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The evolution of maternal effect senescence

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Increased maternal age at reproduction is often associated with decreased offspring performance in numerous species of plants and animals (including humans). Current evolutionary theory considers such maternal effect senescence as part of a unified process of reproductive senescence, which is under identical age-specific selective pressures to fertility. We offer a novel theoretical perspective by combining William Hamilton's evolutionary model for aging with a quantitative genetic model of indirect genetic effects. We demonstrate that fertility and maternal effects senescence are likely to experience different patterns of age-specific selection and thus can evolve to take divergent forms. Applied to neonatal survival, we find that selection for maternal effects is the product of age-specific fertility and Hamilton's age-specific force of selection for fertility. Population genetic models show that senescence for these maternal effects can evolve in the absence of reproductive or actuarial senescence; this implies that maternal effect aging is a fundamentally distinct demographic manifestation of the evolution of aging. However, brief periods of increasingly beneficial maternal effects can evolve when fertility increases with age faster than cumulative survival declines. This is most likely to occur early in life. Our integration of theory provides a general framework with which to model, measure, and compare the evolutionary determinants of the social manifestations of aging. Extension of our maternal effects model to other ecological and social contexts could provide important insights into the drivers of the astonishing diversity of lifespans and aging patterns observed among species.

Significance statement (<120 words):

Authors must submit a 120-word-maximum statement about the significance of their research paper written at a level understandable to an undergraduate-educated scientist outside their field of specialty. The primary goal of the Significance Statement is to explain the relevance of the work in broad context to a broad readership.

Evolutionary theory underpins our understanding of the aging process. The many aspects of reproduction that decline with maternal age in animals include number of offspring born, offspring size, and neonatal survival. Current theories of aging ignore potential differences in the evolutionary pressures on these traits. Here, we combine two important branches of evolutionary theory to allow consideration of age-dependent selection at both offspring and maternal levels. We show that we should actually expect the rates of age-related decline in female fertility and offspring performance to diverge under selection. Our model has the potential to significantly improve our understanding of the evolution of reproductive senescence and, more generally, the variability of aging patterns in nature.

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Senescence is the age-related deterioration of organismal function and fitness. Evolutionary theory explains its pervasiveness as the result of age-related declines in the strength of natural selection to preserve survival and reproduction (1). Genes deleterious to survival or fertility in late life can persist or even come to fixation as a result of this weakening of selection in old age (2-4). To date, most theoretical and empirical research into the evolution of senescence has focused on age-specific survival and fertility (vital rates), as these rates are most proximate to fitness. Both age-related declines in survival (actuarial senescence) and fertility (reproductive senescence) can evolve independently from initially non-senescent life histories (1).

These vital rates are a product of complex interactions among different physiological systems, phenotypic traits, and their environment. One important source of environmental contributions involves social interactions. The influence of other individuals in the environment on a particular phenotype can itself be heritable, and the importance of these so-called indirect genetic effects (IGEs) is now established within evolutionary biology (5-7). IGEs are known to readily alter the evolutionary predictions of standard quantitative genetic models incorporating only direct genetic effects (DGEs). In age-structured populations, social interactions among individuals of different ages are likely to be commonplace, but it is not known how age-dependent IGEs influence the evolution of senescence. Here we incorporate IGEs into the evolutionary theory of aging to provide the necessary conceptual and statistical framework with which to understand how social interactions among individuals of different ages can shape aging patterns. We then develop our model to specifically deal with one particular social interaction of central biological importance: maternal effects influencing neonatal survival.

Amidst the many studies of senescing traits, a clear pattern is emerging that relates maternal age to the health, fitness, and lifespan of their progeny across widely diverse taxa including humans (8), birds (9, 10), mammals (11, 12), *Drosophila* species (13-15) and other arthropods (16-18), and plants (19). Although observations suggest that maternal effect senescence may not proceed at the same rate as fertility senescence (12, 20-24), there is no evolutionary theory yet capable of explaining maternal effect senescence or its distinction from fertility senescence. Biologists have assumed that the age-related decline in selection that shapes fertility and survival generalize to traits under the influence of IGEs, including maternal effects. To address this deficiency in the theory, we develop a general model incorporating IGEs into age-specific phenotypic evolution. We then focus our attention upon maternal effects that influence neonatal survival with the aim to: 1) understand how increases in maternal age will alter the strength of selection for neonatal survival IGEs and 2) predict how neonatal survival will change with maternal age when populations are at a mutation-selection equilibrium.

