355 (1.901)	< 0.001
	Slope	0.020 (8)	0.100 (12)	< 0.001
	Mean Squared Error	0.714 (5.750)	1.020 (9.887)	< 0.001
	Autocorrelation	0.039 (0.446)	0.041 (0.417)	0.011
Females (N = 34,077)	Average	0.198 (0.618)	0.277 (1.165)	< 0.001
	Slope	0.000 (6)	0.200 (9)	< 0.001
	Mean Squared Error	0.446 (3.539)	0.592 (5.583)	< 0.001
	Autocorrelation	0.007 (0.358)	0.009 (0.353)	0.613
65–69 (N = 12,946)	Average	0.130 (0.355)	0.168 (0.458)	< 0.001
	Slope	0.000 (4)	0.001 (6)	< 0.001
	Mean Squared Error	0.239 (1.541)	0.297 (2.290)	< 0.001
	Autocorrelation	-0.020 (0.225)	-0.020 (0.226)	0.535
70–74 (N = 13,361)	Average	0.170 (0.464)	0.229 (0.700)	< 0.001
	Slope	0.000 (4)	0.090 (7)	< 0.001
	Mean Squared Error	0.371 (2.685)	0.485 (3.998)	< 0.001
	Autocorrelation	-0.011 (0.279)	0.009 (0.282)	0.996
75–79 (N = 12,046)	Average	0.232 (0.719)	0.339 (1.454)	< 0.001
	Slope	0.020 (7)	0.200 (11)	< 0.001
	Mean Squared Error	0.623 (4.846)	0.890 (8.292)	< 0.001
	Autocorrelation	0.022 (0.387)	0.026 (0.384)	0.775

Group	DIORs	Pre Bereavement	Post Bereavement	P-value of difference in pairs
80–84 (N = 8,762)	Average	0.328 (1.372)	0.608 (3.454)	< 0.001
	Slope	0.200 (11)	0.400 (20)	0.015
	Mean Squared Error	1.121 (7.534)	1.752 (13.195)	< 0.001
	Autocorrelation	0.107 (0.505)	0.112 (0.489)	0.444
85plus (N = 4,775)	Average	0.736 (3.477)	2.139 (6.952)	< 0.001
	Slope	1.000 (26)	1.100 (39)	0.507
	Mean Squared Error	2.442 (11.412)	3.822 (18.413)	< 0.001
	Autocorrelation	0.316 (0.676)	0.263 (0.572)	< 0.001
IQR = Interquartile Range				
Slope medians and IQRs have been multiplied by 1000 for digit uniformity across the table				

Statistical comparisons indicated that males manifest significantly higher (p-value < 0.001) DIORs than females (p-value < 0.001), both one year before and after bereavement (Additional File 1; Supplementary Table S1). We applied quantile-median regression to verify the association between DIORs and aging. When the DIORs were regressed on age, all the extracted slope coefficients were positive and statistically significant (p-value < 0.001) (Additional File 1; Supplementary Table S2). We observed similar trends on the DIORs in both males and females, as well as within the strata of age (see Table 1).

### 3.3 Predictive Value of DIORs Before Bereavement for Death Thereafter

In order to assess the hypothesis of DIORs before bereavement being quantitative indicators of the level of resilience of a system, we compared them across those bereaved individuals who survived during the first year after bereavement, i.e. ‘Survivors’ and those who did not, i.e. ‘Deceased’. The average was significantly higher (p-value < 0.001) for the latter group (median (IQR) = 1.825 (5.326)) compared with the former (median (IQR) = 0.191 (0.588)). The slope coefficient for the Deceased group (median (IQR) = 0.004 (0.062)) was also significantly higher (p-value < 0.001) than the Survivors group (median (IQR) = 0 (0.006)). The MSE exhibited a similar pattern, that being significantly higher (p-value < 0.001) for the Deceased (median (IQR) = 8.005 (31.389)) when compared with the Survivors (median (IQR) = 0.456 (3.434)). Lag-1 autocorrelation of detrended healthcare expenses was also found to be significantly higher (p-value < 0.001) for those who died earlier (median (IQR) = 0.356 (0.600)) compared with those who survived (median (IQR) = 0.008 (0.360)). Similar differences were found for both sexes separately, as

well as in all age restricted strata (statistical-test results available in Additional File 1; Supplementary Table S3, S4 and S5).

