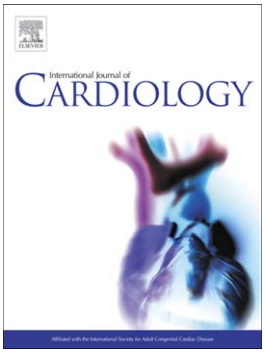

The Fontan epidemic: Population projections from the Australia and New Zealand Fontan Registry

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The Fontan epidemic: population projections from the Australia and New Zealand Fontan Registry.

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Abstract

Background - The number and age demographic of the future Fontan population is unknown.

Methods - Population projections were calculated probabilistically using microsimulation. Mortality hazard rates for each Fontan recipient were calculated from survivorship of 1,353 Fontan recipients in the Australia and New Zealand Fontan Registry, based on Fontan type, age at Fontan, gender and morphology. Projected rates of new Fontan procedures were generated from historical rates of Fontan procedures per population births.

Results - At the end of 2014, the living Fontan population of Australia and New Zealand was 1,265 people from an Australian and New Zealand regional population of 28 million (4.5 per 100,000 population). Of those, 165(13%) received an atrio-pulmonary (AP) procedure, 262(21%) a lateral tunnel (LT) procedure and 838(66%) an extra-cardiac conduit (ECC) procedure. This population is expected to grow to 1,917(95% CI: 1,846: 1,986) by 2025(5.8 per 100,000 population), with 149(8%) AP procedures, 254(13%) LT procedures, and 1,514(79%) ECC procedures. By 2045, the living Fontan population is expected to reach 2,986(95% CI: 2,877: 3,085; 7.2 per 100,000 population). The average age of the Fontan population is expected to increase from 18 years in 2014 to 23 years (95% CI: 22-23) by 2025, and 31 years (95% CI: 30-31) by 2045.

Conclusion - The Australian and New Zealand population of patients alive after a Fontan procedure will double over the next 20 years increasing the demand for heart-failure services and cardiac transplantation. Greater consideration for the needs of this mostly adult Fontan population will be necessary.

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1 Introduction

The introduction of the Fontan procedure in 1971 dramatically improved the chances of survival into adulthood for patients born with a single ventricle (1). Successive changes of techniques have further improved the survival of this population with various teams recently reporting 20 year survival after Fontan superior to 92% for those who received an extra-cardiac conduit (ECC) or lateral tunnel (LT) procedure (2). However this population is still afflicted by a heavy burden of disease. In recent times, it has been estimated that close to half of Fontan recipients suffer from adverse events such as arrhythmias, thrombo-embolic events, reintervention and poor functional status (2). With the lack of population-based data, and the progressive improvements in survival, it has been difficult to build prediction estimates of this population. This lack of prediction leaves us unprepared to face the needs of this growing population. We aimed to utilize the long-term follow-up of this population captured by a multi-site registry to develop a prediction of the growth of this patient population over the next 30 years.

2 Materials and Methods

2.1 Data: the Australia and New Zealand Fontan Registry

The Australia and New Zealand Fontan Registry collects a limited set of health data in all survivors of a Fontan procedure successfully discharged from hospital. The design and implementation of the Registry have been previously reported (3). Authorization for ongoing analysis of the data collected by the Registry has been included within the initial design of the Registry. Data were censored at the end of 2014.

2.2 Definitions

The hazard rate for mortality is the probability of death in the next year, conditional on having survived to that age. The general population hazard rate for mortality can be obtained

from the Australian Bureau of Statistics (4), and captures the mortality due to all causes. We defined the Fontan hazard rate for mortality as the hazard rate for mortality specific to the Fontan population.

2.3 Statistical analysis

Survival was examined with a proportional hazards multivariate model using the factors and groupings identified in previous survival analysis (2): Fontan type (atrio-pulmonary (AP) versus ECC/LT), age at Fontan (> 7 years), gender and morphology (hypoplastic left-heart syndrome (HLHS) versus other). Testing of the proportional hazards assumption was based on the link test of model specification and a Schoenfeld residuals test of the Cox form of the model (5).