THE MODEL

The conventional model of phenotypic evolution describes the relationship between the fitness, phenotypes, and genotypes of individuals. The phenotype of some individual i is the sum of a breeding value (a transmissible genetic quantity) g_i and a non-heritable environmental residual e_i expressed as deviations from the population mean μ . Relative fitness is the numerical representation of the focal individual in the next generation, usually quantified by the number of zygotes produced; it can be described in terms of a function of a phenotype of interest,

$$w_i = \mu + \beta\{w, z\} + e_i \quad [1].$$

$\beta\{w, z\}$ is a selection gradient, the slope of the regression of relative fitness on phenotypes, and e_i is the residual fitness not explained by the trait. The response to selection is the change in the population mean over one generation owing to selection for trait z . Following the conventional quantitative genetic assumption of no covariance between genotype and environment (25), this response follows from the definition of phenotype and [1],

$$\Delta\bar{z} = \beta\{w, z\} \text{var}\{g\} \quad [2].$$

$\text{var}\{g\}$ is the additive genetic variance.

Response with indirect genetic effects: Social interactions alter the response to selection when the phenotype of one individual is modified by the genotype of another. We can define the phenotype to incorporate the effects of social interactions by considering some breeding value g_{Di} that predicts the phenotype of the bearer i (the DGE) and the breeding value g_{Ij} of a social partner j that modifies the focal individual's phenotype (the IGE). Following (26), the phenotype of individual i with some number of social interactors n_i is

$$z_i = \mu + g_{Di} + e_{Di} + \sum_{j=1}^{n_i} (g_{Ij} + e_{Ij}) \quad [3].$$

e_{Di} and e_{Ij} are environmental error terms arising from the focal individual and each of its interactors, respectively. A change in the phenotype due to one generation of selection can be caused by changes in DGEs, IGEs, or both. The change in DGEs caused by selection is

$$\Delta\bar{g}_D = \beta\{w, z\} \text{var}\{g_D\} \quad [4].$$

$\text{var}\{g_D\}$ is the genetic variation for the DGE contribution towards the phenotype. The change in the IGE contribution is $\Delta\bar{g}_I = \text{cov}\{w, E\{n\phi\}g_I\}$, where $E\{n\phi\}$ is the expectation of the relatedness between interactors and focal individuals, weighted by the number of interactors. We consider social effects generated by individuals that share a common relatedness, and we assume that n is constant over time. The change in IGEs caused by selection is

$$\Delta\bar{g}_I = \phi\beta\{w, z\} E\{n\} \text{var}\{g_I\} \quad [5].$$

$\text{var}\{g_I\}$ is the additive genetic variance of the IGE contribution to the phenotype. Eqs. [4] and [5] ignore genetic covariances between DGEs and IGEs, but these can be treated as separate traits and included into a multivariate response to selection (27)

$$\begin{pmatrix} \Delta\bar{g}_D \\ \Delta\bar{g}_I \end{pmatrix} = \begin{pmatrix} \text{var}\{g_D\} & \text{cov}\{g_D, g_I\} \\ \text{cov}\{g_D, g_I\} & \text{var}\{g_I\} \end{pmatrix} \begin{pmatrix} 1 \\ \phi E\{n\} \end{pmatrix} \beta\{w, z\} = \mathbf{G} \begin{pmatrix} 1 \\ \phi E\{n\} \end{pmatrix} \beta\{w, z\} \quad [6],$$

\mathbf{G} is the additive genetic variance-covariance matrix that includes genetic variances on its diagonal elements and genetic covariances on off-diagonals. The response follows from [6]

$$\Delta \bar{z} = \beta \{w, z\} \left[\text{var} \{g_D\} + (1 + \phi E \{n\}) \text{cov} \{g_D, g_I\} + \phi E \{n\} \text{var} \{g_I\} \right] \quad [7].$$

The IGE variance and DGE-IGE covariance shape the response to selection in proportion to the number of interactors weighted by their number and relatedness to the focal individuals. These variances and covariances have been estimated from natural animal populations (28-31). The relationship given in [7] has been derived elsewhere (26, 32), and we extend this model in the next section to account for IGEs with age-specific effects.

