Long-term vs short-term mortality impacts of disease during aging

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We model the effects of diseases during human aging, where disease introduces exogenous damage into an individual. For acute diseases this damage is soon repaired, though propagated secondary damage remains. We consider both short-term and long term mortality effects. Across a wide range of disease duration and severity we find that while excess short-term mortality is highest for the oldest individuals, the total 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 mean-field model coupling damage and mortality. Our results are qualitatively consistent with existing observational disease studies, though they are mostly limited to short time-horizons.

Organismal diseases act at scales ranging from subcellular, to organismal, to population, with a correspondingly broad range of length and timescales that are amenable to the techniques of physics. Accordingly, "disease physics" ranges from viral self-assembly [1], to cancer [2], to epidemic processes [3]. Given the continual emergence of new diseases such as COVID-19, Ebola, SARS, Zika, avian flu, or monkeypox, it is important to understand potentially universal impacts of diseases. Examples include pandemic magnitude [4, 5] or how epidemics are affected by vaccination [6].

Due to heterogeneous interactions, complex networks have been used for modelling disease effects at population scales [3, 5–7]. Network physics can also be applied to disease at the organismal scale [8]. Connectivity damage is a common measure of network attacks [9, 10] and such 'link-damage' can be useful for e.g. characterizing Alzheimer's disease [11]. However, contagion spread in populations is conveniently modelled as the propagation of nodal damage across a fixed topology network [5] – with dynamic binary-state nodes [12]. This is also a useful model of disease damage at the organismal scale.

Rapidly increasing mortality with age of infected individuals is a typical feature of acute disease [13–21]. For example, short-term mortality of COVID-19 rises approximately exponentially with age – more than 30-fold from 55 to 85 years [22, 23]. Is this be a universal feature of acute disease? Why?

Many acute diseases also exhibit post-acute 'sequalae' (PAS) – for example, SARS and MERS [24], Ebola [25], Zika [26], and 'long COVID' [27]. We do not know the long-term effects of most acute diseases – but they may be significant. In a rare study of lifetime impacts of acute exposure, atom bomb victims exhibit higher post-acute risks for younger ages at exposure [28, 29]. Similarly, for dementia – a chronic disease – younger onset leads to more years of life lost [30].

Understanding age-effects of disease is a pressing concern, particularly any universal aspects. For example, assuming that short-term mortality is the dominant impact of acute diseases implies that immunization of older individuals saves more years of life than immunizing younger individuals [23, 31]. If post-acute health impacts of disease, including PAS, lead to substantially shortened lifespans this could affect our response to existing and emerging diseases. It would also suggest adding time-delayed impact to epidemic models [3, 5–7].

Modelling age effects of disease requires some understanding of aging itself. Average human mortality rates exhibit an exponential increase with age known as Gompertz' law [32]. Before death, individuals accumulate damage approximately exponentially with age [33], leading to worsening individual health [34]. This phenomenology of aging can be represented by node damage propagating stochastically within a complex network where nodes correspond to interacting health attributes within an individual. Such a "Generic Network model" (GNM) of human aging recovers population level behaviour of mortality and health [35, 36].

We can model the onset of disease by treating it as an exogenous event that further damages an individual. A GNM model can provide individual aging and also a dynamical context for propagating damage due to the 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 acute duration. We can distinguish acute and chronic diseases by whether recovery to initial damage is nearly complete (acute) or not (chronic). 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 a mean-field model of how exogenous damage leads to earlier mortality. Our model qualitatively supports our computational results.

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) [34], which

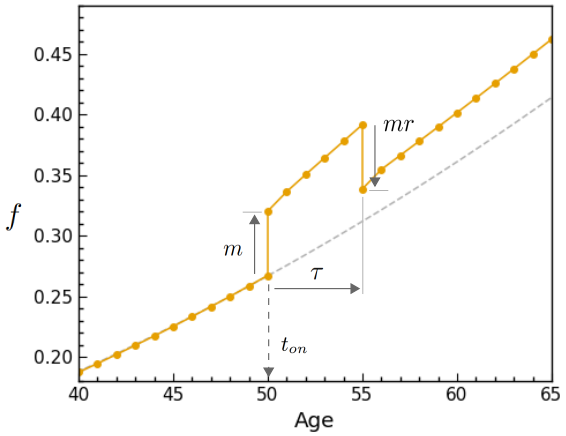

FIG. 1. **Model disease.** A disease is represented by exogenous damage of severity m inserted at onset time t_{on}; a fraction r of the original damage is then removed after duration τ. The average damage vs age, as assessed by the Frailty Index (f), for an acute disease with $r = 1$, $m = 0.05$, $t_{on} = 50$ and $\tau = 5$ is indicated by the gold points. A control population (with $m = 0$) is indicated by the black dashed lines. All ages and times are in years.