The Registry has 34 years of 'at-risk' data on survival for a minimum of 10 patients who have undergone an AP, 26 years for those who received a LT, and 18 years for those who received an ECC, allowing the estimation of the mortality hazards for this period. To estimate the mortality hazards for the future years with yet unaccounted survival, we employed parametric modelling, a standard technique in health economics (6). Parametric curves were fitted to the known survivorship data and used to project the mortality hazards of those living with a Fontan circulation later in life. We employed a Weibull curve for the underlying functional form, and tested a Gompertz curve in a sensitivity analysis. These two functional forms are typically used in survival analysis because their forms are well-suited to modelling human mortality (6).

Parametric modelling techniques are suitable when the hazard trends are thought to be relatively consistent (7). To date, this is true for the Fontan hazard rates (2). However there is uncertainty about how these hazards will change as this population grows older. To evaluate this uncertainty, we modelled two separate scenarios. In the base case scenario, we adopted a

'constant relative risk' assumption that is sometimes used in other diseases such as childhood cancer mortality modelling (8). We assumed that the ratio of mortality risk between Fontan survivors and the wider population at 35 years post-Fontan is maintained as the Fontan recipients grow older (Figure 1a). This suggests a rapidly increasing mortality hazard rate for the AP Fontan population, relative to current trends. In a sensitivity analysis, we tested the "best-case" assumption that the Fontan mortality hazard rates continue on current trends, until reaching the all-cause population-wide hazard rates. At this point, around 65 years after the Fontan procedure, the Fontan mortality hazard rates increase in line with the wider population (Figure 1b). Under this assumption, the all-cause population-wide hazards provided a lower-limit for the unknown later-life Fontan hazards: we would not expect a 70 year old Fontan recipient to have a *lower* chance of death in her 70th year than a 70 year old from the general population. The proportion of AP Fontan recipients that have takedown, transplant or conversion was estimated based on age and Fontan type after the survival analysis. Including these as intermediate events within the survival analysis did not significantly impact on longer term population estimates and was therefore excluded.

Fontan population projections were calculated using microsimulation, a technique commonly used to model heterogeneous life paths at the individual level (9). Projected rates of new Fontan procedures were probabilistically generated based on mean and standard deviation of ten-year historical (2005-2015) rates of Fontan procedures per population births. Australian and New Zealand birth projections were sourced from the Australian Bureau of Statistics (10) and Statistics New Zealand (11) respectively. Survivorship for each Fontan recipient was based on Fontan type (atrio-pulmonary (AP) versus ECC/LT), age at Fontan (> 7 years), gender and morphology (hypoplastic left-heart syndrome (HLHS) versus other) as described above. For each individual, the hazard ratios for these characteristics were randomly drawn from the 95% confidence intervals derived in the Weibull analysis, a standard approach in

microsimulation (9). All new Fontan procedures were assumed to be ECC type, as is the custom in the study region, while age at Fontan, gender and morphology were randomly determined based on current Registry proportions. The microsimulation was repeated 100 times and confidence intervals were calculated for the mean projections. Data analysis was performed using Stata 13.1 (Stata Corp, College Station, USA) and Matlab 2015a (12).

3 Results

Data for the current analyses were extracted from the Fontan Registry on 11 June, 2015. Between 1975 and the end of 2014, the details of 1,423 patients who had received a Fontan procedure within Australia or New Zealand had been recorded by the Registry. Nineteen patients (1%) were excluded as the Fontan procedure was performed overseas; 12 (1%) refused to participate in the Registry or subsequently withdrew; 18 (1%) had a missing date of Fontan procedure; and 15 (1%) were known to be deceased but the specific date of death was missing. Of the remaining total of 1,353 procedures, 211 (16%) were AP connection performed between 1975 and 1996; 285 (21%) were a LT performed from 1980 to 2014; and 857 (63%) were an ECC performed from 1990 to 2014. The characteristics of the patients are displayed in Table 1a. There were 88 deaths after hospital discharge (46 AP, 23 LT and 19 ECC Fontans (Table 1b)). Subsequent takedown, transplant or conversions have been performed on 48 (23%) of the AP recipients, 14 (5%) of the LT recipients, and 14 (2%) of the ECC Fontan recipients (Table 1c). Physical activity as measured by the New York Heart Association score of III or IV (13) was recorded in 53 (4%) recipients (18 AP, 9 LT and 26 ECC Fontans).

