The Pandora Box from 12 Countries: Who Benefits More from Modern Interventions?

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Abstract

Aging constitutes an inevitable decline in vitality, representing a phenomenon that affects the population since the advent of vaccination and the doubling of life expectancy at birth. Preventive medicine stands as the cornerstone of life-saving efforts, offering an opportunity that is shaped by factors such as gender, financial resources, health consciousness, and individual decisions. It has been observed that males tend to experience the onset of chronic illnesses at an earlier stage than females, leading to a shorter life expectancy for males. While this traditional assumption may persist, recent findings in gender-specific mortality rates have revealed a significant reversal. A notable shift in the modern dynamics of gender-based mortality has been attributed to contemporary interventions, which appear to be pivotal in reducing this disparity. This analysis focuses on deaths related to circulatory failure, their comorbidity, and the early diagnosis of diseases in order to examine the Pandora's box hypothesis of gender differences and identify the statistical frailty component affecting mortality selection. The empirical findings of this analysis indicate that patients experiencing renal and circulatory failure face a mortality risk that is at least 10% higher than those with circulatory failure alone. Furthermore, the temporal changes in mortality dynamics suggest that males are reaping greater benefits from current life-extending techniques. These results strongly imply that longitudinal studies should incorporate transplant-related data to obtain a more robust hazard ratio for clinical evaluation.

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Introduction

Diseases affecting the circulatory system have been identified as the primary cause of morbidity and mortality in developed countries, accounting for over 30% of all adult deaths over the age of 40 [1][2][3][4][5]. The 21st century has witnessed a significant increase in human life expectancy at birth compared to past generations, who lacked sufficient knowledge about preventive measures against infectious diseases [6]. Despite advancements, the modern population remains vulnerable to non-communicable diseases, raising questions about whether life-saving interventions benefit women more than men.

Aging is considered a fundamental factor in the biological processes observed in molecular studies and empirical research on risk factors leading to mortality[1][7][8][9][10][11]. The accumulation of cellular damage and chronological age often lead to the onset of one or more diseases. Consequently, it is unsurprising that elderly individuals frequently experience multiple diagnosed morbidities [12]. The presence of comorbidities doubles the risk of mortality, and the shorter life expectancy of males has long been acknowledged by the scientific community and the general public [13][14][15]. While scientific literature has highlighted gender-based differences in adjusted relative risk and odds ratios for various diseases, there is still a lack of clarity regarding the age-specific mortality trends among patients with the same comorbidities resulting in circulatory failure deaths. These disparities in mortality trends may be influenced by gender-specific variations in the administration of life-saving and life-extending interventions. This analytical hypothesis seeks to further explore an alternative explanation for the current finding related to the reversal in age-specific mortality rate ratios between genders in all countries; shown in Results section.

Based on a multinational longitudinal prospective study, my analysis investigates the mortality risks associated with morbidities leading to circulatory failure deaths, and explores the potential of early disease diagnosis as a modifiable risk factor. The analysis focuses on various morbidities, including circulatory failure, renal, respiratory, cancer, and digestive diseases. Additionally, the study rigorously examines temporal changes in mortality trends to understand the impact of life-extending and life-saving measures, as well as the challenges associated with these analyses in longitudinal data.

Results

The analysis included participants recruited since the start of the Survey of Health, Ageing and Retirement in Europe (SHARE) longitudinal study in 2004, totalling 14,310 individuals. In 2017, the survival follow-up revealed that 24.8% had deceased; 1757 females and 1795 males. Among all-cause mortality, 34.4% were classified under circulatory-failure cause-of-death (COD); 33.8% for females and 35.0% for males. However, not all circulatory-failure COD cases had a medical history of diagnosed circulatory disease, such as stroke, heart attack, and other cardiovascular-related illnesses (**Figure 1** & **Table 3**). It is noteworthy that the data exhibits a depleting wave structure whereby only wave 1 recruited participants were included.

Participants who had succumbed to circulatory-failure and had been diagnosed with at least one circulatory disease before their last survival follow-up were categorized as early diagnosed patients (circulatory: Yes). These patients would have received disease management and proper medical treatments. The ages at death among early diagnosed circulatory-failure patients demonstrated a delayed occurrence and a higher median compared to those not diagnosed at their last survival follow-up (late diagnosis, circulatory: No) as depicted in *Supplementary Figure S1*. The median differences in premature circulatory deaths were 11 years for females and six years for males. Additionally, a separate category 'Don’t know/NAs' regarding existing morbidity types was included during the survival analysis.