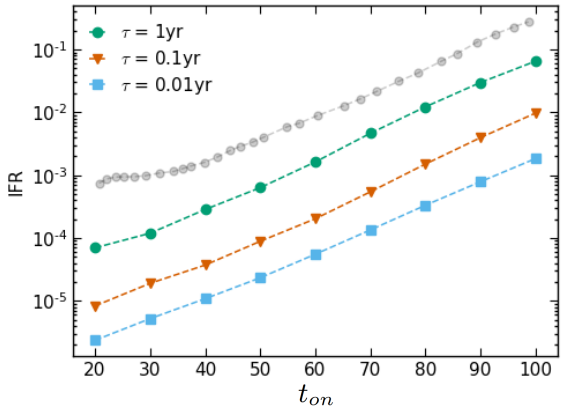

FIG. 2. **Excess Infection Fatality Rate (IFR).** Excess probability of death during the disease (IFR) vs onset age (t_{on}) for acute diseases with duration τ as indicated, and $m = 0.02$. Circular gray markers indicates the all-causes mortality rate (per year) vs. age from the U.S. population [40].

is the fraction of damaged nodes. We use GNM parameters that recover USA population health and mortality statistics for ages $t \gtrsim 20$ [35, 36], though without a false-negative rate q. Stochastic dynamics are exactly sampled [38]. 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.

Our model disease [39] of magnitude m further damages a fraction m of nodes at the onset age t_{on} and then removes a fraction r of that damage after an acute disease duration τ (see Fig. 1). The fraction r of damage that is removed is a "resilience" parameter. For acute diseases we use $r = 1$, while chronic diseases have $r = 0$ (equivalently, $\tau = \infty$). We do not damage already damaged nodes. Accordingly, 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} (10^{-3}) are excluded for $t_{on} \geq 90$ (100).

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 mortality statistics 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.

Results. Our 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 (orange points) or did not (black dashed line) in Fig. 1. Note that with maximal resilience ($r = 1$, our default acute disease) all of the damage introduced at t_{on} is removed after τ.

In Fig. 2, 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 (grey circles).

In Fig. 3a we show the total years lost due to disease (Δt_{tot}) vs the onset age. Surprisingly, we see that the average reduction in lifespan is highest for younger populations. Nevertheless, older individuals retain more damage after the disease than younger individuals (Fig. 3b). Significant individual variability is also observed due to the stochastic propagation of damage during the disease.

In Fig. 4 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 ($w = 0$, orange circles), we find that older populations have the largest number of years lost – as observed with, e.g., COVID-19 [31]. 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 ($\Delta t_\infty \equiv \Delta t_{tot}$, purple squares) is for the youngest individuals, in agreement with Fig. 3a. The same age trend for Δt_{tot} is also observed in chronic diseases with no recovery after onset (with $r = 0$, Fig. 4 inset).

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 ($r < 1$, not shown) 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.

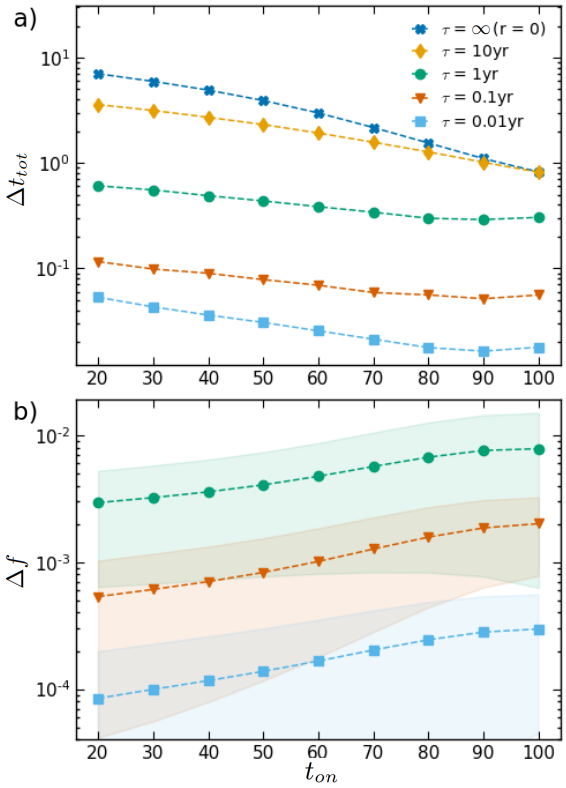

FIG. 3. **Total lifespan reduction.** a) The average total reduction in lifespan due to disease, Δt_{tot}, vs. onset age t_{on} for severity $m = 0.02$ and duration τ as indicated by legend, with $r = 1$. Chronic disease corresponds to $\tau = \infty$ (or $r = 0$). b) Excess increase in the frailty index (Δf) after acute diseases with severity $m = 0.02$ (at $t = t_{on} + \tau$) vs onset age t_{on}, with duration τ as indicated by legend and $r = 1$. The shading indicates the standard deviation of Δf.