3.1 Survival

The 18 year survival was 85% (95% CI: 79-89%) for an AP Fontan, 93% (95% CI: 89-95%) for an LT Fontan and 92% (95% CI: 89-96%) for an ECC Fontan. The 26 year survival was 80% (95% CI: 74-85%) for an AP Fontan, and 89 % (95% CI: 82-94%) for an LT Fontan. The 34 year survival of patients who had an AP Fontan was 75% (95% CI: 67-81%).The Kaplan Meier curve of survival is shown in Figure 2. By multivariate parametric regression, the risk factors predictive of mortality were atrio-pulmonary Fontan type, Fontan operation after 7 years of age and male gender (Table 2). HLHS morphology was not a significant predictor of mortality at the 10% level. The Weibull shape parameter of less than 1 suggests that the Fontan hazards are slightly decreasing with time since Fontan procedure. The model specification and Schoenfeld residuals tests (Appendix 1) suggest that the proportional hazard assumption was not violated.

3.2 Current population

At the end of 2014, the current estimate of the living Fontan population of Australia and New Zealand was 1,265 people (550 females, 715 males) from an Australian and New Zealand population of 28.0 million (population proportion of 4.5 per 100,000). Of those, 165 (13%) received an AP procedure, 262 (21%) a LT procedure and 838 (66%) an ECC procedure. Forty (24%) of the living AP population have had a takedown, conversion or transplant.

3.3 Base case projections using constant relative risk

The microsimulation model projects that the living population of Fontan recipients will grow to 1,917 (95% CI: 1,846: 1,986) by 2025 for a population proportion of 5.8 per 100,000. This will be split between 149 (8%) AP procedures, 254 (13%) LT procedures, and 1,514 (79%) ECC procedures, with 58 (39%) of the AP recipients having had a takedown, transplant or

conversion. By 2045, the living Fontan population is expected to reach 2,986 (95% CI: 2,877: 3,085 for a population proportion of 7.2 per 100,000. The Fontan types will be 88 AP (3%), 220 LT (7%) and 2,678 (90%) ECC procedures respectively (Figure 3), with 52 (66%) of the AP recipients having had a takedown, transplant or conversion.

The average age of the Fontan population increases from 18 years in 2014 to 23 years (95% CI: 22-23) by 2025, and 31 years (95% CI: 30-31) by 2045 (Table 3).

3.4 Sensitivity analyses: projections using current trends in survival and the Gompertz distribution for parametric modelling

In the first sensitivity test, we investigated the impact of more optimistic assumptions around later-life Fontan hazards, where current trends in survival are assumed to continue. Under this assumption, the overall population projections increased relative to the base case, but fell within the base case confidence intervals for the entire projection period. In the second sensitivity test, we investigated the impact of using a Gompertz rather than Weibull function for the parametric curve fitting. Using the Gompertz function, the overall population projections decreased relative to the base case, but fell within the base case confidence intervals for the entire projection period. This indicated the population projections were robust to changes in estimating the Fontan hazards (Figure 4).

4 Discussion

4.1 Significance of results

Growth of the Fontan population will likely put pressures on health systems in the future. However to date, we have failed to produce accurate projections of this population because of the lack of population-based data and the difficulty in producing reliable predictive models. The Australia and New Zealand Fontan Registry provides insight into an entire population; its 34 years survival data allows us to make more accurate predictions because the attrition

rate of this population has remained remarkably constant for patients with each form of Fontan. Our modelling suggests that the living Fontan population in the region will continue to grow steadily, doubling in size by 2036, from 1,265 to 2,531 and reaching 2,986 by 2045. This result is driven by projected survivorship, which shows the mortality hazard rate for a current LT or ECC Fontan recipient to be around 4 deaths per 1,000 per year, the same all-cause mortality rate as a 57 year old from the general population (4).

Such growth will increase demand for heart failure services, in particular heart transplantation, and add cost pressures to our health care systems (forthcoming). We face a chronic shortage of donor organs (14). We have recently demonstrated that patients with failing Fontans have unequal access to heart transplantation, because of shortage of donor organs, the degree of complexity of their often multi-organ disease and the lack of faith in their outcomes after transplantation (forthcoming). The largest North-American multi-centre study of heart transplantation after Fontan comprised only 269 patients over 15 years (15), implying that not all patients who experience failure of the Fontan circulation are being offered transplantation. Our projection raises the concern that access to heart transplantation will decrease relative to need over the next decade, encouraging further research and investment in novel strategies, including long-term assist devices in selected cases(16).

The average age of the Fontan population is expected to increase rapidly to 31 years by 2045, gaining around 5 years per decade. This increase in age of this population will be associated with an increased resource requirement, particularly in adult congenital and heart failure centres.