Time to event analysis was performed to investigate the value of tertile-grouped DIORs before bereavement to predict death in the first year thereafter. The Kaplan-Meier curves of the analysis are presented in Fig. 3, depicting the cumulative percentage of deaths belonging in each tertile group of all the DIORs for the period of 52 weeks after bereavement. The cumulative percentage of deaths within one year after spousal bereavement was the highest for the group of people belonging in the top tertile of each DIOR. The pattern was observed both in males and females, with the latter exhibiting smaller percentage of deaths than the former. The middle and bottom tertile seem to have moderate to weak differences in the survival curves.

The estimated hazard ratios (HRs) of DIORs on mortality risk, along with their respective 95% confidence intervals (CIs), of the Cox regression adjusted for age, are reported in Table 2. When compared with the reference category (bottom tertile), the group of males in the top tertile of average appeared to have a 4.81-fold higher mortality risk [95% confidence interval [CI], 4.04–5.72]. The corresponding mortality risk was found to be 7.28-fold higher [95% CI, 6.03–8.78] for females. Similar risk differences were found for the slope coefficient and MSE. Although we did not necessarily expect autocorrelation to exhibit the same predictive power, a similar trend was observed in the top tertile group for lag-1 autocorrelation. Males exhibited a 2.86-fold higher mortality risk [95% CI, 2.44–3.34] while females' risk being 4.65-fold higher [95% CI, 3.95–5.48], when compared with the bottom tertile.

Table 2

Hazard ratios (95% CI) of all-cause mortality after bereavement dependent on various DIORs in tertiles.

Stratum	DIORs	Tertile	HR [95% CI]	P-value
All (N =51,890)	Average	Bottom	1	
		Middle	1.64 [1.41, 1.90]	< 0.001
		Top	5.95 [5.24, 6.76]	< 0.001
	Slope	Bottom	1	
		Middle	0.51 [0.45, 0.57]	< 0.001
		Top	1.60 [1.47, 1.74]	< 0.001
	Mean Squared Error	Bottom	1	
		Middle	3.38 [2.84, 4.03]	< 0.001
		Top	10.05 [8.54, 11.84]	< 0.001
	Autocorrelation	Bottom	1	
		Middle	1.59 [1.40, 1.81]	< 0.001
		Top	3.66 [3.27, 4.10]	< 0.001
Males (N =17,813)	Average	Bottom	1	
		Middle	1.57 [1.28, 1.92]	< 0.001
		Top	4.81 [4.04, 5.72]	< 0.001
	Slope	Bottom	1	
		Middle	0.64 [0.55, 0.76]	< 0.001
		Top	1.61 [1.43, 1.81]	< 0.001
	Mean Squared Error	Bottom	1	
		Middle	2.83 [2.23, 3.60]	< 0.001
		Top	7.73 [6.19, 9.65]	< 0.001
	Autocorrelation	Bottom	1	
		Middle	1.44 [1.21, 1.71]	< 0.001
		Top	2.86 [2.44, 3.34]	< 0.001
	Average	Bottom	1	
		Middle	1.74 [1.40, 2.16]	< 0.001
		Top	7.28 [6.03, 8.78]	< 0.001

Females (N =34,077)	Slope	Bottom	1	
		Middle	0.41 [0.34, 0.49]	< 0.001
		Top	1.58 [1.41, 1.78]	< 0.001
	Mean Squared Error	Bottom	1	
		Middle	4.00 [3.10, 5.17]	< 0.001
		Top	12.89 [10.14, 16.40]	< 0.001
	Autocorrelation	Bottom	1	
		Middle	1.75 [1.46, 2.11]	< 0.001
		Top	4.65 [3.95, 5.48]	< 0.001
All hazard ratios (HRs) adjusted for age, stratified on sex				
CI = Confidence Interval				

