3 Supporting Text 3–Process models of VMC and death times

3.1 A single-state Markov process

We observe two events in each individual’s life, $v_i$ and $d_i$, the timing of vigorous movement cessation and death respectively. We presume that each event arises as the outcome of some time-dependent physical decline. In this section, we seek to understand how our measurement of the distributions $V$ and $D$ inform us about the relationship between the physical declines determining $v_i$ and $d_i$.

To accomplish this, we introduce a third variable $X$ which we cannot observe directly but infer for each individual $i$ using $v_i$ and $d_i$. Based on the observed residual structure (S2b Fig) we define $X$ such that $x_i = d_i - v_i$ with $x_i \sim X$. Note that S2b Fig of the main text excludes the alternative model $d_i = v_i x_i$, as the regression residuals of the proportional model have higher heteroskedasticity than the additive model. Furthermore, note that $x_i$ is never zero and therefore we need not consider that truncation of $V$ by $D$ might influence the relationship between $V$ and $D$. We diagram this relationship in Fig A in S3 Text.

We consider the case where $V$ and $X$ arise as first-passage times across distinct thresholds of a single Markov process. If the Markov process has a single state that determines both $v_i$ and $d_i$, then all individuals will necessarily share an equivalent state at their VMC times $v_i$ because each will have just passed the same threshold. In consequence, each individual $i$ will have an equivalent remaining lifespan at $v_i$ such that $E(X|V = t)$ becomes independent of $t$.

Consider the linear regression

$$d_i = \alpha v_i + \epsilon_i + c$$

This regression will estimate a value of $\alpha$ that ensures

$$E(D|V = t) = \alpha t + c$$

with $E(\epsilon|V) = 0$. Because $d_i = v_i + x_i$, it follows by construction that

$$E(D|V = t) = t + E(X|V = t)$$

and therefore by substituting in Eq. 1 we arrive at the expression

$$E(X|V = t) = (\alpha - 1)t + c$$

For a single-state Markov process $E(X|V = t)$ must be independent of $t$, which will occur only when $\alpha$ equals exactly 1. Because our data shows that, generally, $\alpha < 1$, we conclude that a single-state Markov process model is inconsistent with our data.

3.2 A system of two Markov processes

We therefore consider whether two Markov Process—or a two-dimensional Markov process which is equivalent—is sufficient to explain our data. We find that $\alpha < 1$, which implies that $X$ and $V$ are negatively correlated. To interpret this we must now be more explicit about our model regarding the causal relationship between $V$ and $D$.

Consider two such relationships between $V, D,$ and a potential upstream confounder $R$.

We diagram this relationship in Fig B in S3 Text: Two possible causal relationships between $V$ and $X$. 

Fig B in S3 Text: Two possible causal relationships between $V$ and $X$. 

...
Causal models (a) and (b) differ in the relationship between $V$ and $X$: causal in (a) but non-causal in (b). How does $\alpha < 1$ constrain these two models? For model (a), $\alpha < 1$ implies that $V$ must exert some negative influence on $X$. The biological implications of this are described in the main text.

In contrast, model (b) allows the correlation between $V$ and $X$ to arise from the action of some upstream factor $R$. Because $V$ is no longer causally upstream of $X$, then the correlation implied by Eq. 1 no longer must be explained by some paradoxical physical interaction between $V$ and $X$. Instead, the value of $\alpha < 1$ would arise based on the particular form of $E(D|V = t)$ determined incidentally by the two conditional distributions $D|R$ and $V|R$. This can be demonstrated by considering the two extremes: if $R$ fully determines the variability in $V$ and $X$, then by definition $E(X|V)$ becomes independent of $R$ and therefore independent of time, yielding an $\alpha = 1$. At the opposite extreme, if $R$ has no influence on $V$ and $X$ then $V$ and $X$ become uncorrelated such that $\alpha = 0$. Any realization of model (b) that falls between these extreme cases would then produce an $\alpha$ whose value lies between 0 and 1.

3.3 A system of two Markov processes (in parallel)

The constrains described in the previous section hold not only if the time-dependent processes $V$ and $X$ occur in series, but also they progress in parallel, as shown in Fig C in S3 Text.

Fig C in S3 Text: A model where $V$ and $D$ run in parallel

Here, $d_i \geq v_i$ remains true only because $E(D) \gg E(V)$ and $E(D) - E(V)$ and the variances of $V$ and $D$ are low enough that the tails of $V$ and $D$ do not overlap. In the case of causal model (a) the process determining $V$ must be coupled to $D$ such that $D$ progresses slower before $t = v_i$ but then faster after $t = d_i$. In contrast, causal model (b) allows $V$ and $D$ to progress in parallel, such that $R$ can have a time-independent influence to act similarly hasten or slow both $V$ and $D$.

3.4 Summary

We therefore conclude that our regression analysis corresponding to Eq. 1 excludes the possibility that $V$ and $D$ are outcomes of a single-state Markov process, which is the assumption underlying much current work. Instead, a system of two Markov processes—or a single two-dimensional Markov process which is equivalent—allows a single systemic factor to act similarly on the processes determining both $D$ and $V$ to produce the observed correlations and in particular a slope $\alpha < 1$ in Eq. 1.