4.2 Strengths and limitations

Fontan survivorship and associated hazard curves remain the major source of uncertainty in this analysis especially for the more recent version of the Fontan. We have completed

sensitivity testing to evaluate the robustness of our results, and found that strongly increasing hazards in the fourth decade post Fontan surgery would not significantly impact on medium term Fontan population projections. This is because of the relatively young average age of the current Fontan population (18 years), and our assumption that the LT/ECC survival continues to surpass the original AP type Fontan. However, should unforeseen late-failures occur, then we may be overestimating the size of the 2045 population. Similarly, the move from AP to LT and ECC procedures over the last 20 years has seen a significant improvement in survivorship. Should similar breakthroughs occur over the next two decades, we may be underestimating the size of the 2045 population. The withdrawal or censoring of 5% of Fontan recipients in the 2014 data is another factor which could contribute to an underestimate of the true population.

Secondly, we modelled survival as a function of Fontan type, age at Fontan, gender and some basic morphology, but events across the life course such as heart transplantation can also impact on survival. The patients who had undergone an ECC seem to represent a significant proportion of the heart transplantations despite having a shorter follow-up time. This is likely related to the increasing complexity of the patients operated on in more recent times and is an example of how these trends could be affected. However the relatively low incidence rates of heart transplantations to date (Table 1) mean this is unlikely to have significantly impacted on the longer term projection estimates.

Finally, this model assumed that the same proportion of live births would be reaching a Fontan procedure. Dramatic changes in infant survival have not been observed in the last two decades in patients born with single left ventricle and in the last decade the survival of those with a single right ventricle has no longer improved dramatically (17). One cannot however exclude societal changes. An increase in the rate of pregnancy interruptions may result in an

overestimate of the 2045 Fontan population, while a decrease may see an underestimate of the true population.

5 Conclusion

The Australian and New Zealand population of patients alive after a Fontan procedure will double over the next 20 years increasing demand for heart failure services and cardiac transplantation. Greater consideration for the needs of this mostly adult Fontan population will be necessary.

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Disclosures

All other authors have nothing to disclose with regard to commercial support.

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Table 1a: Characteristics of the Australia and New Zealand Fontan Registry

	All	AP*	LT*	ECC*
n	1,353	211 (16%)	285 (21%)	857 (63%)
Female	585 (43%)	100 (47%)	124 (44%)	361 (42%)
Age (years)	18.4±10.0	34.8±7.1	25.3±6.1	13.3±5.9
Age at Fontan (years)	5.7±3.9	7.4±6.0	5.2±4.0	5.4±3.0
Number aged > 7 years	254 (19%)	81 (38%)	49 (17%)	124 (14%)
HLHS	165 (12%)	1 (0%)	9 (3%)	145 (17%)
Takedowns	8 (1%)	2 (1%)	3 (1%)	3 (0%)
Transplants	29 (2%)	14 (7%)	4 (1%)	11 (1%)
Conversions	39 (3%)	32 (15%)	7 (2%)	0 (0%)
NYHA III or IV*	53 (4%)	18 (9%)	9 (3%)	26 (3%)
Deaths	88 (7%)	46 (22%)	23 (8%)	19 (2%)

* NYHA = New York Heart Association physical activity classification (III: marked limitation; IV: severe limitation); AP = atrio-pulmonary; LT = lateral tunnel; ECC = extra-cardiac conduit.

Table 1b: Characteristics of deceased patients

	All	AP*	LT*	ECC*
n	88	46	23	19
Deaths/Total Fontans	7%	22%	8%	2%
Female	33 (38%)	21 (46%)	7 (32%)	4 (21%)
Age at death (years)	18.5±10.1	21.7±10.7	16.9±9.5	12.7±5.7
Age at Fontan (years)	7.3±4.8	8.3±5.4	5.9±4.2	6.4±3.4
Number aged > 7 years	35 (40%)	24 (52%)	5 (22%)	6 (32%)
HLHS	6 (7%)	1 (2%)	1 (5%)	4 (21%)

* AP = atrio-pulmonary; LT = lateral tunnel; ECC = extra-cardiac conduit.