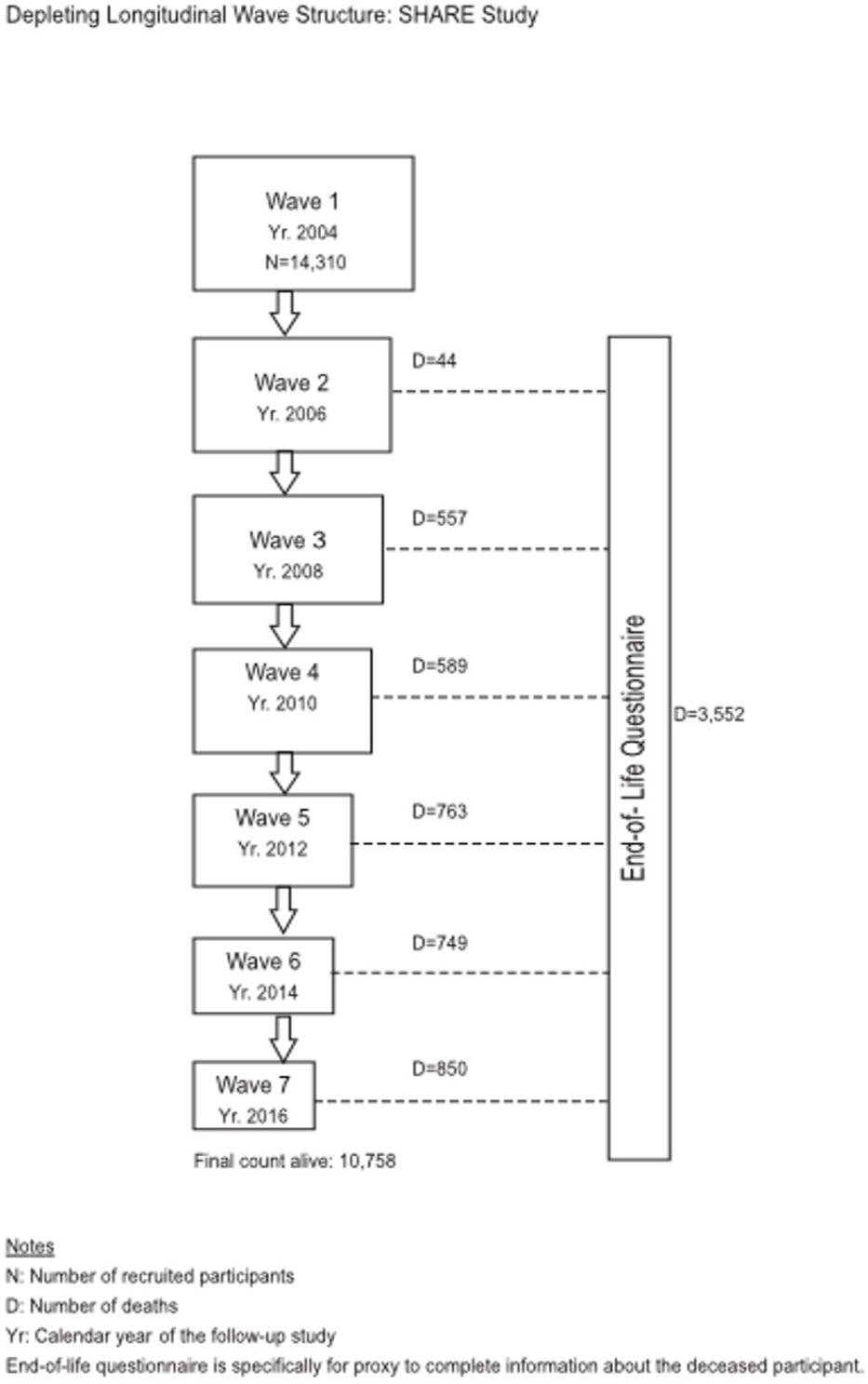

Figure 1. Flowchart for Depleting Wave I SHARE study. Information on lifestyle and health modules were updated from 2004 to 2014; wave 1 to 6. A calendar time-interval delay for survival status update – *e.g.,* the expiry of wave 1 participants can only be traced starting from wave 2 end-of-life questionnaire. Thus, survival status was last updated in year 2017; wave 7. The boxes were not drawn to scale in representing the depleting number of participants. The dotted line traces expired participants out from the study.

The Cox regression model was initially applied to a short data format containing all-cause mortality and right-censored

survival profiles. However, due to changes in smoking status and diagnosed-treated diseases among the participants between 2004 and 2014, the hazard estimates obtained may not be fully representative and could potentially lead to misleading inferences. Consequently, the data was restructured into an event-history format to facilitate the updating of changes in disease diagnosis, smoking habits, and vital status accordingly refer to *Supplementary Table S1*.

Circulatory-failure diseases are often accompanied by comorbidities such as renal or respiratory diseases, which can contribute to circulatory-failure COD. **Figure 2** and **Table 1** present the heterogeneity index by birth cohorts, derived from a multivariate Cox-frailty model. This index measures the frailty-robust members within each categorical birth cohort. A low numeric gamma-distributed index indicates high robustness, with the index always being positive. In contrast, a higher index signifies a greater proportion of frail-robust individuals, indicating increased heterogeneity. Any disparity in the age-specific force of mortality among groups is reflected in the graphical representation in **Figure 2**. An equilateral triangle would indicate no disparity, while an isosceles or irregular-shaped triangle denotes mortality disparity within at least one of the groups. *Supplementary Figure S2* further illustrates the findings of a distortion in age-specific COD, particularly for circulatory-failure deaths. It is observed that circulatory-failure CODs tend to have an earlier age-of-onset, impacting mid-adulthood and mid-elderly individuals, in contrast to aging diseases CODs, which predominantly affect the elderly. The inclusion of year of birth as a frailty component or stratified for its mixed-effects is crucial in the multivariate model.

The study proceeded to compare the risk estimates between early and late circulatory disease diagnoses resulting in circulatory-failure COD. A complete-case approach was employed, considering only deaths from circulatory-failure in this analytical component. **Table 2** and *Supplementary Table S2* indicate that participants who aware of their circulatory diagnosis had a lower mortality risk than those who were not. It is essential to interpret the hazard ratio (HR) in complete-case considering the depleting heterogeneity. For instance, the HR for males-only presented in **Table 1** is interpreted as a protective risk factor (*<1.00*) for current smokers. However, it is vital to acknowledge the potential bias introduced by the median recruitment age of 63, influencing the survival probability due to life-detrimental risk exposures, including tobacco smoking.

A significant limitation of the study is the inability to account for life-saving opportunities such as solid-organ transplants, which remain unrecorded in the SHARE study and other longitudinal prospective studies. To obtain more reliable risk estimations, efforts to disentangle the information from transplant criteria are warranted. **Table 2** showcases the multivariate Cox time-varying analysis of those who had the potential to receive solid-organ transplants, excluding cancer patients.

The implementation of a simplified Cox time-varying model was necessitated by the lack of convergence in the Cox-frailty analysis, primarily due to the low number of occurring deaths in the youngest categorical birth cohort. The stratification by countries and categorical year of birth was therefore adopted to address this issue.

In both the Cox-frailty and simplified time-varying models, renal disease emerged as the sole significant morbidity influencing the survival profiles of circulatory-failure COD. Males demonstrated a higher risk for mortality, while the gender-specific hazard ratios for circulatory-failure disease with renal disease as a comorbidity reflected approximately 10

– 11% elevated risk for mortality (**Table 2** and *Supplementary Table S2*). Accounting for a complete-case by circulatory-failure COD, the finalized multivariate HR continued to indicate males experiencing a higher risk than females, with an 11% risk increment for circulatory-failure mortality, using females as the baseline hazard. Furthermore, the analysis revealed hidden heterogeneity within female patients, suggesting that the interactive risk exposure may be a lagged-effect from the recovery process influencing the probability of death.

The intricate findings hint at varying recovery processes between males and females, potentially favouring male patients in extending longevity; **Figure 2** and **Figure 3**.

Figure 2. A triangular net chart representing the measured heterogeneous-mixing index from Cox-frailty multivariate model for a) right-censored & all-cause mortality, and b) circulatory-failure deaths only. The heterogeneity-index measures the proportion of frail-robust participants within the specified group; categorical birth cohorts: 1902 – 1933 (blue), 1934 – 1945 (orange), 1946 – 1949 (yellow), 1950-1974 (green). Abbreviations: All: all participants; F: Females, and M: Males. Refer to **Table 1** & *Supplementary Table S2* for the hazard ratios and 95% confidence intervals.

a) Right censored & all-cause mortality. Axis ranges from *0.0* to *4.0;*

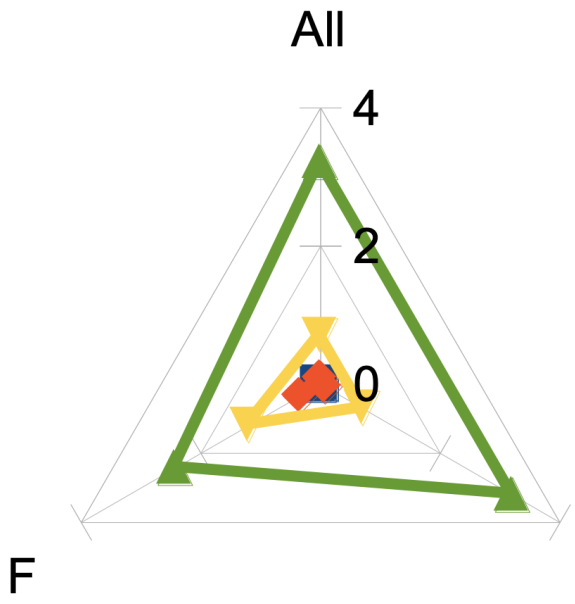

Figure 2a.

b) Circulatory-failure deaths only. Axis ranges from *0.0* to *2.0*.