### 3.4 Discrimination Ability of DIORs

We assessed the added value of DIORs to the discrimination ability, next to age, in predicting mortality within one year after spousal bereavement among all the individuals (N = 51,890) aged 65 years and older. Table 3 summarises the results of the AUC analysis stratified on sex. Age seems to be the main factor of discriminative value with an AUC of 68.9% [95% CI, 67.4% – 70.3%] and 70.2% [95% CI, 68.8% – 71.6%] for males and females, respectively. The addition of average to the model with age, increased AUC by 7.1% [95% CI, 6% – 8.3%] and 8.9% [95% CI, 7.7% – 10.1%] for males and females, respectively. The discriminative value, based on the AUC, was increased with the inclusion of slope by an extra 2.5% [95% CI, 1.8% – 3.2%] for males and by 4.1% [95% CI, 3.2% – 4.9%]. The MSE of healthcare consumption improved the discriminatory power (AUC) to predict all-cause mortality by an extra 8.1% [95% CI, 6.9% – 9.2%] for males and 10% [95% CI, 8.8% – 11.2%] for females. Lag-1 autocorrelation increased the discriminatory value of the model with age, by a further 3.4% [95% CI, 2.6% – 4.3%] in males and 6.5% [95% CI, 5.4% – 7.5%] in females.

Table 3  
Discrimination ability to predict one-year mortality based on DIORs stratified by sex

	<b>Males</b> (N = 17,813, Deceased = 1423)		<b>Females</b> (N = 34,077, Deceased = 1439)	
	AUC [95% CI]	p-Value	AUC [95% CI]	p-Value
Age	68.9 [67.4, 70.3]	< 0.001	70.2 [68.8, 71.6]	< 0.001
Age + Average	76 [74.8, 77.2]	< 0.001	79.1 [78, 80.2]	< 0.001
Age + Slope	71.4 [70.0, 72.7]	< 0.001	74.3 [73.0, 75.5]	< 0.001
Age + MSE	76.9 [75.8, 78.1]	< 0.001	80.2 [79.2, 81.1]	< 0.001
Age + Autocorrelation	72.3 [70.9, 73.6]	< 0.001	76.6 [75.5, 77.8]	< 0.001
Age + MSE + Autocorrelation + Slope	77.7 [76.5, 78.8]	< 0.001	81.8 [80.9, 82.8]	< 0.001
AUC : Area Under the ROC Curve				
P-values < 0.05 indicate significant increase in AUC compared with the null model (only age)				

In order to avoid multicollinearity, we selected those predictors in the final model which were not highly correlated with one another, while providing the highest predictive value. The average indicator was highly correlated with MSE ( $\rho = 0.79$ , Spearman's p-value < 0.001), while the cross-correlations among the rest of the indicators were ranging from 0.07 to 0.33. Hence, the final model's predictor variables consisted of age, the slope coefficient, MSE and lag-1 autocorrelation. The discriminatory power according to the AUC was 77.7% [95% CI, 76.5% – 78.8%] for males and 81.8% [95% CI, 80.9% – 82.8%] for females.

## Discussion

The current research focused on the perturbation of spousal bereavement and the ability of DIORs to capture transitions in human health in response to this perturbation. To this end, we analyzed the healthcare consumption of Danish citizens over the age of 65 by applying the logic of systems failure, as expressed in the dynamical indicators of resilience. Aggregation of all the different types of costs for each person merges all the discrete layers of healthcare together (from treatment to care), thus serving as a read out of their health status and level of resilience.

The analysis of bereaved individuals produced the following observations. First, all the indicators describing the healthcare expenditures data were significantly increasing with age and higher in males, suggesting lower resilience. In addition, the average, slope coefficient and MSE were significantly higher the year after bereavement when compared with the year before. The aforementioned is a strong indication that spousal bereavement seems to be a life-event which apart from causing intense physical and mental distress to peoples' lives, poses the risk of increased, more volatile healthcare consumption and a rate of increase across time. Last, all the dynamical indicators were found to be signals of early loss of resilience before critical transitions in human health, i.e. -death. We inferred the latter by observing that the group of individuals with the highest indicators of resilience, before bereavement, exhibited a significantly higher mortality risk after bereavement when compared to those with low DIORs. Ultimately, we found evidence that these indicators are able to capture the dynamics of human resilience and predict mortality, indicating that with ageing comes frailty, with males being the frail sex.

Time to event and AUC analysis evaluated the hypothesis of DIORs predictive value. Individuals with high DIORs one year before bereavement were found to have significantly increased mortality risk for the year thereafter when compared with low DIORs group. These outcomes were consistent for each respective indicator, both for males and females. Therefore, this finding further enhances the hypothesis of these metrics being indicators of resilience in the life sciences, with higher DIORs indicating less resilient systems.