Table 1c: Characteristics of transplanted patients

	All	AP*	LT*	ECC*
n	29	14	4	11
Transplants/Total Fontans	2%	7%	1%	1%
Female	12 (41%)	7 (50%)	1 (25%)	4 (36%)
Age at transplant (years)	19.7±12.1	26.7±12.5	16.5±12.0	12.0±5.1
Age at Fontan (years)	8.7±7.3	9.5±9.2	9.8±8.7	7.1±3.6
Number aged > 7 years	13 (45%)	6 (43%)	2 (50%)	5 (45%)
HLHS	4 (14%)	0 (0%)	0 (0%)	4 (36%)

* AP = atrio-pulmonary; LT = lateral tunnel; ECC = extra-cardiac conduit.

Table 2: Multivariate Weibull Regression Analysis for Survival

Variable	Hazard Ratio	95% CI	p-value
Fontan type (reference LT/ECC)			
AP	2.6	1.7-4.2	<0.001
Age at Fontan (reference =< 7 years)			
>7 years	1.8	1.2-2.8	0.008
Morphology (reference non-HLHS)			
HLHS	1.8	0.7-4.3	0.195
Gender (reference Female)			
Male	1.4	0.9-2.2	0.094
Constant	0.0028	0.0015-0.0054	<0.001
p (Weibull shape parameter)	0.92	0.76-1.11	na

Table 3: Projected average age of Fontan population

Year	Average age	95% CI
2014	18	
2025	23	22-23
2045	31	30-31

Figure 1a, Figure 1b Fontan hazard assumptions

Legend: Left 1a: Mortality hazard projections based on constant relative risk (base case); Right 1b: Mortality hazard projections based on continued current trends (sensitivity test). AP = atrio-pulmonary; LT = lateral tunnel; ECC = extra-cardiac conduit.

Figure 2: Kaplan Meier Fontan survivorship by Fontan type

Legend: AP = atrio-pulmonary; LT = lateral tunnel; ECC = extra-cardiac conduit.

Figure 3: Fontan population projections by Fontan type

Legend: Fontan population projection by type: AP = atrio-pulmonary; LT = lateral tunnel; ECC = extra-cardiac conduit.

Figure 4: Comparison of Fontan population projections under different assumptions

Legend: Error bars show 95% confidence intervals for mean population from 100 probabilistic microsimulations.

APPENDIX

Tables 4a and 4b show the multivariate Cox regression model and the Schoenfeld residuals test. It suggests that the proportional hazard assumption is not violated.

Table 4a: Multivariate Cox Regression Analysis for Survival

Variable	Hazard Ratio	95% CI	p-value
Fontan type (reference LT/ECC)			
AP	2.4	1.5-3.9	<0.001
Age at Fontan (reference =< 7 years)			
>7 years	1.8	1.2-2.8	0.009
Morphology (reference non-HLHS)			
HLHS	1.8	0.7-4.3	0.191
Gender (reference Female)			
Male	1.5	0.9-2.2	0.090

Table 4b: Schoenfeld residual test of proportion hazards

Variable	Rho	Chi2	p-value
Fontan type (reference LT/ECC)			
AP	-0.05	0.23	0.631
Age at Fontan (reference =< 7 years)			
>7 years	0.03	0.07	0.794
Morphology (reference non-HLHS)			
HLHS	0.08	0.59	0.441
Gender (reference Female)			
Male	-0.08	0.51	0.475
Global test		1.45	0.835

The Schoenfeld residuals test suggests that the proportional hazard assumption is not violated.