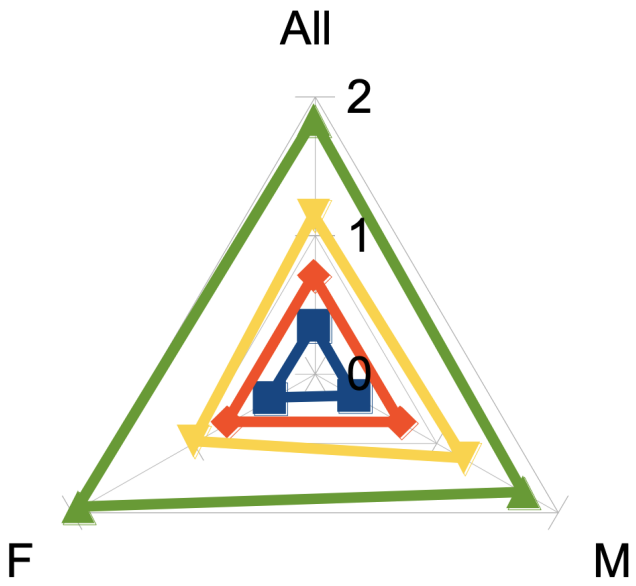

Figure 2b.

Figure 3. Gender disparities in mortality rate ratio females to males were observed in multiple countries including Sweden, the Netherlands, France and Switzerland. All EU countries in SHARE exhibited a mortality u-turn or retardation in gender disparities in the year 1980; *x-axis* is calendar year. Remarkably, this point of inflection is highly similar across all EU countries and marks a significant milestone for the standardization of renal transplantation, and subsequently other organ transplants. When the ratio gets closer to 1.0, it is an implication that males are gaining improvements in survival. This shift is evident across all age-specific deaths including childhood mortality ≥3 years old; *Supplementary Figure S4*.

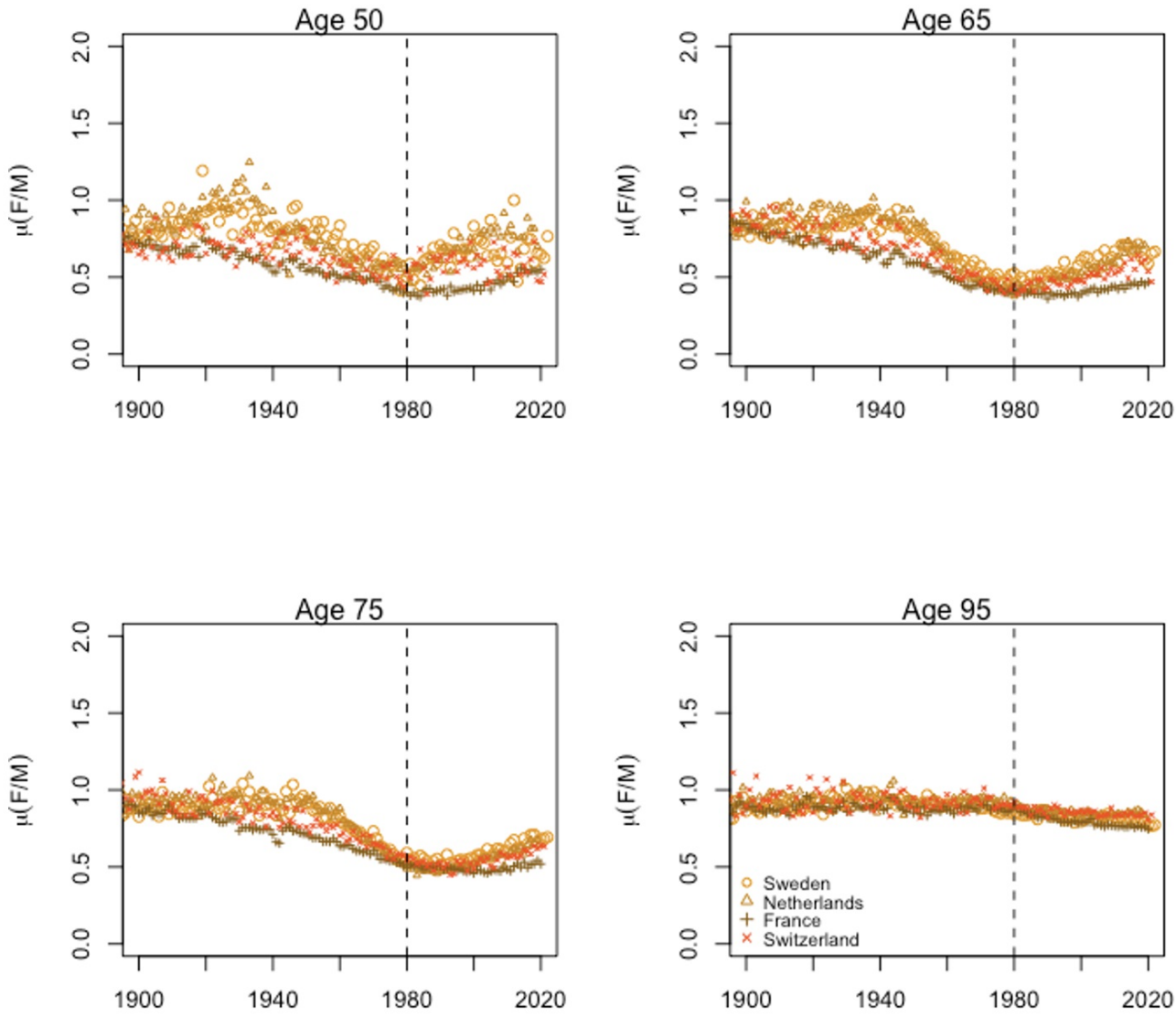

Figure 3.