Age-specific IGEs: We develop the above models of IGEs further by incorporating age-specific variation to elucidate the role of IGEs in the evolution of aging. We consider the phenotype as specific to some age and some paired ages x_D, x_I corresponding to the ages of the focal individual and the social interactors, respectively. Thus, the phenotype of the focal individual taking into account the influence of social partners of only age x_I is

$$z_i(x_D, x_I) = \mu + g_{Di}(x_D) + e_{Di}(x_D) + \sum_{j=1}^{n_i(x_D, x_I)} \left[g_{Ij}(x_D, x_I) + e_{Ij}(x_D, x_I) \right] \quad [8].$$

Using this age-specific notation, we can rewrite the genetic response to selection [6]. However, the determination of selection gradients becomes more complicated in age-structured populations with overlapping generations. Here we consider a demographic model with discrete time units. When populations are at a steady-state with respect to age-structure, these can be identified by partial regression coefficients estimated by conventional multiple regression approaches (27), provided that the relative fitness of individuals are defined as $w_i = \sum \exp(-rx) l_i(x) m_i(x)$ (33, 34), where the summation continues to the last possible age of reproduction (34, 35), $l_i(x) m_i(x)$ is the individual's reproductive output at age x , and r is the population's Malthusian growth rate (35).

In the special case where one is interested in multivariate selection for vital rates, Hamilton theory provides analytically-derived selection gradients (1, 2). While these can be derived empirically by applying multiple regression of individual relative fitness to individual vital rates (34), Hamilton's 'sensitivities' have the advantage that they can be identified using only the population means of age-specific vital rates, which are far more widely available than the individual-based data that are required for regressions. The sensitivities relevant to the current study are for age-specific fertility and neonatal survival; these are $\partial r / \partial m(x) = \exp(-rx) \bar{l}(x) / T$ and $\partial r / \partial P(1) = 1 / \bar{P}(1) T$, respectively. $\bar{P}(1)$ is mean neonatal survival, and generation time T is the mean age of mothers in the population $\sum y \exp(-ry) \bar{l}(y) \bar{m}(y)$ (2). Multiplying by generation time rescales Hamilton's sensitivities from time units to generations (34, 36); this scale fits best with the quantitative genetic models developed here. Thus, for any vital rate expressed at age x_D in the presence of interactors of age x_I , the bivariate response to DGEs and IGEs over one generation is

$$\begin{pmatrix} \Delta \bar{g}_D(x_D) \\ \Delta \bar{g}_I(x_D x_I) \end{pmatrix} = \mathbf{G} \begin{pmatrix} 1 \\ \phi E \{n(x_D x_I)\} \end{pmatrix} \frac{\partial r}{\partial z(x_D)} T \quad [9].$$

$\partial r/\partial z(x_D)T$ is the selection gradient for the vital rate of interest, and \mathbf{G} is the genetic variance-covariance matrix of DGEs and IGEs specific to ages x_D, x_I respectively. From [8-9], the change in age-specific trait mean for those individuals with interactors aged x_I caused by selection after one generation of selection is

$$z_{ij}(x_D x_I) = \left(\text{var}\{g_D(x_D)\} + [1 + \phi E\{n(x_D x_I)\}] \text{cov}\{g_D(x_D), g_I(x_D x_I)\} + \phi E\{n(x_D x_I)\} \text{var}\{g_I(x_D x_I)\} \right) \frac{T \partial r}{\partial z(x_D)}$$

[10],

or $\text{var}\{g_D(x_D)\}T \partial r/\partial z(x_D)$ in the absence of IGEs (e.g., 36).

AGE-SPECIFIC MATERNAL IGEs ON NEONATAL SURVIVAL Many different types of age-specific social interactions could modify the evolution of aging. We focus on maternal effects for two reasons. First, the relationship between mother and offspring is the most profound social interaction to affect fitness in many species (37). Second, maternal-neonate IGE models are relatively simple applications of the social aging model above, and provide an obvious starting point from which to derive predictions from the general model. Here, we derive a model of age-related change in selection for maternal effects on neonatal survival. We use simple population genetic models to compare predicted evolutionary changes in age-specific maternal effects and their underlying genetic variance to changes in age-specific fertility.