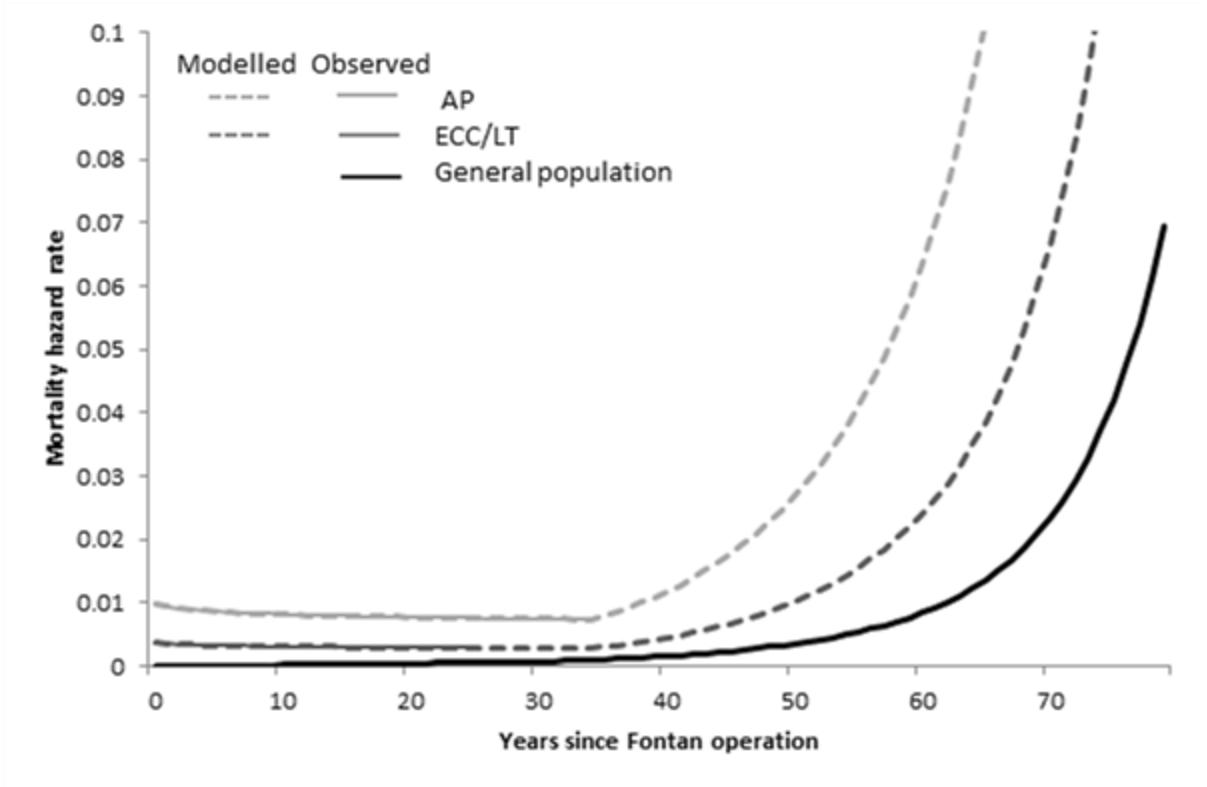
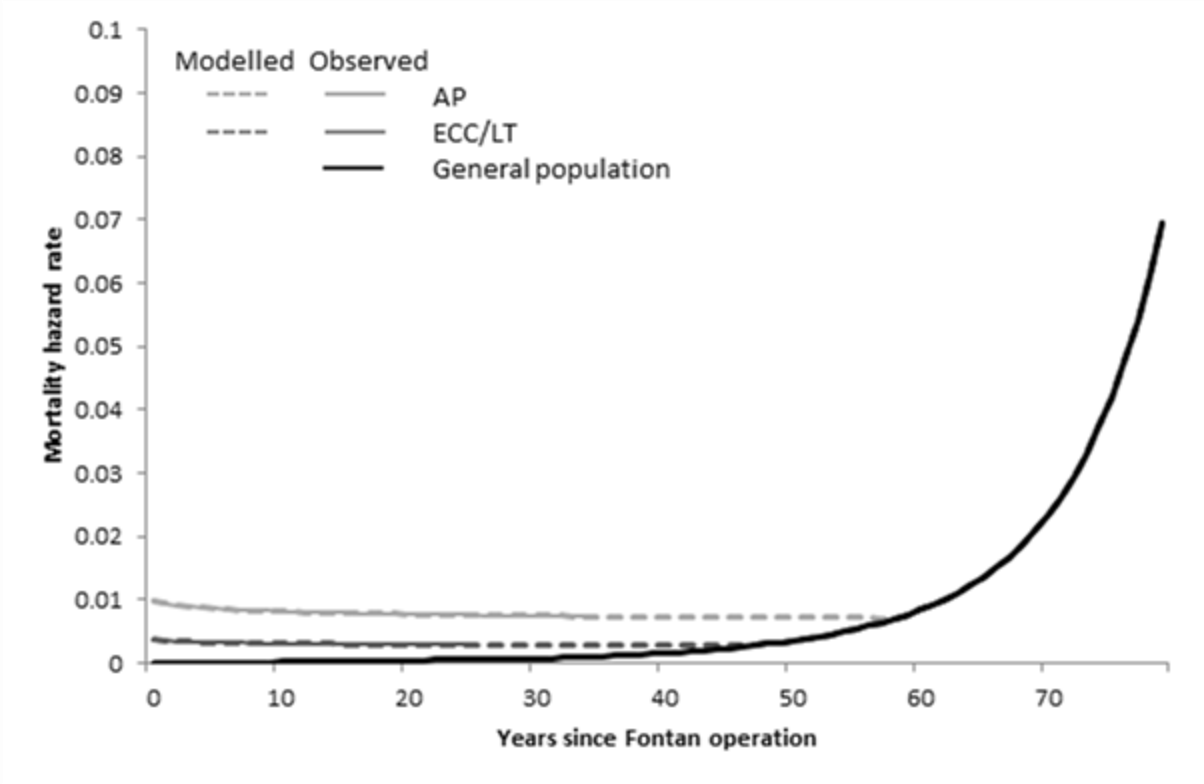