Discussion

Heterogeneity plays a significant role in shaping the dynamics of mortality and fertility in population studies [16][17][18][19][20]. From the perspective of Darwinian selection of the fittest to the Hayflick Limit on cell division, the variation among individuals contributes to a wide range of observed and measured indicators [21]. It has long been a subject of inquiry why certain individuals are unable to stave off the early onset of chronic diseases, while others manage to evade premature death. Some research studies have suggested that the latter group may have adapted themselves to a healthier and more active lifestyle, including abstaining from smoking, receiving seasonal flu vaccinations, belonging to an affluent socioeconomic status, and recognizing early signs of diseases [22][23][24]. Despite life expectancy surpassing the age of 75 in developed countries, it remains a perplexing issue whether the advancements in disease diagnosis and treatments have diminished heterogeneous selection for mortality among affected individuals. Healthcare serves as a provider of health and longevity, functioning as a resource to be shared among individuals of all genders and ages, and is

influenced by financial costs. As this life-saving resource must be distributed, analyses should be based on the heterogeneous mixing by gender and age or year of birth.

Circulatory disease stands as the most prevalent malady in adulthood, often operating stealthily as a silent yet lethal threat to those affected. The absence of timely medical interventions and comprehensive disease management heightens the risk of permanent disability and premature mortality [25][26]. Given its escalating incidence in the adult population, there is a growing interest within the healthcare domain to explore gender disparities in succumbing to circulatory failure as a cause of death. Research indicates that females exhibit a greater propensity to pursue early disease diagnosis compared to males. Along with the Cox survival analysis, analytical process in this study also revealed that males, especially those in poor health, were less inclined to acknowledge their condition as patients, potentially leading to unfavorable prognoses and limited treatment options prior to decease. Moreover, while gender-based mortality differentials have been extensively documented, it is only recently that the empirical age-specific mortality rate ratio inflection point has emerged μF(x)/ μM(x) **Figure 3**, *Supplementary Figure S3 & S4*. Although it is widely acknowledged that males constitute the preponderance of risk-takers in the population, resulting in a distinct mortality peak during young adulthood μM(x), an aspect that has been thoroughly debated with numerous mathematical endeavors to unveil the distribution characteristics (*i.e.,* young adulthood: ages 10 to 35), studies have thus far neglected to assess temporal changes in mortality dynamics and gender-based disparities. The current study serves to present an alternative explanation for the observed μF(x)/ μM(x) inflection point, which has been evident since the 1980s. This phenomenon is attributed to the introduction of standardized solid organ transplant protocols [27]. If both males and females have equal access to medical treatments and organ transplants, and equal prospects for disease remission, the 1980 inflection point μF(x)/ μM(x) would not have materialized. For instance, μF(x)/ μM(x) for the period from the 1980s to the present conveys that males have been availing themselves of more favorable life-saving opportunities or exhibiting a greater likelihood of recuperating more efficiently than females, consequently resulting in a more pronounced reduction in their age-specific mortality rate; **Figure 3**. Any increment or decrement in the rate ratio implies that one gender is faring significantly better in reducing their mortality risk at the specified age, *x*, over the years. Thus, it is evident that since the 1980s, the observed gender mortality rate ratio suggests that males have been benefiting from more favorable life-saving interventions or are more likely to recover efficiently compared to females, thereby effecting a more conspicuous reduction in their age-specific mortality rate; μM(x) (*Supplementary Figure S3*).

Though there have been instances of males exhibiting a distinct hazard-risk trend compared to females, two contradictory trends diverging from existing literature warrant discussion. When the multivariate Cox-frailty model for circulatory-failure causes of death (CODs) incorporated the variable of early diagnosed circulatory disease (Circulatory: Yes; **Table 2**), the male-only hazard ratio (HR) estimates indicated a 14% excess risk, whereas the female-only estimates portrayed early diagnosis as a protective risk factor. Early disease diagnosis is anticipated to consistently function as a protective risk variable. However, a segment of male respondents did not disclose information about their circulatory health and faced a >400% likelihood of mortality. From **Table 1** and **Table 2**, the estimated HRs suggest that smoking status is not the sole life-detrimental risk factor for males with circulatory-failure CODs. An intriguing observation emerged when renal disease was introduced as a comorbidity in the multivariate survival model, revealing a 41% excess hazard risk exclusively among

females, while males exhibited no increment; HR=1.00. The plausible explanation is that females undergoing circulatory diseases have a different recovery trajectory than males following similar medical interventions and may not fare well in terms of survival when renal disease is a comorbidity. If this explanation is deemed scientifically acceptable, it further bolsters cardiac intervention studies indicating gender-specific differences in the recovery process [28][29]. The disparity in HR estimates illustrates that male patients derived greater benefit from life-saving opportunities than females; **Figure 2**, acting as a remedy to interrupt the persistent widening of mortality disparity between the two genders that occurred from 1900 to 1980; **Figure 3**, Supplementary Figure S3 & S4.

This study is subject to limitations in further investigating the findings and research hypothesis due to the insufficient information on organ transplantation, both as a recipient or donor, as well as special cases that exempt individuals from the transplant waiting list. Additionally, potential complications such as the development of blood disorders, such as Non-Hodgkin's lymphoma, which is commonly observed among post-transplant patients, present an additional challenge [30][31]. Moreover, certain liver-failure patients may undergo up to five liver transplants during their lifetimes, and childhood diseases, once rare, are now increasingly prevalent due to advancements in medical and technological innovations, such as cystic fibrosis (CF), a recessive rare genetic disease. While CF historically limited affected children to a life expectancy of merely six months, recent medical reports indicate that affected individuals can now anticipate survival into mid-adulthood, often having undergone at least one organ transplant before the age of 20 [32][33][34]. Furthermore, diabetes, a metabolic disorder characterized by impaired insulin production, and a progressive contributor to renal failure, particularly affecting males. In age-adjusted chronic renal disease treatment and survival outcomes, it has been noted that women exhibit poorer performance than men [14]. Although detailed research on the natural history of gender-differences in diabetic patients is warranted, it is widely acknowledged within the medical community that renal failure significantly mediates death from cardiac failure [4][35][36]. Despite its limitations, this study reaffirms the prevailing interaction between renal and circulatory diseases as indicated in current medical literature.

If artificial censoring and truncation are not factored into the design of the statistical algorithm or survival analysis protocol, it would pose a significant challenge to optimize risk estimates and accurately define the most representative hazard shape, including its frailty distribution. This presents crucial implications for healthcare management reports and the clinical audit process.

This empirical study serves as an example of the inability to accurately determine the frailty component of circulatory failure deaths among females, as it lacks the statistical landmark indicating when, or if, any transplantation had occurred. The lack of convergence during a Cox-gamma frailty analysis suggests that the gamma distribution may not be the most suitable to accommodate the extended life-years resulting from post-transplantation. This is particularly pertinent as the hazard shape and its age-specific mortality trajectory, when examined, are likely to deviate from the norm and the respective baseline hazard [37][38].

Conclusion

Renal disease as a comorbidity among patients with circulatory failure significantly increases the risk of mortality by at least 10% in both genders. Timely diagnosis of circulatory diseases is a preventive measure that reduces the risk of mortality from all causes and circulatory failure-related causes. To promote better healthcare and awareness for healthy aging, the detrimental effects of smoking on health and mortality should be emphasized from a young age. Longitudinal and cross-sectional epidemiological studies should take into account the changes in mortality risk dynamics resulting from the standardization of organ transplantation. Including information on transplants can help elucidate certain puzzling and unexplained trends in some studies, including the role of frailty in female circulatory failure-related causes of death.

