A damage propagation model of infectious disease: how lasting damage can outweigh infection mortality in younger individuals

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ABSTRACT

We model the effects of disease and other exogenous damage during human aging. While the exogenous damage is repaired at the end of acute infectious disease, propagated secondary damage remains. We consider both short-term mortality effects due to acute damage and long-term mortality effects due to propagated damage within the context of a generic network model (GNM) of individual aging. Across a wide range of disease duration and severity we find that while excess short-term mortality is highest for the oldest individuals, the long-term years of life lost are highest for the youngest individuals. These appear to be universal effects of human disease. We support this conclusion with a phenomenological model coupling damage and mortality. Our results are qualitatively consistent with existing observational disease studies, though these are mostly limited to short time-horizons. We suggest that short-time horizon studies may have significant limitations for understanding the lifetime impacts of infectious diseases on both individuals and populations.

Infectious disease has shaped historical human life-expectancy[1,2]. Even today, antibiotic resistance is an ongoing concern[3,4] and the emergence of novel diseases– such as COVID-19, Ebola, SARS, Zika, avian flu, or monkeypox – is a worsening trend[5] exacerbated by climate change[6]. New diseases introduce key questions about how they could impact both infected individuals and the population at large. How can we know what to expect before they can be studied and characterized? One approach is to consider potentially universal effects of disease. At the population level, this includes studying how vaccination can mitigate epidemic impact[7] or how frequent large pandemics are[8]. There are also indications of universal or 'generic' effects of disease for individuals.

Rapidly increasing mortality with age of infected individuals is a typical feature of infectious diseases[9–17]. For example, short-term mortality of COVID-19 rises approximately exponentially with age – more than 30-fold from 55 to 85 years[18,19]. These short-term mortality effects are important and relatively straightforward to attribute to the disease. Nevertheless, many infectious diseases also exhibit long-term complications, exemplified by post-acute 'sequelae' (PAS) – for example, SARS and MERS[20], Ebola[21], Zika[22], 'long COVID'[23], and COVID complications[24] Surprisingly, we do not know the long-term effects of most PAS, how prevalent they are, how they depend on age, or how they compare to the impact of short-term mortality. This is because there are very few long-term large-scale studies of the impact of acute disease; most studies are limited to less than 5 years. One notable exception is the ongoing study of lifetime impacts of exposure to the atomic bombs at Hiroshima and Nagasaki[25,26]. While this does not represent the effects of an infectious disease, it does represent the long-term effects of acute exogenous damage.

Understanding age-effects of infectious disease is particularly important. For example, assuming that short-term mortality is the only impact of acute diseases implies that immunization of older individuals will typically[27] save more years of life than immunizing younger individuals[19,28]. However, if post-acute health impacts of disease – including PAS – lead to substantial shortened lifespans then immunizing *young* individuals could save move years of life. Resolving these question of age-effects for individual diseases is not easily done, since lifetime observational studies require many decades. An alternative approach is to computationally model the age effects of disease. However, modelling age effects of disease first requires a good model of normal aging.

Encouragingly, aging populations exhibit some universal behavior. Average human mortality rates exhibit an exponential increase with age known as Gompertz' law[29], which is reminiscent of the increased short-term mortality of infectious disease with age. Before death, individuals also accumulate damage approximately exponentially with age[30], leading to worsening individual health[31]. The random but inexorable accumulation of damage during aging can be modelled at the individual level by a complex network of binary health attributes (healthy or not)[32], where damage propagates stochastically across static links

(edges). Such a "Generic Network model" (GNM) of human aging recovers the population-level behaviour of mortality and health[33–36].

A GNM model can provide individual aging trajectories and also a dynamical context for propagating damage due to the disease. We can model the onset of disease by treating it as an exogenous event that further damages an individual. As such, we can also consider any exogenous damage – and are not specifically limited to infectious disease. While the generic nature of the health attributes in the GNM precludes a detailed study of specific diseases, we can use it to understand potentially universal effects of disease in aging individuals.

We will consider the effects of disease timing (onset age), severity, and duration. We will first consider excess mortality (fatality) rates due to disease. To assess the long-term impact of diseases we also need to consider years-of-life lost due to disease. We can use years-of-life lost within different time horizons to compare short and long-term impacts of disease. We also develop and explore a simplified phenomenological model of how exogenous damage leads to earlier mortality.

Generic Network Model (GNM) of Infectious Disease and Exogenous Damage

The GNM represents individual health by an undirected scale-free network[37]. Links, defining network topology, are static. Nodes are dynamic binary health attributes – either damaged or not. A summary measure of individual health is the frailty index (f)[31], which is the fraction of damaged nodes. An undirected scale-free network is generating using the Barabási-Albert preferential attachment model[38], with an average node degree $\langle k\rangle$ and scale-free exponent α_{GNM}. Nodes are initially undamaged at age $t = 0$, but damage at a rate $\Gamma_+ = \Gamma_0 \exp(\gamma_+ f_i)$, where f_i is the fraction of damaged neighbours for node i. Damaged nodes repair at a rate $\Gamma_- = (\Gamma_0/R)\exp(\gamma_- f_i)$, though repair has a negligible effect on population statistics in practice. Individual mortality occurs when the two most connected nodes are both damaged. We use parameters that recover USA population health and mortality statistics for ages $t \gtrsim 20$: $\langle k\rangle = 4$, $\alpha_{GNM} = 2.27$, $\Gamma_0 = 0.00183$, $\gamma_+ = 7.5$, with small repair ($\gamma_- = 6.5$ and $R = 3.0$) and $N = 10^4$ nodes[33,35]. For simplicity and clarity we do not use a false-negative correction[33] to reduce the range of f to $[0, 1-q]$ – i.e. we use $q = 0$ and have $f \in [0,1]$. Stochastic dynamics are exactly sampled[39]. All plotted data corresponds to at least 10^6 simulated individuals. Errorbars for averages, unless indicated, are smaller than point sizes. All times are measured in years.