Age-specific selection for maternal effects: While all individuals must have exactly one mother each, the ages of these mothers can differ. Consequently, the expected value describing the numbers of interactors at each age class in [9-10] is the frequency distribution of mothers' ages at birth. This is defined by the age-specific reproductive output, $\exp(-rx)\bar{l}(x)\bar{m}(x)$, standardized by its summation over all ages, or $\sum \exp(-ry)\bar{l}(y)\bar{m}(y)$. When populations are in stable age distribution, however, the Euler-Lotka relationship defines this summation to be one (2). Furthermore, given that Hamilton's sensitivity for age-specific fertility is $\partial r/\partial m(x) = \exp(-rx)\bar{l}(x)/T$ (1), the relevant bivariate change in breeding values over one generation can be written as

$$\begin{pmatrix} \Delta \bar{g}_D(1) \\ \Delta \bar{g}_I(1, x_M) \end{pmatrix} = \mathbf{G} \frac{T}{P(1)} \begin{pmatrix} 1 \\ \phi \frac{\partial r}{\partial m_x} \bar{m}_x \end{pmatrix} \quad [11].$$

Note that the expectation term in [9-10] has been replaced in the lower element of the rightmost vector of [11]. This new term clearly indicates how age-specific maternal IGEs can fundamentally change predictions from those made from the classical formulation of age-specific selection on vital rates. The strength of selection for breeding values for age-specific maternal effect on neonatal survival is proportional to the product of the selection gradient for age-specific fertility, mean age-specific reproduction, and the relatedness between mother and offspring (one-half with biparental reproduction and random mating). Note that a general concern of maternal effect models involves the potential for time lags in the response to selection if the maternally influenced trait contributes to a maternal effect (38, 39). The model described by [11] avoids this issue because the assumption of demographic stability that is required for Hamilton's theory ensures that the strength of selection for neonatal survival is held constant over time. For this reason, the rates of change given by [11]

and all subsequent derivations can be considered to be asymptotically correct as age-structures converge on stability (38).

The fundamental insight from our model is that age-related selection for maternal effects can differ from age-related selection for fertility. This is illustrated for different population patterns of vital rates in Fig. 1. Fig. 1A illustrates the unlikely situation where female fertility is constant with age, and selection for fertility and maternal effects must change at an identical rate with age. Fig. 1B illustrates a very important prediction when mean fertility declines with age: selection for maternal effects on neonatal survival declines faster with increased age than selection for maternal fertility. Although the simple genetic models of aging predict ever-decreasing fertility with age (e.g., 1, 2), physiological and ecological constraints place limits on the age of first reproduction and the reproductive capacity of young breeders (40). In systems with indeterminate growth, such as many trees, fish, and reptiles, fertility can continue to increase well into old age (41, 42) despite attenuated fertility selection with age. Furthermore, in longer-lived organisms with determinate growth (such as birds and mammals), fertility often follows an ‘inverted bath tub’ shape with increases through early adulthood as females continue to develop and gain experience before reaching a plateau and beginning to senesce (43). From [11], we can infer that the strength of selection for maternal effects will increase over those ages when the increase in $\bar{m}(x)$ exceeds the decrease in the strength of selection for $m(x)$, or $\exp(-rx)\bar{l}(x)$. In these cases, selection for the offspring vital rate will show a hump-shaped function of maternal effects with age in which there is an intermediate optimal maternal age (Figs 1C-D).

Evolution of age-specific maternal effects: The size and shape of the **G**-matrix, including the covariance between maternal IGEs and offsprings’ DGE, will influence the response to selection for neonatal survival (see [11]). Putting these details aside by making some simplifying assumptions about the nature of the genetic effects, we can modify existing population genetic models of aging to make simplistic predictions for how maternal effect senescence manifested on neonatal survival might evolve under mutation-selection equilibrium. These assumptions are shared with earlier models of aging by DGEs (2, 3, 44). We imagine that new mutations for maternal IGEs that increase neonatal mortality are independent and identically distributed across specific ages. Furthermore, we assume that mutations are partially recessive and occur at any locus k with rate u_{km} . Under these conditions, the mean trait value for an equilibrium population can be approximated as $\bar{z} \approx \exp(-2 \sum u_k / S(z))$, where $S(z)$ is selection against alleles that have deleterious effects upon z (44). In keeping with classical population genetic theory (e.g., 2), we assume that mutations act multiplicatively on survival, or additively on the scale of mortality, which is defined as $\mu = -\ln(P)$. To express mutational effects and selection on the same scale, survival selection can be converted as $S(P) = -S(\mu)/P$ (1). Given these assumptions and the relationship $S(\mu_1) = -1$, the DGE contribution to neonatal mortality is $\exp(2\sum u_{kD})$, and from [11] the equilibrium contribution to neonatal survival by maternal IGEs is approximately

$$P_1(x) \approx \exp\left(-2 \sum u_{kl} / e^{-rx} \bar{l}(x) \bar{m}(x) \phi\right) \quad [12].$$