Analysis of time series data consisting of longitudinal measurements of individuals provides the opportunity to study the dynamics of a given system across time, which can be reflected in its variability, rate of change and correlation, moving beyond the mean or just a snapshot value at a given time point. Therefore, it is possible to acquire a variety of distinct signals which can be further researched for their respective effect, either individually or combined, on specific clinical endpoints. Based on the aforementioned, it seems that the implementation of dynamical indicators (average, slope coefficient, MSE, and lag-1 autocorrelation) as covariates for predicting outcomes such as death, could be insightful as being shown in the values of the hazard ratios and the AUC of the analysis, since a more thorough analysis investigating various dynamic properties is considered.

The AUC analysis indicated that all of the DIORs seem to increase the AUC when included in a model with age. We observed the highest increase in the AUC by adding the MSE, followed by the average, then lag-1 autocorrelation and last, the slope. The final model with MSE, lag-1 autocorrelation, slope, and age as predictors reached an AUC of 77.7% and 81.8% for males and females, respectively. Therefore, it appears that the various signals extracted from the dynamic behavior of health-related time-series are capable of discriminating mortality risks amongst older persons well, both for males and females.

We consider the current study as an extension of the ideas of previous work on complex systems and DIORs, in the field of life sciences (6, 14, 17, 18), aiming to make the logic applicable in register-based longitudinal healthcare data. For that purpose, indicators were chosen primarily based on their ability to capture distinct dynamics of healthcare consumption, without being restricted to match the paradigm of

critical slowing down. Interestingly, using DIORs as explanatory variables, along with age and sex, reached an AUC of over 80% for a multifactorial event such as death. We believe that by combining dynamical metrics with more static variables, such as socioeconomic status, education, marital status, Body Mass Index, or comorbidities could greatly enhance the overall performance while also contributing to an even better understanding of resilience and thus death. In addition, the recent advances of wearable and sensor data can provide us with time series of plenty of data, which when analyzed properly by extracting dynamical indicators from them, can depict the dynamics of human health across time. Of course, the applications of these DIORs and their research can be extended beyond healthcare costs, investigating physiological responses across time, such as blood pressure, temperature, glucose levels, electric activity of the heart etc.

The strengths of this research are the sample size, the completeness of healthcare costs, which is based on national register data and is representative of the bereaved population, as well as the time to event analysis to study the behavior of these dynamical indicators in the field of Health sciences.

However, the study also has its limitations. First, while there were over 50 thousand individuals included in the study, in order to study an abrupt stressor such as bereavement, DIORs were measured for a maximum of 52 consecutive weeks before and after bereavement. We are aware that the aforementioned is marginally enough to study the behavior of these indicators and their accompanied dynamics in rolling windows. Second, the results cannot be generalized for the whole population of Denmark since the data include only individuals with age 65 or older who have experienced spousal bereavement. Last, further research is needed to investigate if the constructed tertiles and overall analysis can be applied to bereaved individuals over the age of 65 in countries other than Denmark. The reason for that is that healthcare expenditures are bonded with the healthcare system and social welfare of each country, a factor which may lead to different patterns in the data.

In conclusion, the current research focused on the metrics of average, slope, MSE and lag-1 autocorrelation and evaluated their ability to signal loss of resilience within the health sciences. Spousal bereavement is a stressor which is known to shift the dynamics of human health. Older people who suffer bereavement seem to have increased average consumption, rate of increase, and variability in the healthcare consumption patterns. We showed that these indicators which signal loss of stability in the physical sciences, seem to be also capable of depicting the dynamics of human resilience as well. Indeed, individuals exhibiting high values of the respective DIORs before bereavement, were the ones who had increased mortality risk after the stressor. Hence, the higher these indicators are, the less resilient an individual seems to be. We believe that the implementation of a dynamical approach, which not only considers static predictors but also these ones that capture physiological and dynamic responses (variability, drift), can add significant value to the understanding and assessment of human's health status.

## Declarations

# Authors Contributions

AK, PN and RGJW were involved in the conceptualization of the research question, identified and appraised relevant literature. MJ acted as fourth reviewer, providing critical input in the analysis, and assisted in the interpretation of the results. AK drafted the manuscript and performed the computational analysis with critical input from all other authors. All authors read and approved the final manuscript.