The GNM models damage from all sources that arises during the aging process, including the propagation or amplification of earlier damage. It then captures mortality effects due to that damage. Since the GNM is parameterized from population health and mortality statistics, it implicitly includes many extrinsic events such as disease or injury – the usual stressors of living. As such we expect that the GNM will allow us to model the effects of an individual infectious disease, which we consider as additional or perturbative to the normal aging process in order to estimate its effect.

We will not model details of the infection process, rather we will assume infection has taken place at some onset age t_{on} and lasts for a duration τ. In a similar spirit we will assume that the disease has a fixed severity or magnitude m. In terms of the GNM, our model disease damages a fraction m of nodes at the onset age t_{on}. While formally $m \in [0,1]$, we do not damage already damaged nodes so m should be kept small. We exclude individuals from analysis who have initial damage $f > 1-m$. For $m \leq 0.02$ no individuals are excluded, while for $m = 0.05$ a small fraction 10^{-4} are excluded for $t_{on} \geq 90$. (All ages and times are in years.) At the end of the disease (at $t_{on} + \tau$) a fraction r of the applied damage is removed. The fraction r of damage that is removed is a recovery or "resilience" parameter. For acute diseases we typically use $r = 1$, while chronic diseases could be modelled with $r = 0$ (equivalently, $\tau \to \infty$). Since we model disease by introducing exogenous damage m at time t_{on}, and allow for a fraction r to be repaired after τ through resilience, we can use the same model for any exogenous damage. The effect of our model disease is illustrated in Fig. 1a with respect to the Frailty Index f, which is simply the overall fraction of damaged nodes. The control population with no disease is indicated by the grey dashed line. We see that even with $r = 1$ there is excess damage Δf left in the individual after the end of the disease. This residual damage leads to the long-term mortality effects that we characterize.

We measure long-term mortality using the average reduction in lifespan (Δt_{tot}) and also by the average years lost within a window of w years after the disease (Δt_w), assuming the mortality rate of the control population after that window. All disease results are with respect to a large control population with no disease ($m = 0$). The excess probability of death due to the disease corresponds to an excess Infection Fatality Rate (IFR) as compared to the control population.

GNM Results

Our GNM model disease has a significant impact on long-term health, as shown by the average frailty index (f) vs age for large simulated populations that received a disease (blue points) or did not (grey dashed line) in Fig. 1a. With maximal resilience ($r = 1$, our default acute disease) all of the damage introduced at t_{on} is removed after τ. Nevertheless excess damage propagates within the GNM and is left at $t_{on} + \tau$, as indicated by Δf. For a variety of onset ages, and for selected durations τ as indicated,