Figure 1a



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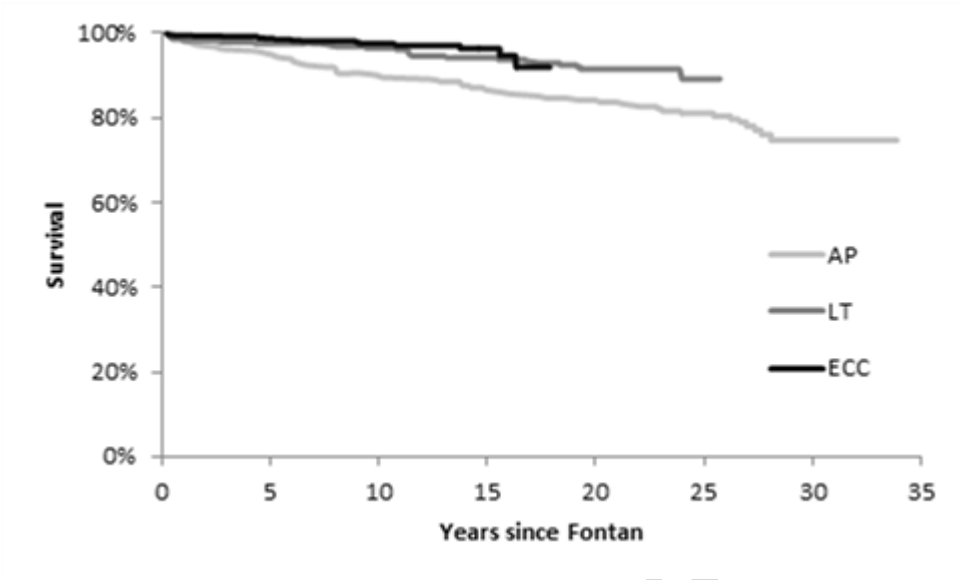