# Acknowledgements

This work is supported by grants from Novo Nordisk Fonden [NNF170C0027812].

# Competing Interests

The authors declare that they do not have any competing interests.

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## Figures

# Analysis of Denmark's Population

Study Period :  
2011 - 2017

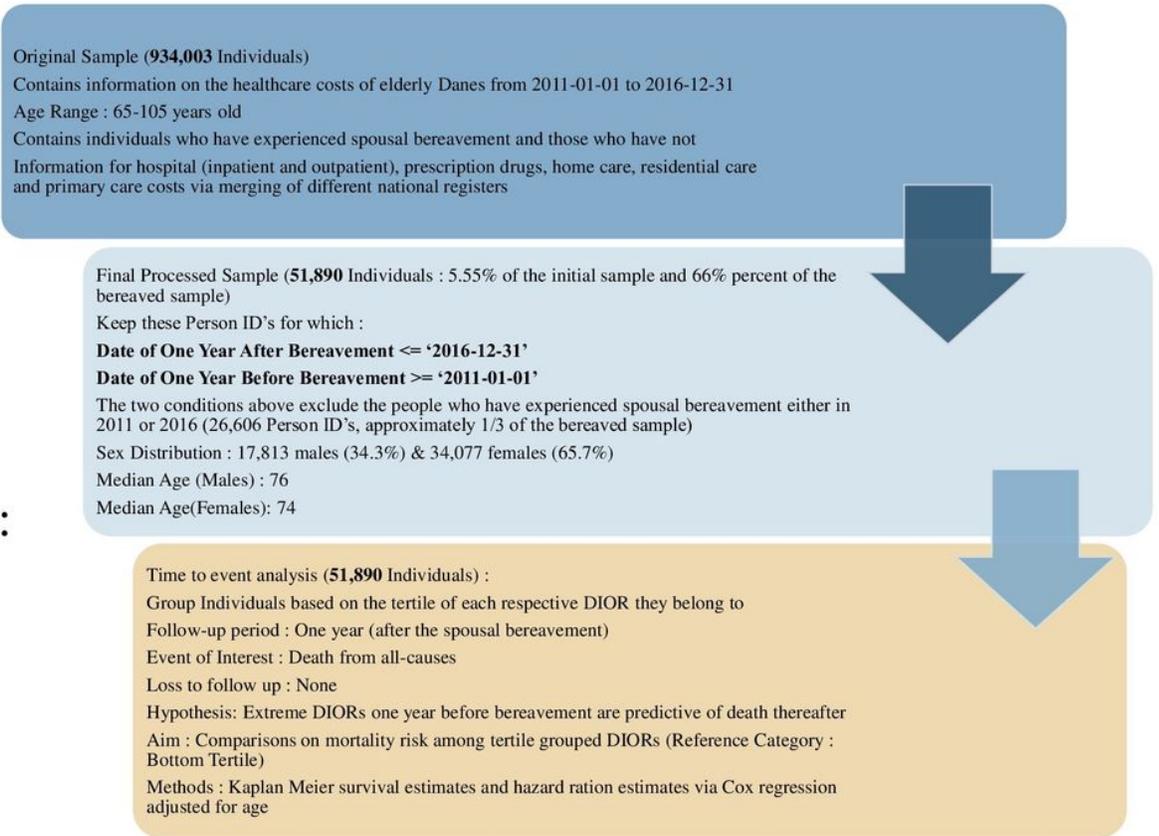
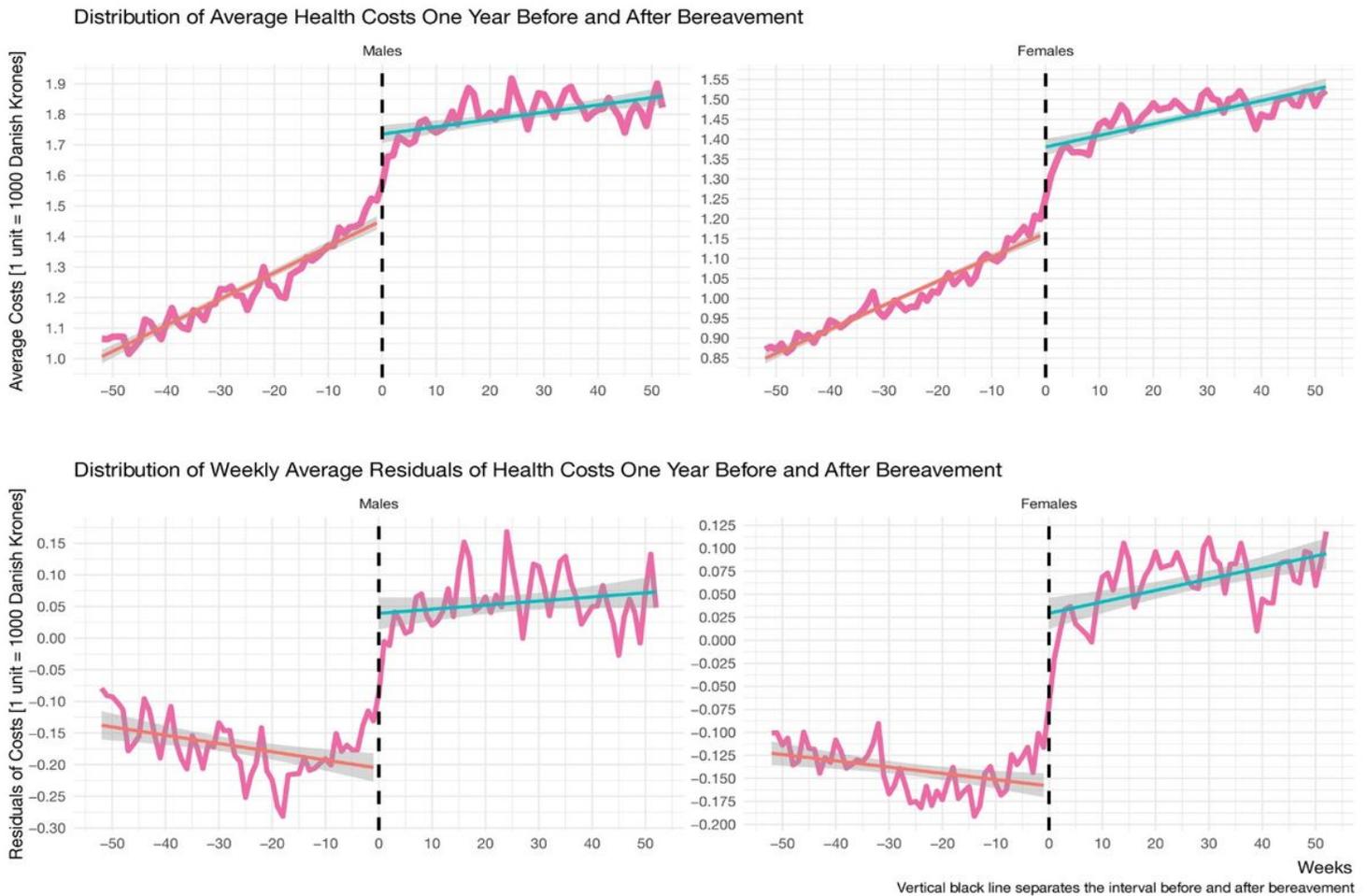