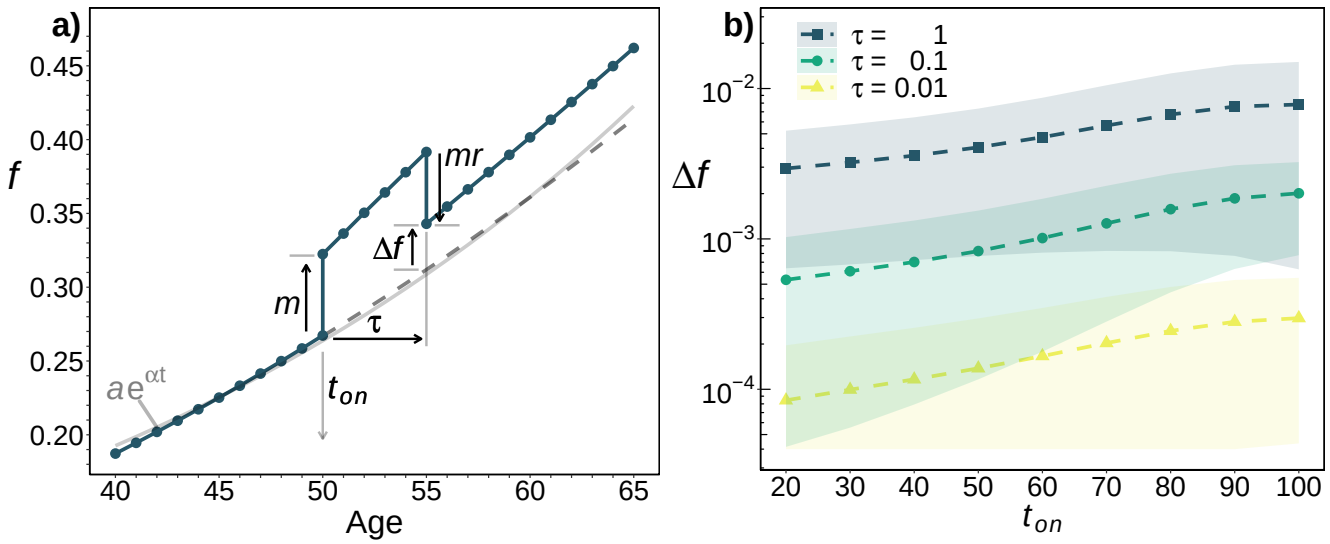

Figure 1. **(a) Model disease.** A disease is represented by exogenous damage of severity m inserted at onset time t_{on}; a fraction r of the original damage is then removed after duration τ. Excess damage that is left at $t_{on}+\tau$ is indicated by Δf. The average damage vs age, as assessed by the Frailty Index (f), for an acute disease with $r=1$, $m=0.05$, $t_{on}=50$ and $\tau=5$ is indicated by the blue points. A control population (with $m=0$) is indicated by the grey dashed line, and is well approximated by an exponential $f=ae^{\alpha t}$ where $a=0.0548\pm0.0009$, $\alpha=0.0314\pm0.0003$, and t is the age in years – as indicated by the solid grey curve. **(b) Excess damage.** Increase in the frailty index (Δf at $t=t_{on}+\tau$) at the end of an acute diseases with severity $m=0.02$ vs onset age t_{on}, with duration τ as indicated by legend and $r=1$. The shading indicates the standard deviation of Δf. All ages and times, in this and other figures, are in years.

we show Δf in Fig. 1b. We see that Δf increases with onset age, and also that the individual variability of propagated damage (indicated by the shaded regions) is large. This reflects the stochastic nature of damage propagation within the GNM.

In Fig. 2a, we show the excess mortality during an acute disease (IFR) vs onset age t_{on}. The IFR increases monotonically with t_{on} for all m and τ investigated, and maintains an approximately exponential age dependence similar to the all-causes mortality curve (μ, grey squares). In Fig. 2b we show the total years lost due to disease (Δt_{tot}) vs the onset age. Strikingly, we see that the average reduction in lifespan is highest for younger populations (note the log-scale). There are two mechanisms that could contribute to the reduction of lifespan of younger individuals. The first is that mortality during the disease leads to more years of life lost for younger individuals – who have a larger life expectancy. The second is that long-term mortality effects could be worse for younger individuals. We can separate these effects by considering different observation windows w after the disease.

In Fig. 3a we show the average years lost Δt_w within a window of duration w after the end of the disease. We account for all excess mortality between t_{on} and $t_{on}+\tau+w$. Just considering deaths during the disease ($w=0$, yellow open triangles), we find that older populations have the largest number of years lost – as observed with, e.g., COVID-19[28]. The larger total lost lifespan of younger individuals is not enough to offset their much lower IFR. As we increase w, Δt_w increases, and its peak shifts towards younger ages. For younger ages, years lost due to deaths during the disease account for a small fraction of the total years lost. The largest lifetime impact ($\Delta t_\infty \equiv \Delta t_{tot}$, blue squares) is for the youngest individuals, in agreement with Fig. 2b. Strikingly, the peak (mode) of lifespan impact only moves away from the oldest ages with long observation windows of $w \gtrsim 20$ years. The ratio of lifespan reduction $\Delta t_{tot}/\Delta t_0$ exceeds 100 for the youngest onset ages, and does not strongly depend on duration τ or severity m (data not shown). The ratio will further increase for lower resilience ($r<1$) since acute mortality IFR and acute life lost Δt_0 are unchanged but mortality after the disease is increased due to larger residual damage Δf. For example, in Fig. 3b with $r=0$ we show that Δt_{tot} is more than ten-fold larger than with $r=1$.

Phenomenological Model of Disease and Exogenous Damage

While the GNM allows for stochastic and high-dimensional individual health trajectories, the connection between modelling assumptions and phenomenological behavior is obscured by its complexity. A simpler model would be more interpretable – allowing us to see how and when our modelling assumptions lead to the behavior we see. A simpler model would also be easier