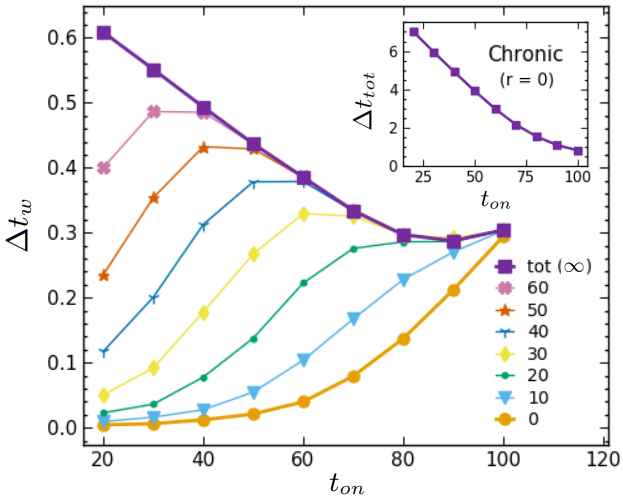

FIG. 4. **Lifespan reduction for different observation windows.** The average years lost Δt_w vs t_{on} for different observation windows w past the end of acute disease (with $r = 1$). The inset shows Δt_{tot} for a chronic disease ($r = 0$). All with $\tau = 1$yr and $m = 0.02$.

Mean-field theory. While effects during the disease (excess mortality IFR in Fig. 2 and years lost during the disease Δt_0 in Fig. 4) increase with age, the total lifespan lost Δt_{tot} decreases with age. Lifetime disease effects are largest in the young. To understand the potential universality of these results, we develop a mean-field theory of disease effects that neglects both individual stochasticity and network topology.

We start with the phenomenological observation that the frailty index increases approximately exponentially with age $f(t) = f(t_s)e^{\alpha(t-t_s)}$ from any starting age t_s. With the addition of exogenous damage m at t_s, we effectively age an individual by Δt_{eff} where $f(t_s + \Delta t_{eff}) = f(t_s) + m$. We obtain

$$\Delta t_{eff} = \frac{1}{\alpha} \ln(1 + m/f(t_s)), \tag{1}$$

For chronic disease, we use $t_s = t_{on}$. After an acute disease with resilience factor r, the exponential growth of $f(t)$ leads to excess damage $m_{eff} = m(e^{\alpha\tau} - r)$, which can be used in Eqn. 1 and which corresponds to Δf in Fig. 3b). In the limit of small severities m we obtain $\Delta t_{eff} \approx m_{eff}/(\alpha f_{on})$, where f_{on} is the frailty at t_{on}.

Δt_{eff} is the increase in biological age following disease, and, if mortality rates only depend on f, estimates the reduction in lifespan for mild diseases. Since $f(t_s)$ increases with age, Δt_{eff} is largest in youngest individuals. We find qualitative agreement with short acute disease in Fig. 3a and chronic disease in the inset of Fig. 4.

To obtain excess probability of mortality during acute disease Δp_{death}, we use the mortality rate $\mu = \mu_0 f^{\beta/\alpha} \propto e^{\beta t}$ to solve the survival probability using $\dot{S} = -\mu S$. With this we assume that mortality only depends on accumulated damage through f. We obtain

$$S = \exp[-\frac{\mu_0}{\beta} f_s^{\beta/\alpha}(e^{\beta(t-t_s)} - 1)], \tag{2}$$

conditional on being alive with $S = 1$ at t_s. We estimate $\beta \approx 0.088$ from grey points for μ in Fig. 2.

The probability of mortality during acute diseases is $1 - S(t_s + \tau)$ and we obtain the excess short-term mortality Δp_{death} due to the acute disease by the difference in the survival function between $f_s = f_{on} + m$ and $f_s = f_{on}$ at $t_s = t_{on} + \tau$. For small m and τ we obtain $\Delta p_{death} = m\tau\beta\mu/(\alpha f_s)$. We see Δp_{death} is highest for older individuals (we estimate $\alpha \approx 0.037$, so $\beta > \alpha$), which agrees with the higher excess IFR at older ages observed with the GNM in Fig. 2.