Methods & Materials

Data format

The SHARE longitudinal study is a comprehensive long-term survival follow-up of participants who were enrolled in 2004. [39] This study involves a biennial collection of participants' self-reported lifestyle behaviors and health information. In cases where participants did not survive during subsequent follow-ups, a proxy was tasked with completing their end-of-life module, which comprised information about the deceased individual's health, life insurance, causes of death, as well as medical and hospitalization records. For detailed information and updates related to the questionnaires used since the inception of the study, please visit https://share-eric.eu/data/. Lifetables for European countries and Israel are available from the Human Mortality Database (HMD). [40] All statistical analyses were performed using *Rstudio* and *R-software version 3.5.1*. [41][42]

In the present analysis, the study focused on participants recruited during "wave 1," who were subsequently monitored from 2004 to 2017. The final survival follow-up in 2017 involved 11 participating European countries and one Middle Eastern country; Austria, Belgium, Sweden, Switzerland, Germany, Denmark, Spain, Greece, France, the Netherlands, Italy, and Israel. Information on lifestyle behaviours, vital status, and health conditions, including diagnosed morbidity and hospitalization duration, was continually updated. From a technical standpoint, this data format is classified as a depleting longitudinal wave; refer to **Figure 1**. Following the exclusion of cases with missing vital status information and inconsistencies in self-reported modifiable risk behaviours, such as current and never smoking statuses, the study included 7974 female and 6336 male participants for the survival analysis; **Table 3**. The principal hypothesis aimed to explore potential gender-based differences in morbidity types from diagnosis to death, and to investigate whether early disease diagnosis could prevent premature mortality.

It is important to note that the event of interest, "death," can only occur once in an individual's lifetime. Therefore, the coded causes of death (COD) are highly selective and survival is influenced by factors such as health status, existing comorbidities, and the patient's age. Among the elderly and frail population, long-term comorbidities, organ function deterioration, and damage resulting from adverse lifestyle behaviours were likely to be significant confounding factors; refer to *Supplementary Table S1*. In contrast, sudden health deterioration leading to death is more common among younger and middle-aged individuals; refer to *Supplementary Figure S2* for ages at death by COD.

Variables I - V

A comprehensive set of variables was considered in the multivariate analysis of the time-varying Cox and Cox-frailty regression models. Each model was finalized using a forward-selection process, during which the likelihood ratio test was applied, with a significance level of $p \leq 0.05$ for goodness-of-fit criteria. Among the variables available in the SHARE catalog, particular attention was given to monitoring changes in smoking status, including participants who declined to disclose their smoking habits. Smoking status is extensively documented as a life-threatening risk factor, and discontinuation of long-term smoking is likely to be an indicator of poor health, especially among the elderly.

I) *Smoking habits*

The questionnaire was designed to accommodate participants' willingness to declare their lifestyle habits, with possible responses being 'Yes', 'No', 'Refusal', or 'Don't know'. The majority of participants disclosed their smoking status at the beginning of the study, with only 0.3% having missing information on their smoking habits. Additionally, it was only one participant (N=1) responded with “Don't know”. An observational correlation was also noted during the analysis, indicating that participants were less likely to disclose or complete information on their smoking habits in subsequent follow-up questionnaires. In cases of incomplete information on smoking habits during follow-up, the missing data was substituted with the information previously provided in earlier follow-up waves or with the last declared status, when deemed more appropriate.

Under the long-format data condition, only one participant had never disclosed any information regarding their ever- and current-smoking status in the generic health module.

II) *Vaccinations*

The SHARE study recorded information on childhood vaccination during the 2008 and 2012 wave follow-up, with a response rate of 86.7% from participants. Vaccination is recognized for its role in aiding the immune system to develop lifelong immunity against specific antigens. Although at the time of this analysis the SHARE study solely tracked childhood vaccination, this preventative medicine variable provided a broad indication of the societal acceptance and awareness of health priorities related to vaccination. While it may not be fully representative or serve as a meaningful variable for regression analyses on non-communicable diseases and causes of death, it does serve as a valuable variable when analyzing gender-driven risk-taking behaviors. Furthermore, the impact of growing up in an environment where vaccination is not a health priority may have adverse effects on survival in adulthood. The significance of this primary preventative medicine on mortality risk and long-term survival seems to hold consistently true.

III) *Marital Status and Cohabitation*

Marital status has been reported as a significant risk factor for longevity among elderly, more specifically married males are likely to enjoy a lower risk for mortality at old age. There was a substantial interest to introduce variables on partnerships and cohabitation-types during the survival regression analysis, but the numerous incomplete information at

each follow-up wave made it not sustainable for reliable estimation; 93.9% missing updates among survivors at last survival update. If the multivariate regression models were to contain hidden heterogeneity attributed from variables such as marital status and partnerships, the Cox-frailty analysis would present a measurable frailty index. *N.B.,* A measurable frailty index does not necessarily imply the goodness-of-fit of the assumed frailty distribution.

IV) *Comorbidity-types and CODs*

Circulatory disease is the primary focus of this study. Participants who self-reported health conditions and received diagnoses of high blood pressure, high cholesterol, stroke, and heart attack were classified as patients diagnosed and treated for circulatory diseases. Health conditions declared alongside circulatory diseases were further categorized based on their respective organ types; for example, diabetes and chronic kidney diseases were categorized as renal diseases, while asthma and chronic bronchitis were categorized as respiratory diseases. Cancer was treated as a separate category, regardless of organ type. The majority of participants reported experiencing at least one of the aforementioned diseases (81.8%), and 32.8% had succumbed to circulatory-failure causes of death, accompanied by a diagnosed non-circulatory comorbidity. A total of 6812 participants had at least one instance of inactivity during follow-up participation. In such cases, updates regarding health conditions were recorded as 'NA' in the tracked and traced event-history data format. Responses categorized as 'Refusal' and 'Don't know' were grouped together as a collective category with 'NA' and were not treated as list-wise deletions. This approach aimed to enhance the statistical power for the semi-parametric frailty analysis; Cox-frailty survival regression.