If we assume that the IGE mutations are independent of the mutations with DGEs on neonatal survival, then the expected equilibrium value for neonatal survival is the product of the age-dependent [12] and the age-independent $\exp(2\sum u_{kD})$. The relationship between maternally derived neonatal survival and maternal age can be partitioned and its sources expressed more clearly on the scale of the natural logarithm of mortality,

$$\ln[\mu_1(x)] \approx \ln(2\phi^{-1} \sum u_{kM}) + rx - \ln[\bar{m}(x)] - \ln(\bar{l}(x)) \quad [13].$$

This shows us that the maternal source of neonatal mortality is increased (on the natural log scale) in proportion to the frequency of IGE mutations and in inverse proportion to the relatedness between mother and neonate, but both of these contributions to mortality are age-independent. The population growth rate can cause log-linear age-related changes in response to changes in maternal age: this source of mortality will increase in shrinking populations ($r < 0$) and decrease in growing populations ($r > 0$). Age-related decreases in either maternal fertility or cumulative survival will cause linear increases in neonatal mortality.

We can use [13] to determine whether the senescence that is predicted to evolve by the classical theory (1, 4, 44, 45) is necessary for maternal effect senescence to evolve. Let us assume for the moment that age-specific fertility and mortality are independent of age. In general, $l(x) = \exp(-\sum_1^x \mu(y))$, but given our temporary assumption of non-senescent mortality, this can be simplified as $\exp(-x\mu)$. Without either type of senescence

$$\ln(\mu_1(x)) \approx \ln(2\phi^{-1} \sum u_{kM}) - \ln[\bar{m}(x)] + (\mu + r)x \quad [14].$$

Equilibrium neonatal mortality will increase log-linearly in response to age-independent adult mortality (μ) and maternal age (x) under this model. This happens even in the absence of other manifestations of senescence (Fig. 2A, top). Differently put, maternal effect senescence can evolve without the pre-existence of other forms of aging. This happens because selection for the age-specific maternal effect is proportional to the product of age-specific fertility (which is a constant in this case) and cumulative survival, and the latter can never increase with increased age. These results are similar to those derived by Charlesworth's population genetic model of mutation accumulation for DGEs that predicted the evolution of log-linear age-related increases in mortality at mutation-selection balance (3). More realistic models of mortality will yield better predictions of how maternal effects will evolve. For example, a Gompertz model of mortality (and no fertility senescence), $\mu_x = A \exp(Bx)$, yields

$$\ln(\mu_1(x)) \approx \ln(2\phi^{-1} \sum u_{kM}) - \ln[\bar{m}(x)] + rx + A \sum_1^x e^{By} \quad [15].$$

As age-specific mortality accelerates with age, its accumulation with age must also accelerate. As a result, a log-linear increasing relationship between adult age and mortality translates into a *faster* than log-linear increase in neonatal mortality with maternal age (Fig. 2B, top). Neonatal mortality will be predicted to increase even faster with reproductive senescence.

Eqs. [13-15] show us that maternal IGEs on neonatal survival will senesce over large changes in maternal age. However, Fig. 1 shows us short-term conditions in which selection can favor increases in maternal effect selection. Accordingly, [13] can be used to identify these. The derivative of neonatal log-mortality with respect to maternal age and recognizing that $d \ln[l(x)]/dx = -\mu(x)$ identifies these in terms of the rate of change of fertility over time as $d\bar{m}(x)/dx = \bar{m}(x)(r + \mu(x))$. Neonatal mortality is expected to decline with increased maternal age at those ages where fertility increases faster than the product of mean age-specific fertility and the sum of age-specific mortality and the population growth rate. This may happen at early ages in populations with ever-increasing or inverted bathtub-shaped fertility (Fig. 2C, top).