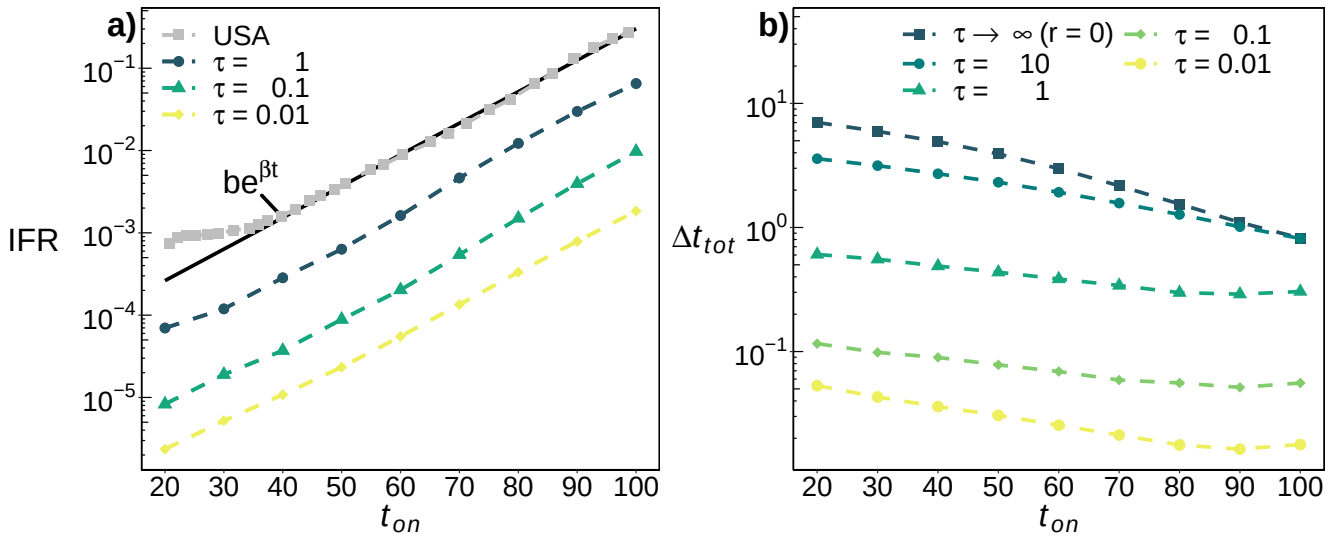

Figure 2. **(a) Mortality** Excess probability of death during the disease (IFR) vs onset age (t_{on}) for acute diseases with duration τ as indicated, and $m = 0.02$. Square grey markers indicates the all-causes mortality rate (per year) vs. age from the U.S. population[40]. Exponential fit (solid black line): $(4.3 \pm 0.3)10^{-5} \exp[(0.089 \pm 0.001)t_{on}]$. **(b) Lifespan reduction** The average total reduction in lifespan due to disease, Δt_{tot}, vs. onset age t_{on} for severity $m = 0.02$ and duration τ as indicated by legend, with $r = 1$. Chronic disease corresponds to $\tau = \infty$ (or $r = 0$).

to generalize, since we would expect that all models with similar assumptions would exhibit similar behavior. While mean-field versions of the GNM exist[33,35], here we develop a simple model that is directly rooted in the observed aging phenomenology: damage accumulates non-linearly with age and this damage drives mortality. The essential simplification is that the health-state is described only by the average damage – rather than by the N internal nodes of the GNM. This phenomenological model complements our network-based simulations using the GNM, and can be easily modified for different phenomenological assumptions.

We start with the observation that the average damage, or frailty index, increases approximately exponentially with age $f_0(t) = ae^{\alpha t}$.[41] From the GNM, we have $\alpha \approx 0.031$ (and $a \approx 0.055$, see Fig. 1) which is consistent with observational estimates for adults with $t \gtrsim 20$ ($\alpha \approx 0.035 \pm 0.02$[41]). We assume that exogenous damage, such as from infectious disease or injury, forms part of — and behaves similarly to — the damage exhibited during aging. As such it satisfies the differential equation $df/dt = \alpha f$ and any exogenous damage m grows exponentially thereafter. By including resilience, we then have simple expressions for the average damage before, during, and after the disease:

$$f(t) = \begin{cases} ae^{\alpha t} & t < t_{on}, \\ ae^{\alpha t} + me^{\alpha(t-t_{on})} & t_{on} < t < t_{on} + \tau, \\ ae^{\alpha t} + \Delta f\, e^{\alpha(t-(t_{on}+\tau))} & t > t_{on} + \tau, \end{cases} \tag{1}$$

where

$$\Delta f = m(e^{\alpha\tau} - r) \tag{2}$$

is the propagated damage at the end of the acute disease (at $t_{end} = t_{on} + \tau$, and with resilience r).

This phenomenological damage model is already considerably simplified compared to the GNM: we have a single deterministic health state variable (f) rather than $N = 10^4$ stochastic health-nodes. By comparing our expression for the propagated damage Δf (Eqn. 2) with Fig. 1b, we see that the phenomenological model has a single value of Δf that is independent of onset age t_{on} while the GNM has a broad range of Δf with an average that increases with t_{on} – though by much less than the individual variability.

We also need an explicit mortality model. We use the well-established but phenomenological Gompertz law of $\mu_0 = be^{\beta t}$,[42] whereby the mortality rate of adults increases exponentially with age. We estimate $\beta \approx 0.089$ (and $b \approx 4.3 \cdot 10^{-5}$, see Fig. 2a). We then assume that the increasing mortality rate results *only* from the increasing frailty-index $f(t)$. To obtain the correct