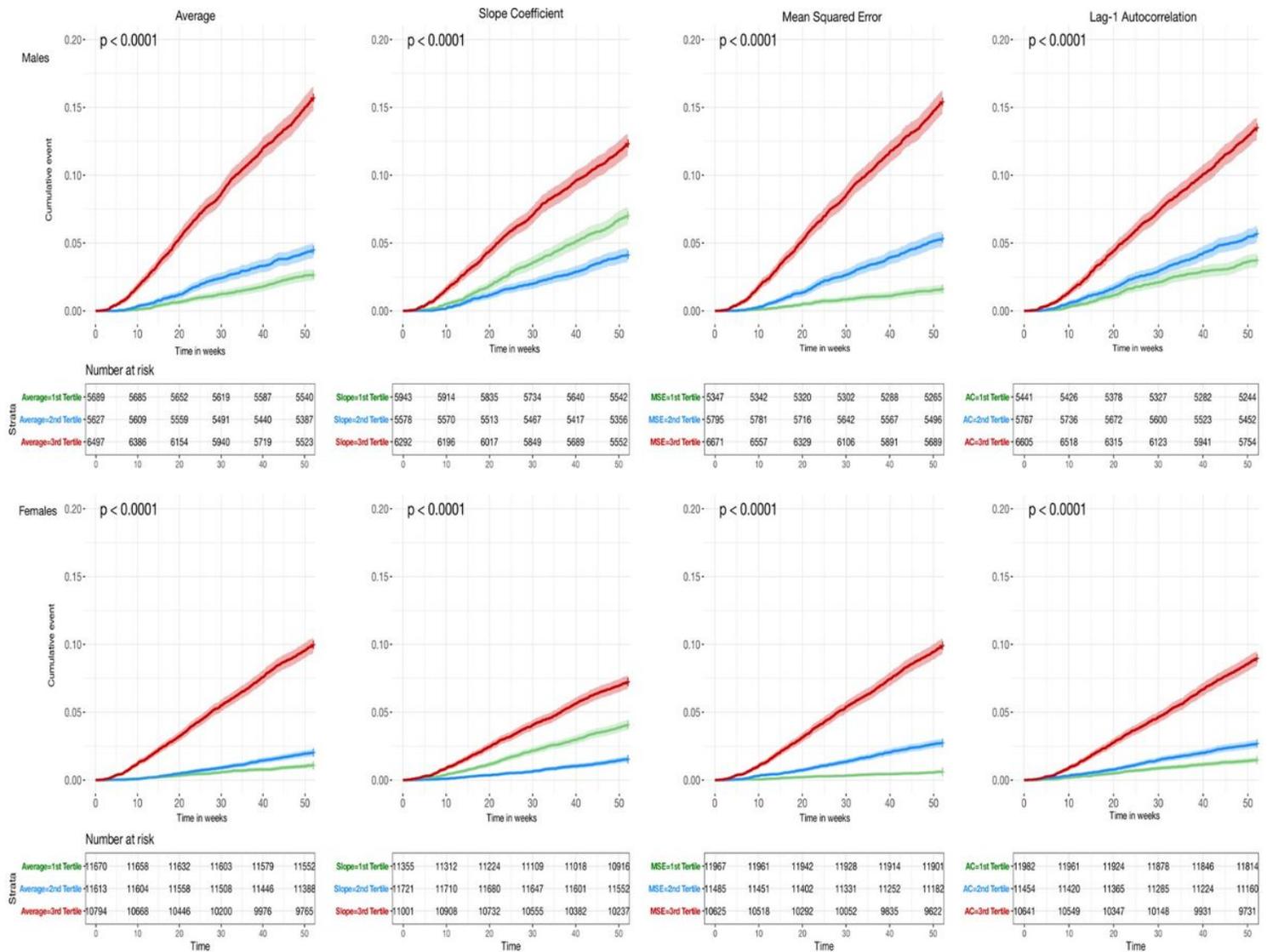
Figure 1

Flowchart of the analysis of Danish healthcare register data. Upper box presents the initial sample of Danes over 65 years for the general population. Middle box explains the process from the original sample towards the final one containing only the spousal bereaved individuals suitable for the analysis. The box at the bottom illustrates the process of time to event analysis.



**Figure 2**

Sex stratified weekly average and residuals of healthcare expenditures pre- and post-bereavement. Week 0 depicts the date of the standardized stressor of bereavement, splitting the time interval one year before and after bereavement. Linear regression lines are fitted both before and after the stressor, indicating the differences in the healthcare consumption pattern between the two periods. Average healthcare consumption after bereavement is higher than before, for both males and females. The average of weekly-based residuals also seems to be following the same pattern, that being increased after bereavement. Females seem to exhibit a more resilient behavior, with smaller deviations when compared with males, manifested in the weekly average and the residuals of their respective healthcare costs.



**Figure 3**

Sex stratified Kaplan-Meier curves of DIORs on cumulative deaths (%) up to one-year after bereavement. Time is measured in weeks with each respective number at risk in the tables below each curve. P-values indicate the significance of log-rank test for difference in survival between the tertiles. Shaded areas represent 95% CIs. First row depicts the results for males, whereas second row is for females. The colors depict the tertiles of each respective DIOR (red: top-3rd tertile, blue: middle-2nd tertile, green: bottom-1st tertile).

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