Upon finalization of the multivariate Cox-frailty model, the complete-case multivariate Cox-frailty excluded cancer patients based on transplant criteria. The assumption was that only non-cancer patients had the potential to undergo graft replacement, offering a life-saving opportunity that could delay the expected ages at death. Consequently, the occurrence of a survival bias would make it challenging to achieve convergence with a gamma-distributed frailty. It is noteworthy that empirical and simulated population-based studies have demonstrated that the gamma-distributed frailty best describes the exponential mortality risk trajectory of human adults. [20][43][44][45][46][47] This mathematical concept characterizes exponential growth and can be validated using a semi-logarithmic scale on the *y-axis*, resulting in a hazard shape akin to a logistic-type function. When the gamma-distributed frailty is no longer able to account for the natural mortality selection process of the population, the mortality dynamics are likely influenced by a force intercepted through a standardized intervention for the ill or an exposure leading to mass destruction. [38][48][49]

V) *Recruitment age and ages at death*

All participants' recruitment age, age at death, and vital status at the last follow-up were incorporated into the Cox models as standard survival variables to adjust for left-truncation and right censoring. The maximum lifespan attained was 107.1 years (female) and 104.1 years (male). Year of birth was included during the stratification of the final model and was categorized as: 1902-1933; 1934-1945; 1946-1949; 1950-1975. Reference to the descriptive analysis can be found in **Table 3**. Participants who were lost to follow-up were excluded. This exclusion also encompassed delayed end-of-life questionnaire module submission of deceased participants.

	All (N=1223)	Females (N=594)	Males (N=629)
Demographic			
Gender			
Female	*Ref.*	-	-
Male	*1.11 (0.98 – 1.27)*	-	-
Smoking status			
Never	*Ref.*	*Ref.*	*Ref.*
Former	*1.02 (0.87 – 1.18)*	*0.91 (0.68 – 1.23)*	*1.08 (0.89 – 1.31)*
Current	*0.94 (0.77 – 1.13)*	*1.12 (0.80 – 1.56)*	*1.02 (0.79 – 1.31)*
Morbidity			
Renal			
No	*Ref.*	*Ref.*	*Ref.*
Yes	*1.15 (0.72 – 1.84)*	*1.03 (0.50 – 2.09)*	*1.29 (0.67 – 2.50)*
Don't know/NA	*1.24 (0.44 – 3.49)*	*2.32 (0.36 – 14.76)*	*0.96 (0.22 – 4.20)*
Circulatory			
No	*Ref.*	*Ref.*	*Ref.*
Yes	*1.07 (0.90 – 1.28)*	*1.00 (0.77 – 1.30)*	*1.14 (0.89 – 1.47)*
Don't know/NA	*1.60 (0.57 – 4.47)*	*0.86 (0.13 – 5.47)*	*2.04 (0.47 – 8.84)*
Renal:Circulatory			
Renal(No): Circ (Yes)	*Ref.*	*Ref.*	*Ref.*
Renal(Yes): Circ (Yes)	*1.19 (0.71 – 1.98)*	*1.41 (0.65 – 3.07)*	*1.03 (0.50 – 2.11)*
Heterogeneity Index Measurement (Gamma)			
Cohort			
1902-1933	***0.01*** *(0.00 – 0.05)*	***0.03*** *(0.00 – 0.18)*	***0.01*** *(0.00 – 0.06)*
1934-1945	***0.09*** *(0.02 – 0.47)*	*0.34 (0.06 – 2.11)*	***0.08*** *(0.01 – 0.47)*
1946-1949	*0.70 (0.13- 3.61)*	*1.20 (0.21 – 6.82)*	*0.70 (0.13 – 3.79)*
1950-1974	*3.21 (0.68-15.20)*	*2.43 (0.53 – 11.18)*	*3.21(0.68 – 15.24)*

Table 1. Multivariate Cox-frailty regression model stratified by countries for circulatory-failure CODs. Frailty component was assumed to be gamma-distributed, categorical year of birth. This model imposed a strict complete-case for participants must be declared deceased and recorded as death due to circulatory-failure. Renal disease is the only morbidity with a significant fit to the finalized model. Childhood vaccination variable was initially included as a housekeeping variable *Supplementary Table S1*, but it may not serve inference purpose since circulatory diseases are not generalized as infectious diseases. 'Don't know/ NA' categories in morbidity-type were not included in the interactive variable as it provided no convergence for a coefficient output. Estimates shown are presented as hazard ratios; HR and its lower and upper confidence intervals; CI. HRs in bold are statistically significant; *p-value≤0.05.* For the exclusion of cancer patients, and the statistical decision on whether to include respiratory and digestive morbidities in the finalized model; refer to Table 2. *Ref.* as reference category, also known as baseline hazard.

	All (N=1112)	Females (N=544)	Males (N=568)
Demographic			
Gender			
Female	*Ref.*	-	-
Male	*1.11 (0.97 – 1.28)*	-	-
Smoking status			
Never	*Ref.*	*Ref.*	*Ref.*
Former	*1.00 (0.85 – 1.17)*	*0.88 (0.64 – 1.21)*	*1.05 (0.85 – 1.29)*
Current	*0.97 (0.78 – 1.19)*	*1.15 (0.82 – 1.63)*	*0.97 (0.73 – 1.29)*
Morbidity			
Renal			
No	*Ref.*	*Ref.*	*Ref.*
Yes	*1.20 (0.73 – 1.99)*	*0.99 (0.45 – 2.16)*	*1.26 (0.60 – 2.64)*
Don't know/NA	*1.33 (0.45 – 3.94)*	*1.59 (0.17 – 15.19)*	*0.43 (0.05 – 3.51)*
Circulatory			
No	*Ref.*	*Ref.*	*Ref.*
Yes	*1.07 (0.89 – 1.29)*	*0.99 (0.75 – 1.31)*	*1.14 (0.87 – 1.50)*
Don't know/NA	*1.54 (0.53 – 4.53)*	*1.28 (0.13 – 12.24)*	*4.90 (0.60 – 40.09)*
Renal:Circulatory			
Renal(No): Circ (Yes)	*Ref.*	*Ref.*	*Ref.*
Renal(Yes): Circ (Yes)	*1.07 (0.62 – 1.86)*	*1.41 (0.60 – 3.33)*	*1.00 (0.44 – 2.25)*

Table 2. Time-varying multivariate Cox stratified by countries and categorical year of birth for circulatory-failure CODs. Renal disease is the only morbidity that retains its significant interaction with circulatory disease leading to circulatory-failure deaths. Diagnosed cancer patients do not qualify as a recipient for solid-organ transplant. Thus, this model has excluded cancer morbidity that had contributed to circulatory-failure deaths. 'Don't know/ NA' categories in morbidity-type were not included in the interactive variable as it provided no convergence for a coefficient output. Estimates shown are presented as hazard ratios; HR and its lower and upper confidence intervals; CI. HRs in bold are statistically significant; *p-value≤0.05. Ref.* as reference category, also known as baseline hazard.