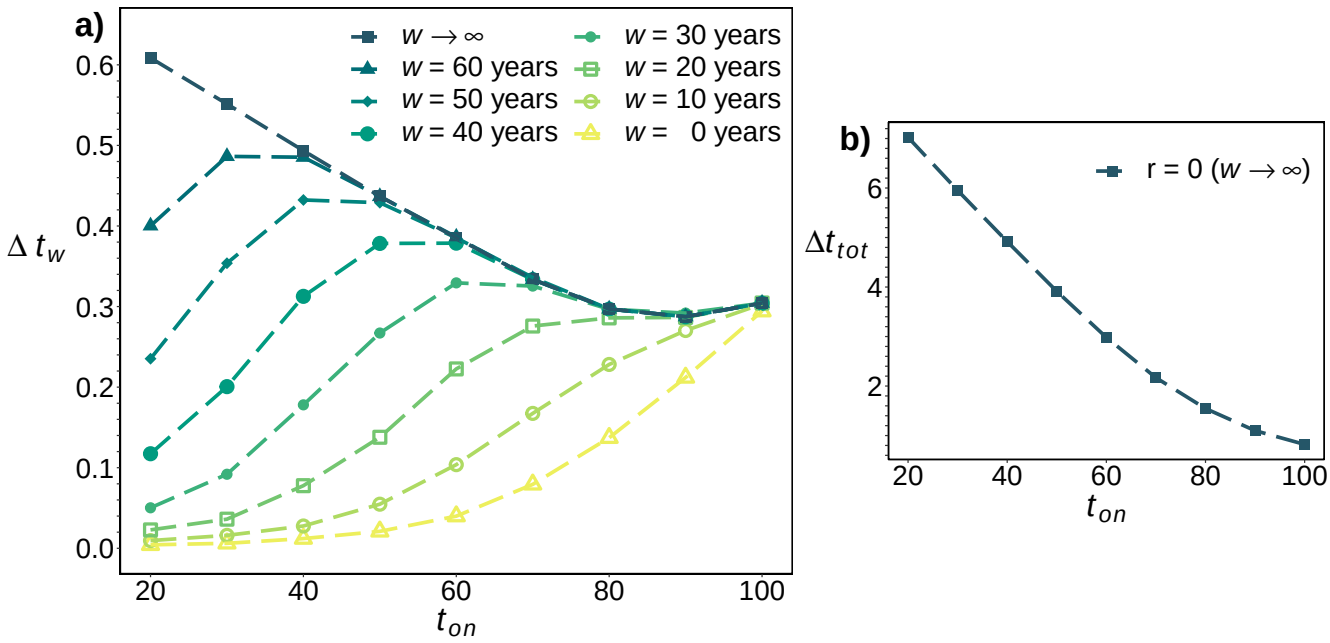

Figure 3. Lifespan reduction for different observation windows. **(a)** The average years lost Δt_w vs t_{on} for different observation windows w past the end of acute disease (with $r = 1$). The effects of mortality during the disease ($w = 0$) are largest for older individuals. The effects of lifetime mortality ($w \to \infty$) are largest for younger individuals. All with $\tau = 1$ and $m = 0.02$. **(b)** Δt_{tot} for a chronic disease ($r = 0$). The lifetime effects ($w \to \infty$) are approximately ten-fold larger than in Fig. 3a.

time-dependence for mortality from $f_0 \propto e^{\alpha t}$ we have

$$\mu = b(f/a)^{\beta/\alpha}. \tag{3}$$

This expression will hold for both the disease and control populations, since by assumption the mortality is expressed only through the health. With a disease, for $t > t_{end}$ we can express this as

$$\mu(t) = be^{\beta t}\left(1 + \frac{\Delta f}{f_{end}}\right)^{\beta/\alpha}, \tag{4}$$

where $f_{end} = f_0(t_{end}) = ae^{\alpha(t_{on}+\tau)}$ is the control (non-disease) frailty at the end of the disease. Note that a chronic disease corresponds to a disease with no acute period and no resilience – i.e. $\tau = r = 0$. A similar expression for the hazard applies during the disease, with m and f_{on} instead of Δf and f_{end}.

The lifespan mortality rates, $\mu(t)$, uniquely determine the survival statistics[43]. In Fig. 4a we present the death age distributions for several disease parameter values. Just as with the GNM, the disease has two lifespan-shortening effects: a short-term, acute effect that increases mortality during the disease, reducing lifespan by Δt_{short}; and a long-term, chronic effect that shifts the death age distribution to younger ages, further reducing lifespan by Δt_{long}. In Fig. 4b we numerically calculate the ratio of acute to chronic effects. As with the GNM, we see that long-term effects dominate for younger individuals whereas short-term effects dominate for older individuals, and are essentially independent of disease severity.

We can also obtain simpler expressions for mortality effects – particularly in the 'weak' limit of small m and τ. These are useful both to develop an understanding of the origins of the effects exhibited by the GNM and by diseases, and also to obtain simpler models that could be used for a statistical analysis of observational data.

Long-term effects

While short-term survival does mediate long-term effects (see supplemental for details) this coupling is small in the weak limit. For simplicity, here we will condition on short-term survival – i.e. assume that individuals are alive at $t_{end} = t_{on} + \tau$ with excess damage Δf.