Evolution of age-specific maternal IGE variance: As the evolutionary theory of aging predicts that additive genetic variance for age-specific fertility and mortality should increase with age (44, 46, 47), it is sensible to ask if the theory also predicts an age-related increase in maternal IGE variance for neonatal mortality. Following our early assumptions of rare, recessive deleterious

alleles, the equilibrium allele frequency at any locus i is approximately $q_i \approx u_i/S(z)h_i\delta z_i$ (44), where h_i is the dominance coefficient, and δz_i is the phenotypic difference between the wild-type and mutant homozygotes. As the additive genetic variance generated at locus i is $2q_i(h_i\delta z_i)^2$ (25), the relationship between this variance and selection for the trait is $V_{A_i}(z) = 2u_i h_i \delta z_i / S(z)$. Following our earlier assumption that mutations act multiplicatively on survival and noting that because we have assumed that $q_i \ll 1$, the genetic variance generated by each locus is small. Under these conditions, an additive model gives a fairly good approximation of a multiplicative model (44), and the variation for maternal IGEs on neonatal mortality is approximately

$$V_A(\mu_1(x)) \approx 2 \sum h_i \delta z_i u_i / e^{-rx} \bar{l}(x) \bar{m}(x) \phi \quad [16].$$

Variation for age-specific maternal IGEs will tend to increase with age as cumulative survival amongst adults inevitably declines (Figs 2A-B, bottom). However, it is possible that genetic variation can decrease over some age ranges if survival rates are very high and fertility rates increase with age (Fig. 2C, bottom).

DISCUSSION

Biologists have implicitly assumed that selective pressures on the trajectories of maternal age effects on offspring traits such as early size and survival do not differ from those acting on age-specific fertility. We have shown that this is unlikely to be true with an in-depth look at age-dependent maternal effects on neonatal survival, which are likely to be ubiquitous in natural systems. The age-specific selection for maternal IGEs that influence neonatal survival can differ from age-specific selection for fertility. The key prediction is that wherever fertility senescence occurs, selection for maternal effects will tend to decline more rapidly with age than selection for fertility. Simple population genetic models extend this finding to predict that: 1) maternal effect senescence will evolve to be more rapid than fertility senescence and 2) there should be a greater age-related increase in genetic variation for maternal effects than for direct effects on fertility. Because female fertility is very often age-dependent, we would expect this divergence in age-dependent selection between maternal effects and fertility to be ubiquitous, and differences in the rates and patterns of aging between female fertility and traits under strong influences of maternal effects should be observable.

The rapidly growing literature on senescence in wild animal populations provides evidence for divergent aging patterns in female reproductive traits (48). Numerous studies of mammals, birds and reptiles have presented simultaneous age-dependent estimates of female fecundity as well as estimates of offspring survival in mammals (11, 20, 24, 49, 50), birds (21, 23, 51-54), and reptiles (22, 55). However, very few have formally compared the patterns of aging between these two measures. A statistically supportable difference in aging rates was found in red deer, with offspring neonatal survival showing an earlier onset of senescence than fertility (12). While a similar trend appeared in Soay sheep, the difference in aging patterns was not found to be significant (56). A reliable method for quantifying and comparing aging patterns in traits like these from published data is needed to allow meta-analyses to be conducted to test whether aging patterns fit our models' predictions. One such approach might be to ask which model better fits maternal effect aging: 1) one proportional to age-specific fertility or 2) one proportional to the product of age-specific fertility and cumulative survival rates (e.g., the solid or dotted lines in Fig. 1).

Our population genetic models (eqs. 13-16) assume no DGE-IGE correlations for neonatal survival. In reality, these effects may be correlated. If these are correlations are positive, then viability selection will act in concert over DGE and IGE pathways, and neonatal survival at all maternal ages will be higher than with no correlations. If the correlations are negative, than

selection will act antagonistically upon the two pathways, and neonatal survival will suffer. Furthermore, the predicted neonatal mortality curves illustrated in Figs 1 and 2 reflect an assumption that IGEs with different ages of effect will be uncorrelated across maternal ages. This is likely an overly simplistic model of reality, but it is a sensible place to start to understand the evolution of IGE senescence. We may infer from DGE senescence models that positive genetic correlations across ages-of-effects will lower rates of aging (3, 57), and negative genetic correlations will intensify these (4, 44). Clearly, an understanding of the genetic architecture underpinning age-dependent variation in maternally influenced traits in natural populations will be essential for predicting senescence trajectories. Studies have found evidence for maternal age-dependent genetic variation in reproductive traits in the wild (see 58 for recent review), and one study has explicitly shown that maternal IGE variance for offspring birth weight increases with age in red deer (59). Similar studies of age-specific maternal IGEs are lacking from the literature. However, as discussed above, there is good evidence to suggest maternal effects and IGEs are widespread and important in nature (29-31) and that maternal age is a powerful predictor of a range of offspring traits (8-19). Given that age-specific maternal effects have been detected and estimated in a wild mammal system (59), the estimation of age-specific IGEs in other experimental and observational studies should be feasible. The theoretical perspective offered here highlights the potential importance of age-specific IGEs to our understanding of the evolution of ageing, and it should motivate further empirical efforts to measure them.