	Birth Cohorts			
	1902-1933	***1934-1945***	***1946-1949***	***1950-1975***
N	4315	5473	2154	2368
Demographic				
Died %	55.6	16.4	6.8	4.7
Females %	55.9	52.5	56.2	62.5
Recruitment Age (mean ± sd)	76.8±5.4	63.3±3.5	55.5±1.1	50.5±2.6
Aged (mean ± sd)	86.7±5.8	72.7±4.5	63.8±3.2	59.5±3.2
Smoking status %				
Never	67.6	59.2	55.8	54.5
Former	24.3	26.1	23.6	19.7
Current	8.1	14.7	20.6	25.8
Diagnosed morbidity-types (*N*)				
Circulatory	2118	3286	1117	1040
Renal	581	974	283	247
Respiratory	338	396	127	113
Digestive	125	200	62	87
Cancer	165	192	28	44
≥ 1 morbidity %	88.8	85.1	76.3	66.3
Renal : Circulatory (*N*)				
Renal (No) : Circulatory (Yes)	1651	2485	895	850
Renal (Yes) : Circulatory (Yes)	467	801	222	190
Renal (No) : Circulatory (No)	1230	1680	928	1234
Renal (Yes) : Circulatory (No)	114	173	61	57
Unknown/ Not declared/ NAs	853	334	48	37
Circulatory-failure deaths %				
Circulatory CODs	36.2	31.8	27.4	26.1
Females	53.3	40.4	25.0	20.7
Not diagnosed for circulatory disease prior to circulatory COD	20.3	22.1	32.5	27.6
Females	38.2	31.6	22.5	20.7

Table 3. Descriptive table. Characteristics of SHARE participants originating from Wave I-only recruitment. Variables shown are expressed in crude numbers (*N*), mean or percentages (%). Information was retrieved from last survival follow-up. Morbidity-types may not sum up to total count as it is usual for elderly to be diagnosed for more than one underlying disease. For examples of heterogeneous selection for mortality, smoking

status is a prime indicator for a depleting robust-frail proportion among recruited participants. COD: Causes of death; sd: standard deviation. Circulatory COD % is the total number circulatory deaths/ total deaths by cohort, and among females.

Statements and Declarations

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Conflict of interests

At project initiation (2019), Y Lin is the founder of The Waterhouse. Analysis was completed in 2019.

Author's Contribution

Y Lin raised the hypothesis and obtained the permission to conduct analytical research themes using the SHARE study in January 2019. Lin performed all analyses using R-software and R-studio. The analytical content was finalized by Lin in December 2019.

References

1. [a, b]*Johnson NB, Hayes LD, Brown K, Hoo EC, Ethier KA, Centers for Disease Control and Prevention (CDC). CDC National Health Report: leading causes of morbidity and mortality and associated behavioral risk and protective factors--United States, 2005-2013. MMWR supplements. 2014 Oct 31;63(4):3–27.*
2. [^]*Kendir C, van den Akker M, Vos R, Metsemakers J. Cardiovascular disease patients have increased risk for comorbidity: A cross-sectional study in the Netherlands. Eur J Gen Pract. 2017 Nov 23;24(1):45–50.*
3. [^]*Nayor M, Enserro DM, Xanthakis V, Larson MG, Benjamin EJ, Aragam J, et al. Comorbidities and Cardiometabolic*

Disease: Relationship With Longitudinal Changes in Diastolic Function. J Am Coll Cardiol HF. 2018 Mar 26;6(4):317–25.

4. [a, b]*Collins AJ. Cardiovascular Mortality in End-Stage Renal Disease. The American Journal of the Medical Sciences. 2003 Apr 1;325(4):163–7.*
5. [^]*Melonie Heron. Deaths: Leading Causes for 2017 [Internet]. U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES: Centers for Disease Control and Prevention; 2017 Mar [cited 2019 Dec 21] p. 77. Report No.: 68; 6. Available from: https://www.cdc.gov/nchs/fastats/leading-causes-of-death.htm*
6. [^]*Oeppen J, Vaupel JW. Broken limits to life expectancy. Science. 2002 May;296(5570):1029–31.*
7. [^]*Hayflick L, Moorhead PS. The serial cultivation of human diploid cell strains. Experimental Cell Research. 1961 Dec;25(3):585–621.*
8. [^]*Chen BH, Marioni RE, Colicino E, Peters MJ, Ward-Caviness CK, Tsai PC, et al. DNA methylation-based measures of biological age: meta-analysis predicting time to death. Aging (Albany NY). 2016 Sep 28;8(9):1844–59.*
9. [^]*Sharpless NE, DePinho RA. How stem cells age and why this makes us grow old. Nat Rev Mol Cell Biol. 2007 Sep;8(9):703–13.*
10. [^]*Vogel H, Lim DS, Karsenty G, Finegold M, Hasty P. Deletion of Ku86 causes early onset of senescence in mice. Proc Natl Acad Sci U S A. 1999 Sep;96(19):10770–5.*
11. [^]*Heijmans BT, Tobi EW, Stein AD, Putter H, Blauw GJ, Susser ES, et al. Persistent epigenetic differences associated with prenatal exposure to famine in humans. Proc Natl Acad Sci U S A. 2008 Nov;105(44):17046–9.*
12. [^]*Campisi J, Kapahi P, Lithgow GJ, Melov S, Newman JC, Verdin E. From discoveries in ageing research to therapeutics for healthy ageing. Nature. 2019 Jul;571(7764):183–92.*
13. [^]*Carrero JJ, Hecking M, Chesnaye NC, Jager KJ. Sex and gender disparities in the epidemiology and outcomes of chronic kidney disease. Nature Reviews Nephrology. 2018 Mar;14(3):151–64.*
14. [a, b]*Sun D, Zhou T, Li X, Heianza Y, Shang X, Fonseca V, et al. Diabetes Comorbidity and All-Cause, Cardiovascular, and Cancer Mortality in U.S. Adults. Diabetes [Internet]. 2018 Jul 1 [cited 2019 Dec 22];67(Supplement 1). Available from: https://diabetes.diabetesjournals.org/content/67/Supplement_1/1580-P*
15. [^]*Rashid M, Kwok CS, Gale CP, Doherty P, Olier I, Sperrin M, et al. Impact of co-morbid burden on mortality in patients with coronary heart disease, heart failure, and cerebrovascular accident: a systematic review and meta-analysis. Eur Heart J Qual Care Clin Outcomes. 2017 Jan 1;3(1):20–36.*
16. [^]*Tuljapurkar S, Steiner UK. Dynamic heterogeneity and life histories. Annals of the New York Academy of Sciences. 1204:65–72.*
17. [^]*Gurven M, Kaplan H. Longevity Among Hunter- Gatherers: A Cross-Cultural Examination. Population and Development Review. 2007;33:321–65.*
18. [^]*Metcalf CJE, Cohen C, Lessler J, McAnerney JM, Ntshoe GM, Puren A, et al. Implications of spatially heterogeneous vaccination coverage for the risk of congenital rubella syndrome in South Africa. J R Soc Interface. 2013 Jan;10(78):20120756.*
19. [^]*Olshansky SJ, Passaro DJ, Hershow RC, Layden J, Carnes BA, Brody J, et al. A potential decline in life expectancy in the United States in the 21st century. N Engl J Med. 2005 Mar;352(11):1138–45.*