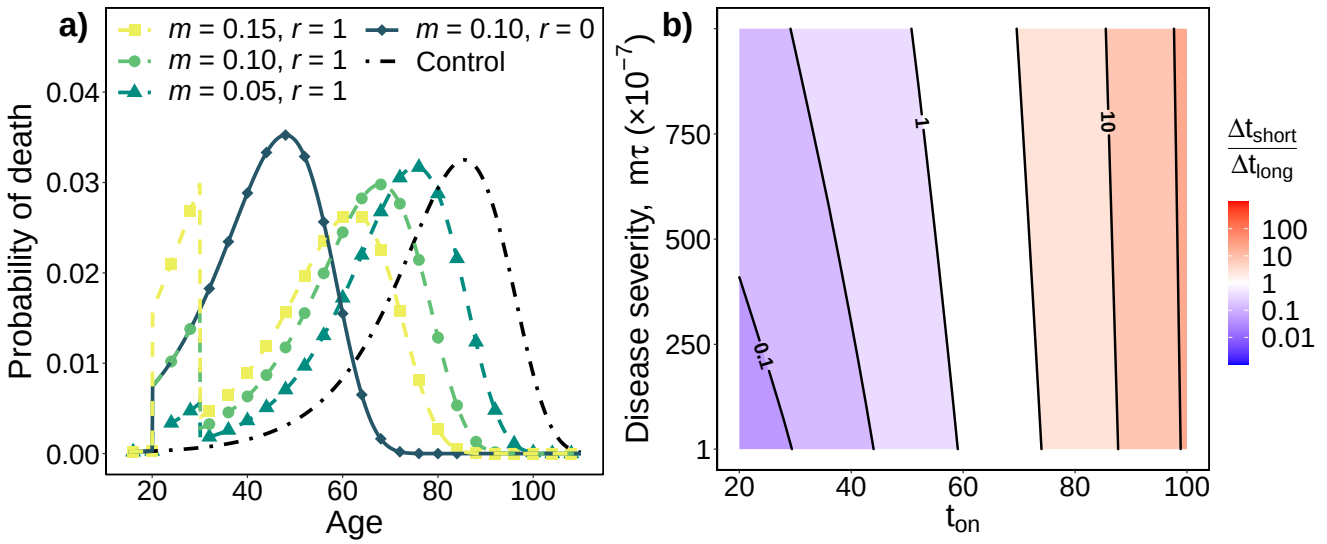

Figure 4. Phenomenological model. (a) **Effect of varying m and r on death age**. The control distribution (dot-dashed line) is shifted to lower ages by the disease. Without resilience, the distribution is permanently shifted to lower ages (solid line). With resilience (dashed lines), two phases emerge: an acute phase during the disease (ages 20-30) and a chronic phase after the disease ends, due to propagated damage. Each phase contributes to the overall loss of life due to the disease. ($\tau = 10$, $t_{on} = 20$) (b) **Acute vs chronic effects**. Ratio of expected life lost during acute phase, Δt_{short}, over chronic phase, Δt_{long}. Ratio increases exponentially with increasing age of onset, t_{on}, nearly independently of disease severity ($m\tau$). ($\tau = 10^{-3}$, $10^{-4} \leq m \leq 10^{-1}$, $r = 1$)

Since mortality is determined by health, then the addition of exogenous damage Δf at t_{end} effectively ages an individual by Δt_{long} where $f_0(t_{end} + \Delta t_{long}) = f_0(t_{end}) + \Delta f$. This is independent of the form of the mortality law. We obtain

$$\Delta t_{long} = \frac{1}{\alpha} \ln\left(1 + \frac{\Delta f}{f_0(t_{end})}\right). \tag{5}$$

This expression neglects a monotonic memory term which is small for young t_{on}, but significantly decreases Δt_{long} at old t_{on} (Supplemental). Note that Δt_{long} estimates the increase in biological age following disease[41]. Using Eq. 2, and assuming small severities m we obtain $\Delta t_{long} \approx \Delta f / (\alpha f_0(t_{end}))$. Further assuming small durations τ we obtain

$$\Delta t_{long} \approx \frac{m\tau}{f_0(t_{on})}\left(r + \frac{1-r}{\alpha\tau}\right). \tag{6}$$

Since mortality only depends on f, Δt_{long} estimates the long-term reduction in lifespan *after* the survival of mild diseases – excluding any short-term mortality during the disease. Since $f(t)$ increases with age, Δt_{long} is largest in youngest individuals – independent of disease parameters m, τ, and r. We note that for imperfect resilience, with $r < 1$, chronic effects dominate the long-term impact of disease-survivors and $\Delta t_{long} \approx m(1-r)/\left[\alpha f_0(t_{on})\right]$.

Long-term excess relative risk (ERR) and the Life-Span Study (LSS) of Atom-bomb survivors

The Life-Span Study (LSS) of approximately 120,000 survivors of the atomic bombs dropped on Nagasaki and Hiroshima has tracked excess lifetime mortality due to radiation exposure for more than 50 years, and found that excess relative risk increased with current age, decreased with age of exposure, and was approximately linear with dosage[25,26]. Deaths due to solid-tumor cancer predominate the excess mortality.

While our phenomenological model allows for any source of exogenous damage m, not just from infectious disease, we need to recast it in terms of excess long-term hazard to be able to directly compare with the LSS results. Using Eq. 4 with $\tau = 0$ we obtain

$$\mu(t) = be^{\beta t}\left(1 + \frac{\Delta f}{a} e^{-\alpha t_{on}}\right)^{\beta/\alpha}. \tag{7}$$

If we linearize in the hazard in Δf we obtain

$$\mu(t) \approx be^{\beta t}\left(1+\frac{\beta}{\alpha}\frac{\Delta f}{a}e^{-\alpha t_{on}}\right) = \tilde{\mu}_0(t,\vec{c})\left(1+\gamma(\vec{c})de^{\theta t_{on}}\right), \tag{8}$$

where on the right we show a model of excess relative risk (ERR) from the LSS[25] – here the covariates $\vec{c}$ such as sex, city, and birth year are indicated. Qualitatively both approaches have excess absolute risk with attained age t, declining risk with age of exposure t_{on}, and linear dosage response (m or d in Sv). We can identify $\theta = -\alpha$. Their model estimates $\alpha = 0.045$ (90% CI: [0.031, 0.060])[25], which agrees with our estimate of 0.031 (which is population-dependent). We suggest that the increased radiation sensitivity at younger exposure ages reported by the LSS[25] may be a general effect of increased damage sensitivity at younger exposure ages.