We can approximate remaining lifespan t_D by imposing $S = 1/e$. In the limit of small p we obtain the change $\Delta t_D \approx p/[\alpha f(t_s)(1 + \mu/\beta)]$. This agrees with our earlier estimate from Δt_{eff} when $\mu \ll \beta$ – which holds for younger individuals.

The years of life lost during acute disease is given by

$\Delta t_0 = \Delta p_{death} t_D$. In the limit of small m and τ, and with $r = 1$, the years of life lost due to deaths both during and after the disease is given by $\Delta t_{tot} = \Delta t_0 + \Delta t_{eff}$. Their ratio $\Delta t_{tot}/\Delta t_0 \approx 1 + \alpha/\mu$. This ratio increases for younger individuals, in agreement with Fig. 4, indicating that a greater proportion of the mortality burden of disease in younger populations is due to deaths after the acute phase of disease.

Discussion. We have developed and explored a three-parameter (age of onset t_{on}, severity m, and duration τ) model of generic acute ($r = 1$) or chronic ($r = 0$) 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 for both acute and chronic diseases 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, 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 m_{eff} to impact mortality, and more years to be lost as a result of it. Chronic diseases ($r = 0$) also lead to younger populations exhibiting the greatest loss of lifespan.

Our results are qualitatively consistent with higher short-term mortality for older populations as reported for many acute diseases, including COVID-19 [22], SARS [13], influenza [14, 15], H1N1 [16, 17], Ebola [18], varicella (chickenpox) [19, 21], and meningococcal disease [20].

Long-term impacts of post-acute sequelae (PAS) are common [24–27, 41–46], 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 [27, 44], 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.

If confirmed, our results could have significant implications for how we prioritize medical interventions across age. Cost effectiveness of e.g. rotavirus vaccine [47] or allocation of COVID-19 vaccine [31] currently only consider mortality during disease. Our results indicate that larger observation windows w are needed.

Our disease model is essentially one of exogenous damage m, with a fraction r repaired after an interval τ. As such it should apply to any exogenous damage. Atomic bomb survivors provide a unique long-term dataset for exogenous damage due to radiation [28] – though mostly limited to the impact of excess cancers. In agreement with our findings, lifetime risks are greatest for younger exposure ages t_{on}. Meta-analysis of hip fracture studies also show evidence of greater lifetime impacts due to younger injury ages t_{on} [48, 49]. We also predict that post-acute effects should increase with acute severity m, in qualitative agreement with, e.g., studies of long-COVID [50, 51].

Aging individuals exhibit changing robustness (resistance to damage) and resilience (recovery from damage) with age [52, 53]. 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 bone fractures. Our model explicitly includes resilience through r. Smaller resilience (r) should lead to larger m_{eff} and more long-term effects. Since resilience is expected to decrease with age [53, 54], we would expect more long-term effects in older individuals. The result would be a greater ratio of $\Delta t_{tot}/\Delta t_0$ for older individuals.

Robustness could affect the frequency and/or severity of disease for older individuals. Disease frequency typically increases with age [55], indicating declining disease robustness. Our results are for a fixed severity (m) so direct comparisons between ages require caution. Nevertheless, the ratio $\Delta t_{tot}/\Delta t_0$ is conditioned on the disease occurring, and is largely independent of disease severity (data not shown). 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 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 [34, 56]. For example, high f has been shown to increase risk of worse outcomes from COVID-19 at a given age [57–59]. Nevertheless, our disease model is stochastic which leads to considerable variability of, e.g., excess post-acute damage Δf (see Fig. 3b). We also see that our disease model shows an increasing Δf with age, in contrast to our mean-field theory m_{eff} but in qualitative agreement with the severity of, e.g., long-COVID [27].

Our mean-field theory qualitatively shares with the full disease model our assumptions that residual damage and mortality are determined by health f. Subject to these assumptions, the qualitative agreement of our models indicates the potential universality of our results. From the mean-field 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 excess IFR grows with age. Decreasing mortality with age increases β [60], indicating that IFR will grow more strongly with age if lifespans continue to increase. Our mean-field theory also indicates that the years of life lost Δt_{eff} is universally greatest for the young – depending only on $\alpha > 0$.

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 (m_{eff}) in an aging population. We find large long-term effects at younger onset ages. Including such disease age-effects in epidemic [3] or vaccination [6] models would help us better understand and mitigate the impacts of disease on aging societies. We also suggest long-term observational studies of health and mortality after acute disease or exposure to better capture lifetime disease and damage impacts.

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