Previous studies have recognized that age-specific maternal effects may constitute an important component of the evolution of aging (11, 52, 60-63), but little specific guidance has been given for understanding why. Some have proposed that offspring quality should be taken into account in determining how we define aging (14). Others have more explicitly called for the development of new age-structured evolutionary models of aging that explicitly incorporate parental effects (15). The age-structured model presented here accomplishes these goals by explicitly determining the relationship between maternal effect senescence and the actuarial and reproductive senescence that constitutes the classical theory of senescence. Notably, we retain the fundamental structure of Hamilton's fundamental theory of aging, including its implied definition of individual fitness that is wholly determined by the vital rates of the individual. There is no need to modify this by offspring quality, such has been suggested elsewhere (64-66). This strict separation of fitness across generations is a necessary feature of quantitative genetic analyses of social evolution (67).

While we explored in detail only the evolution of age-specific maternal effects for neonatal survival, there are many other applications of age-specific IGEs that may help us understand the evolution of life histories. For example, we may reverse the direction of the IGE from the neonate to the mother to ask how selection for neonate survival shapes the evolution of adult survival. A fuller model might consider survival of neonates *and* mothers (two traits) and the direct and indirect genetic effects working in both directions (four genetic values). The relevant 4x4 **G**-matrix would incorporate genetic trade-offs in the form of IGE/DGE covariances. Previous development of the quantitative genetics of parental effects discusses the statistical signatures of parent-offspring interaction in great detail (38, 68, 69). Our contribution to this area is to point out how age-specificity can be included in order to gain a better understanding of senescence. Other applications and developments of IGE models of senescence could include other forms of social cooperation or competition for mates, food, or other resources. Biologists are interested in understanding the enormous variation in lifespan and senescence among species, and some have suggested that

classical evolutionary theory fails to predict this (42). Age-specific IGEs may play an important role in causing this diversity. The genes of many social partners beyond mothers, including grandparents, siblings, mates, and neighbours, may shape individual phenotypes. The complexity of the genetic basis for aging should follow to some degree from the complexity of the social context, and the wide diversity of social systems among plant and animal species may engender tremendous diversity in evolved aging patterns.

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FIGURE LEGENDS

Figure 1. Age-specific strength of selection for maternal neonatal survival IGEs. Plots illustrates age-functions of fertility selection (dotted line), fertility (broken line), and maternal IGE selection (solid line) for different hypothetical populations. Age-specific values are standardized by their maxima. Survival rates follow from a Gompertz model of mortality, $\mu_x = A \exp(Bx)$, with parameters $A = -2, B = 0.12$. Maximum age-specific fertility values for the four populations were 0.12, 0.70, 0.30, 0.29; these values were chosen to make r equal to zero. For this reason, selection for fertility is proportional to cumulative survival, and the strength of fertility selection (dotted lines) can be directly compared to maternal IGE selection (solid lines). The vital rates chosen for 1A cause age-related selection for maternal IGEs and fertility to decline at the same rates.

Figure 2. Age-specific maternal neonatal survival IGEs at mutation-selection equilibrium. Plots illustrate equilibrium age-specific maternal IGEs upon the means (top) and variances (bottom) of neonatal mortality. Three demographic scenarios are considered: A) No actuarial senescence (Gompertz parameters: $A = -2, B = 0$) or fertility senescence ($m = 0.17$); B) Gompertz mortality ($A = -2, B = 0.12$) and no fertility senescence ($m = 0.21$); and C) No actuarial senescence (Gompertz parameters: $A = -2, B = 0$) and “inverted-bathtub” fertility in the same shape as in Figure 1D with intermediate maximum of 0.23 at ages 5 and 6. The three lines on each graph represent equilibrium age-trajectories with different genome-wide mutation rates U . Population growth rates are $r = 0$.