Our phenomenological model also suggests different risk models that could be applied to the LSS data, including nonlinear effects in Eqn. 7. Using $\alpha = -\theta$ and $\beta = 0.089$ (Fig. 2a), we estimate $\Delta f/a = 0.98d$, where d is the exposure dose in Sieverts (Sv)[25]. The dose is approximately equal to the propagated damage, Δf, in natural units. Since doses range up to 5 Sv, the linearized approximation may start to break down for younger individuals.

Short-term effects

We can use the hazard $\mu(t)$ in Eq. 4 to solve for the survival probability $S(t)$, using $dS/dt = -\mu S$; details are in the supplemental material. Conditional on being alive $S = 1$ at t_{on} we obtain

$$S(t) = \exp[-\frac{b}{\beta}(f_{on}/a)^{\beta/\alpha}(e^{\beta(t-t_{on})}-1)], \tag{9}$$

where f_{on} is the frailty at t_{on}. The probability of mortality by the end of an acute disease is $1-S(t_{end})$ therefore we obtain the excess short-term mortality Δp_{death} due to the acute disease by the difference in the survival function between using $f_{on} = f_0(t_{on})$ and $f_{on}+m$ at t_{on}. For small m and τ we obtain

$$\Delta p_{death} \approx m\tau\beta\mu/(\alpha f_{on}). \tag{10}$$

We see that $\Delta p_{death} \propto e^{(\beta-\alpha)t}$ is highest for older individuals since $\beta > \alpha$. This is consistent with the observation of increasing short-term mortality with age in many infectious diseases.

Comparing short- and long-term effects

To compare short- and long-term effects, we need to estimate the years of life lost due to death during the disease – all within the small m and τ limit. We can approximate the remaining lifespan Δt_D from the survival curve by imposing $S(t_{on}+\Delta t_D) = 1/e$, this assumes the survival curve sharply decays. Using Eqn. 9 we obtain $\Delta t_D = \beta^{-1}\ln(1+\beta/\mu_0(t_{on}))$. The years of life lost during acute disease is then $\Delta t_{short} = \Delta p_{death}\Delta t_D$ which gives

$$\Delta t_{short} \approx \frac{m\tau}{f_{on}}\frac{\mu}{\alpha}\ln(1+\frac{\beta}{\mu}). \tag{11}$$

In the limit of small m and τ, the ratio of short to long-term lifespan effects is then

$$\frac{\Delta t_{short}}{\Delta t_{long}} \approx \frac{\beta}{\alpha}\ln(1+\frac{\beta}{\mu})/(\beta/\mu), \tag{12}$$

where we have also allowed for maximal recovery after the disease ($r = 1$). Interestingly, this ratio is independent of disease details. We note that $\ln(1+x)/x \approx 1$ for $x \approx 0$ and monotonically decreases towards 0 with increasing $x = \beta/\mu$, i.e. with decreasing age. At large ages $\Delta t_{short}/\Delta t_{long} \approx \beta/\alpha > 1$, so that short term mortality during disease affects lifespan more than long-term effects. Conversely, at sufficiently young ages, we expect long-term mortality effects after the disease to have greater impact on lifespan than short-term mortality during the disease. From our estimates of α and β, $\Delta t_{short}/\Delta t_{long} = 1$ for $\mu \approx 0.024$. From all-causes mortality statistics from the U.S. population (Fig. 2a, grey squares) we have $\mu \lesssim 0.024$ for ages $t_{on} \lesssim 70$. So, our phenomenological model indicates that most people would have a greater reduction of lifespan due to premature death long after the disease than from death during the disease. Similar results are observed away from the small m and τ limit (see Fig. 4a) and in the GNM (see Fig. 3b).

Discussion

We have developed and explored a three-parameter (age of onset t_{on}, severity m, and duration τ) model of generic acute disease, which is built upon a generic network model (GNM) of organismal aging. We evaluated short-term mortality outcomes using the excess infection fatality rate (IFR) and long-term mortality outcomes using the average reduction in lifespan due to the disease (Δt_{tot}). We found that while mortality during acute diseases is highest for older populations, the total reduction in lifespan is highest for younger populations. The majority of the years of life lost for younger populations are due to premature deaths later in life. Older populations have worse short-term outcomes because they have greater frailty f (worse health), which leads to a greater likelihood of death during the disease. Younger populations lose more years of life both because there is more time for propagated damage Δf to impact mortality, and more years to be lost as a result of it.