Figure 2

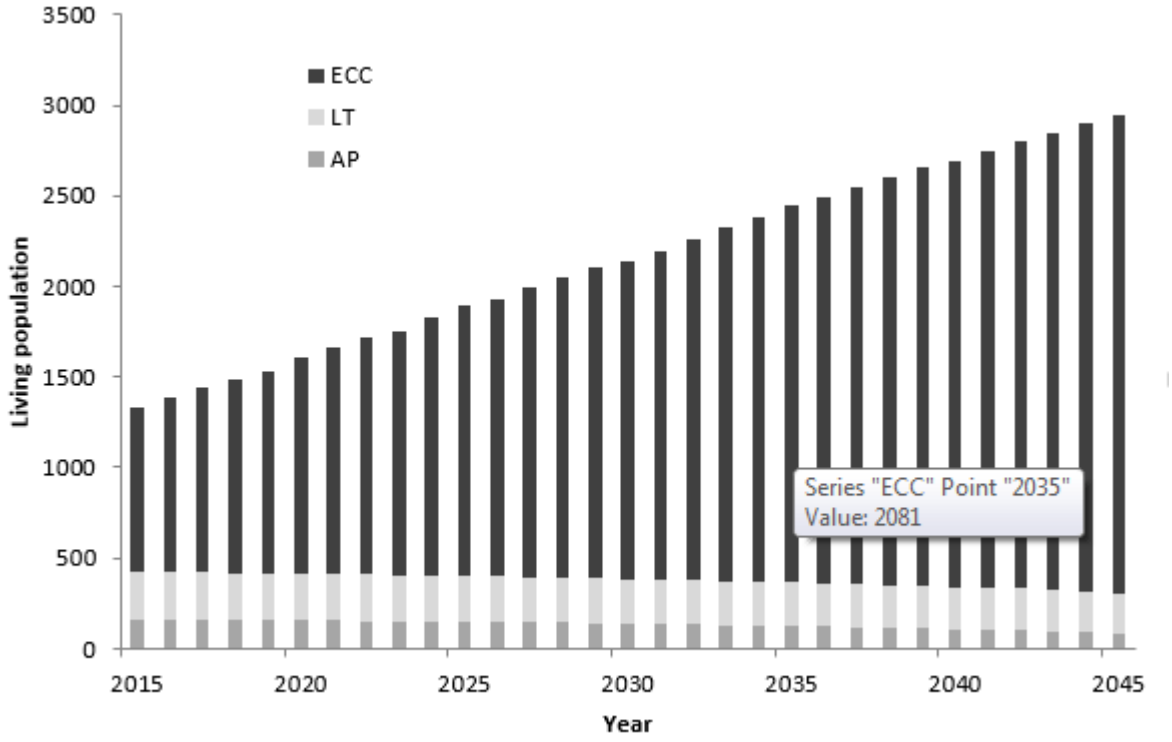

Figure 3

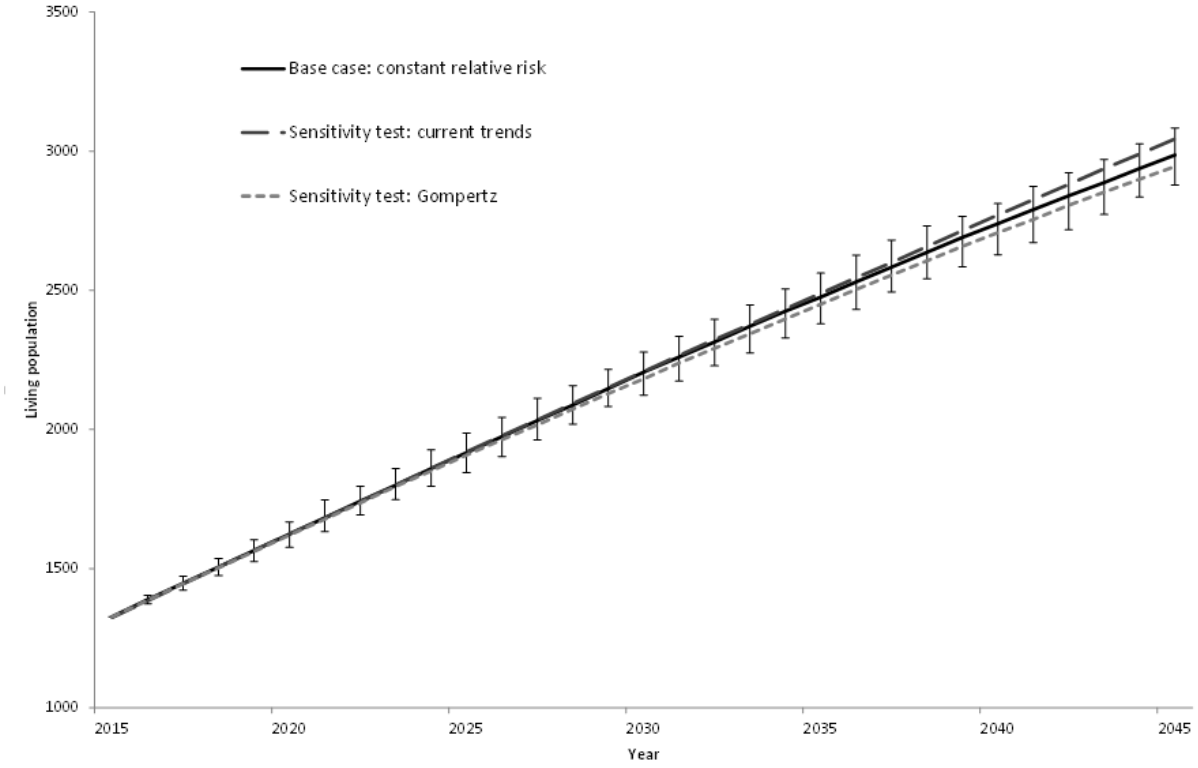

Figure 4