20. [a, b]*Lin Y. The Oddity of Heterogeneity: A Blessing in Disguise. Scientific Reports. 2018 Jul 17;8(1):10782.*
21. ^*Hayflick L. The limited in vitro lifetime of human diploid cell strains. Experimental Cell Research. 1965 Mar;37(3):614–36.*
22. ^*Fiscella K, Tancredi D, Franks P. Adding socioeconomic status to Framingham scoring to reduce disparities in coronary risk assessment. American Heart Journal. 2009;157:988–94.*
23. ^*Wenau G, Grigoriev P, Shkolnikov V. Socioeconomic disparities in life expectancy gains among retired German men, 1997–2016. J Epidemiol Community Health. 2019 Jul 1;73(7):605–11.*
24. ^*Fireman B, Lee J, Lewis N, Bembom O, van der Laan M, Baxter R. Influenza Vaccination and Mortality: Differentiating Vaccine Effects From Bias. Am J Epidemiol. 2009 Sep 1;170(5):650–6.*
25. ^*Galvao M, Kalman J, Demarco T, Fonarow GC, Galvin C, Ghali JK, et al. Gender Differences in In-Hospital Management and Outcomes in Patients With Decompensated Heart Failure: Analysis From the Acute Decompensated Heart Failure National Registry (ADHERE). Journal of Cardiac Failure. 2006 Mar 1;12(2):100–7.*
26. ^*Bradshaw PJ, Stobie P, Knuiman MW, Briffa TG, Hobbs MST. Life expectancy after implantation of a first cardiac permanent pacemaker (1995–2008): A population-based study. International Journal of Cardiology. 2015 Jul 1;190:42–6.*
27. ^*Starzl TE, Makowka L. Organ Transplantation — Then and Now. Hosp Physician. 1987 Aug;23(8):28–36.*
28. ^*Vaccarino V, Lin ZQ, Kasl SV, Mattera JA, Roumanis SA, Abramson JL, et al. Gender differences in recovery after coronary artery bypass surgery. Journal of the American College of Cardiology. 2003 Jan 15;41(2):307–14.*
29. ^*Nicolini F, Vezzani A, Fortuna D, Contini GA, Pacini D, Gabbieri D, et al. Gender differences in outcomes following isolated coronary artery bypass grafting: long-term results. J Cardiothorac Surg [Internet]. 2016 Sep 30 [cited 2019 Dec 21];11. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5045636/*
30. ^*Bates WD, Gray DWR, Dada MA, Chetty R, Gatter KC, Davies DR, et al. Lymphoproliferative disorders in Oxford renal transplant recipients. J Clin Pathol. 2003 Jun;56(6):439–46.*
31. ^*Clarke CA, Morton LM, Lynch C, Pfeiffer RM, Hall EC, Gibson TM, et al. Risk of lymphoma subtypes after solid organ transplantation in the United States. British Journal of Cancer. 2013 Jul;109(1):280–8.*
32. ^*Adam R, Karam V, Cailliez V, Grady JGO, Mirza D, Cherqui D, et al. 2018 Annual Report of the European Liver Transplant Registry (ELTR) – 50-year evolution of liver transplantation. Transplant International. 2018;31(12):1293–317.*
33. ^*Elborn JS, Shale DJ, Britton JR. Cystic fibrosis: current survival and population estimates to the year 2000. Thorax. 1991 Dec;46(12):881–5.*
34. ^*Buzzetti R, Salvatore D, Baldo E, Forneris MP, Lucidi V, Manunza D, et al. An overview of international literature from cystic fibrosis registries: 1. Mortality and survival studies in cystic fibrosis. Journal of cystic fibrosis official journal of the European Cystic Fibrosis Society. 2009;8:229–37.*
35. ^*Meier-Kriesche HU, Schold JD. The impact of pretransplant dialysis on outcomes in renal transplantation. Seminars in Dialysis. 1995;18:499–504.*
36. ^*Marsico F, Paolillo S, Gargiulo P, Parisi V, Nappi C, Assante R, et al. Renal function and cardiac adrenergic impairment in patients affected by heart failure. J Nucl Cardiol. 2021 Oct;28(5):2112–22.*

37. ^*Lin Y. 3D Age-Specific Mortality Trajectory: A Survival Analysis Protocol. In: Turksen K, editor. Stem Cells and Aging : Methods and Protocols [Internet]. New York, NY: Springer; 2019 [cited 2019 Dec 22]. p. 311–21. (Methods in Molecular Biology). Available from: https://doi.org/10.1007/7651_2018_189*
38. [a, b]*Lin Y. AFT survival model to capture the rate of aging and age-specific mortality trajectories among first-allogeneic hematopoietic stem cells transplant patients. PLoS One. 2018;13(3):e0193287.*
39. ^*Börsch-Supan A, Brandt M, Hunkler C, Kneip T, Korbmacher J, Malter F, et al. Data Resource Profile: The Survey of Health, Ageing and Retirement in Europe (SHARE). Int J Epidemiol. 2013 Aug 1;42(4):992–1001.*
40. ^*Human Mortality Database. University of California, Berkeley (USA), and Max Planck Institute for Demographic Research (Germany). [Internet]. 2022. Available from: http://www.mortality.org/*
41. ^*RStudio Team. RStudio: Integrated Development Environment for R. RStudio, PBC, Boston, MA URL http://www.rstudio.com/. 2022.*
42. ^*Team RDC. R: A language and environment for statistical computing [Internet]. 2022. Available from: http://www.R-project.org*
43. ^*Vaupel JW, Yashin AI. Unobserved population heterogeneity.\ldots : Analysis and Synthesis: A Treatise in\ldots [Internet]. 2006; Available from: http://user.mpidr.de/jwv/pdf/unobserved%20population%20heterogeneity.pdf*
44. ^*Yashin AI, Arbeev KG, Akushevich I, Kulminski A, Akushevich L, Ukraintseva SV. Model of hidden heterogeneity in longitudinal data. Theoretical population biology. 2008;73(1):1–10.*
45. ^*Izumi S, Ohtaki M. Aspects of the Armitage–Doll gamma frailty model for cancer incidence data. Environmetrics. 2004;15:209–18.*
46. ^*Wienke A. Frailty Models. Demographic Research. 2003;49:0–13.*
47. ^*Lin Y, Gajewski A, Poznańska A. Examining mortality risk and rate of ageing among Polish Olympic athletes: a survival follow-up from 1924 to 2012. BMJ Open. 2016 Jan 4;6(4):e010965.*
48. ^*Cologne JB, Preston DL. Longevity of atomic-bomb survivors. The Lancet. 2000 Jul 22;356(9226):303–7.*
49. ^*Lin Y. The Lesser Evil: Plutonium-239 or Uranium-235? A Study on F0 Atomic Bomb Survivors. Qeios [Internet]. 2023 Nov 22 [cited 2023 Nov 24]; Available from: https://www.qeios.com/read/6GKULJ*