Our results are qualitatively consistent with higher short-term mortality for older populations as reported for many acute diseases, including COVID-19[18], SARS[9], influenza[10,11], H1N1[12,13], Ebola[14], varicella (chickenpox)[15,17], and meningococcal disease[16]. We predict that post-acute effects should increase with acute severity m, in qualitative agreement with, e.g., studies of long-COVID[44–46]. Long-term impacts of post-acute sequelae (PAS) are common[20–23,47–52], but studies typically only have a $w \lesssim 5$ yr observation window. Two that consider the impact of onset age find PAS are more prevalent and/or severe among older populations[23,50], which agree with our findings for $w \lesssim 5$ yr. We found that $w \gtrsim 20$ yr is needed to observe the largest PAS impacts, which we predict occur for smaller onset ages. Larger observation windows w are needed. If confirmed, our results could have significant implications for how we prioritize medical interventions across age. Cost effectiveness of e.g. rotavirus vaccine[53] or allocation of COVID-19 vaccine[28] currently only consider mortality during disease.

Our disease model is essentially one of exogenous damage, and so should be more general than just acute disease. Long-term studies of hip-fracture survivors have shown significant excess relative risk that is approximately independent of attained age[54,55] in agreement with our simple phenomenological model (Eqn. 7). While the followup window extends to $w = 15$ years, according to our results this is still too short to observe that the lifetime effects peak at younger ages (Fig. 3a) — and most of the individuals are older at time of hip-fracture. Atomic bomb survivors provide a unique long-term dataset for exogenous damage due to radiation[25] – with exposure ages ranging from $0-60$ and with more than 50 years of followup. In agreement with our findings, lifetime risks are greatest for younger exposure ages t_{on}.

Our simple phenomenological theory shares with the full disease model our assumptions that residual damage and mortality are determined by health via f. Subject to these assumptions, the qualitative agreement of our models indicates the potential universality of our results. From the phenomenological theory we see the key role of the exponential growth rates of mortality and frailty, β and α respectively. Empirically we have $\beta > \alpha$, so short-term excess IFR (Δp_{death}) grows with age. Our phenomenological theory also indicates that post-survivor years of life lost Δt_{long} is universally greatest for the young – depending only on $\alpha > 0$.

Aging individuals exhibit changing robustness (resistance to damage) and resilience (recovery from damage) with age[56–58]. Robustness and resilience can be considered tunable parameters during aging since, e.g., vaccinations increase robustness to infectious disease while orthopaedic surgery can improve recovery from hip fractures. Robustness could affect the frequency and/or severity of disease for older individuals. Disease frequency typically increases with age[59], indicating declining disease robustness. Our results are for a fixed severity (m) so direct comparisons between ages require caution. Nevertheless, the ratio $\Delta t_{long}/\Delta t_{short}$ is conditioned on the disease occurring, and is largely independent of disease severity (Fig. 4b). The observation that the lifespan impact of disease can be more than 100-fold worse than the acute impact of disease for younger individuals is independent of robustness.

Our model explicitly includes resilience through r. Smaller resilience (r) should lead to larger Δf and more long-term effects. Since resilience is expected to decrease with age[57,58], we would expect more long-term effects in older individuals. The result would be a greater ratio of $\Delta t_{long}/\Delta t_{short}$ for older individuals. We do note however that we could also include a resilience parameter r_{prop} for propagated damage, see supplemental Eqn. S7. In this paper all propagated damage is retained and contributes to long-term effects. With a non-zero r_{prop} we can reduce the effects of propagated damage and hence tune the relative impact of Δt_{long} and Δt_{short}. For long-term effects, such as studied in the atomic-bomb survivor cohort of the LSS, r_{prop} will affect Δf but not the greater impact of Δf on younger individuals. Nevertheless, r_{prop} may be needed to reconcile short-term and long-term mortality for long-term studies when both are available.

Our disease model has no explicit age dependent dynamics, so all effects occur via individual health. Consistent with this, the prognosis of disease generally worsens with a higher frailty index f[31,60]. For example, high f has been shown to increase risk of worse outcomes from COVID-19 at a given age[61–63]. Nevertheless, our disease model is stochastic which leads to considerable variability of, e.g., excess post-acute damage Δf (see Fig. 1b). We also see that our disease model shows an increasing Δf with age, in contrast to our phenomenological model but in qualitative agreement with the severity of, e.g., long-COVID[23].

Our disease model is simple and generic. While it does not allow us to track specific impacts of particular diseases, it does allow us to examine the effects of direct (m) and secondary damage (Δf) in an aging population. We find large long-term

effects at younger onset ages. Including such disease age-effects in epidemic[64] or vaccination[7] models would help us better understand and mitigate the impacts of disease on aging societies. For example, acute-phase modelling of COVID-19 has introduced a debate on vaccine rollout strategies. Is it better to vaccinate the old to reduce direct risk, or vaccinate the young to reduce overall infections[24,27]? Neglected are the chronic effects due to propagated damage, which would increase the value of vaccinating the young, despite the widespread policy of vaccinating them last[24]. We also suggest long-term observational studies of health and mortality after acute disease or exposure to better capture lifetime disease and damage impacts.

Data availability

The disease model code used to generate the data presented in this paper are available at `https://github.com/RebeccaTobin/DiseaseModel`. The data used for plots is available on request from A.R..

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Author contributions statement

R.T. conducted the simulations and data analysis and drafted the manuscript. All authors contributed to the design of the research, the data interpretation and the manuscript production.

Competing interests

The authors declare no competing interests.

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