nature ecology & evolution

ARTICLES

https://doi.org/10.1038/s41559-020-1173-y

An age-dependent ovulatory strategy explains the evolution of dizygotic twinning in humans

Wade N. Hazel[1] ✉, **Robert Black**[2], **Richard C. Smock**[3], **Rebecca Sear**[4] and **Joseph L. Tomkins**[5] ✉

Dizygotic twinning, the simultaneous birth of siblings when multiple ova are released, is an evolutionary paradox. Twin-bearing mothers often have elevated fitness, but despite twinning being heritable, twin births occur only at low frequencies in human populations. We resolve this paradox by showing that twinning and non-twinning are not competing strategies; instead, dizygotic twinning is the outcome of an adaptive conditional ovulatory strategy of switching from single to double ovulation with increasing age. This conditional strategy, when coupled with the well-known decline in fertility as women age, maximizes reproductive success and explains the increase and subsequent decrease in the twinning rate with maternal age that is observed across human populations. We show that the most successful ovulatory strategy would be to always double ovulate as an insurance against early fetal loss, but to never bear twins. This finding supports the hypothesis that twinning is a by-product of selection for double ovulation rather than selection for twinning.

The stable existence of alternative phenotypes in a single population is of interest because it suggests a balance of evolutionary forces at play. Elucidating those forces, particularly when they apply to humans, is an important focus of evolutionary biology[1]. For example, the tendency to produce dizygotic twins, where the ovulation of two ova gives rise to the birth of siblings, is heritable[2] and varies within and among populations, its rate rising and then falling with increasing maternal age[3]. Here we show that a conditional strategy of switching from single to double ovulation with increasing age explains why the twinning rate rises and falls as females age, and how switching from single to double ovulation with increasing age maximizes individual reproductive success, thus explaining why dizygotic twinning persists in humans.

The evolutionary forces that account for twinning and the age-dependent change in its rate are poorly understood. While the birthing of twins has fitness costs for both mothers and offspring, mothers that produce twins often have greater fitness than mothers who have never produced twins[4–8]. We focus on how selection operates on the reproductive trait that makes dizygotic twins possible, double ovulation. The ova insurance hypothesis[9] posits that twinning is a maladaptive consequence of the ovulation of multiple ova, which serves as an adaptive counter to poor prenatal offspring survival. Because prenatal mortality is known to dramatically increase with maternal age[10–12], we hypothesized that the age-dependent pattern of dizygotic twinning observed in humans might be due to an adaptive ovulatory strategy of switching from single ovulation to double ovulation with increasing age. This hypothesis makes two predictions. First, an increasing rate of double ovulation coupled with a decreasing live birth rate should explain the observed pattern of age-dependent twinning in humans. Second, the expected lifetime reproductive success of women using this conditional strategy should exceed that of women who always single or always double ovulate. We verified the first prediction by extending a simple mathematical model that derives the twinning rate given the probabilities of double ovulation and live birth. We asked whether a declining probability of live birth coupled with an increasing probability of double ovulation with increasing maternal age could explain the pattern of age-dependent twinning observed in human populations. To verify the second prediction, we used postnatal and maternal survival rates for twins and singletons from a natural-fertility population and age-dependent prenatal survival rates at different stages of pregnancy to compare the expected lifetime reproductive success of women who always single or double ovulate with that of women who switch from single to double ovulating with increasing age.

With respect to the first prediction, only two parameters, the rate of double ovulation and the live birth rate, are needed to predict the twinning rate. For a woman at age t, the twinning rate (T_t) at birth is given by the equation $T_t = F_t\, p_t/(1 + F_t(1 - p_t))$ (1), where F_t is the double ovulation rate and p_t is the probability of survival from fertilization to birth[13] (see Supplementary Methods for the derivation). If the observed change in T_t is due to a conditional ovulatory strategy that compensates for declining fertility, then an F_t that increases with age and a p_t that decreases with age should produce T_t that closely match those observed in human populations. We used a cumulative normal function for F_t so that the probability of double ovulation increases with age depending on the mean and standard deviation of a normal distribution in the age of switching from single to double ovulation. We chose this function because it forms the basis of the environmental threshold model, the most commonly used quantitative genetic model for conditional strategies[14] (Extended Data Fig. 1 and Supplementary Discussion). On the basis of studies of a natural-fertility population[10], we used a declining exponential function for p_t, where p_t declines at a constant rate with female age from a value of 0.55 at age 18. We then derived T_t (equation (1)) using combinations of values for the mean and standard deviation of the cumulative normal distribution for the age of switching from single to double ovulation (F_t) and the annual rate of decline in p_t. We used Microsoft Excel's iterative model fitting function Solver to compare the expected T_t with the rates observed in nine datasets from human populations unbiased by fertility treatments[3,15–19]. Solver identified

---

[1]Department of Biology, DePauw University, Greencastle, IN, USA. [2]School of Biological Sciences, The University of Western Australia, Crawley, Western Australia, Australia. [3]Department of Mathematics, DePauw University, Greencastle, IN, USA. [4]London School of Hygiene and Tropical Medicine, London, UK. [5]Centre for Evolutionary Biology, School of Biological Sciences, The University of Western Australia, Crawley, Western Australia, Australia.
✉e-mail: wnh@depauw.edu; joseph.tomkins@uwa.edu.au

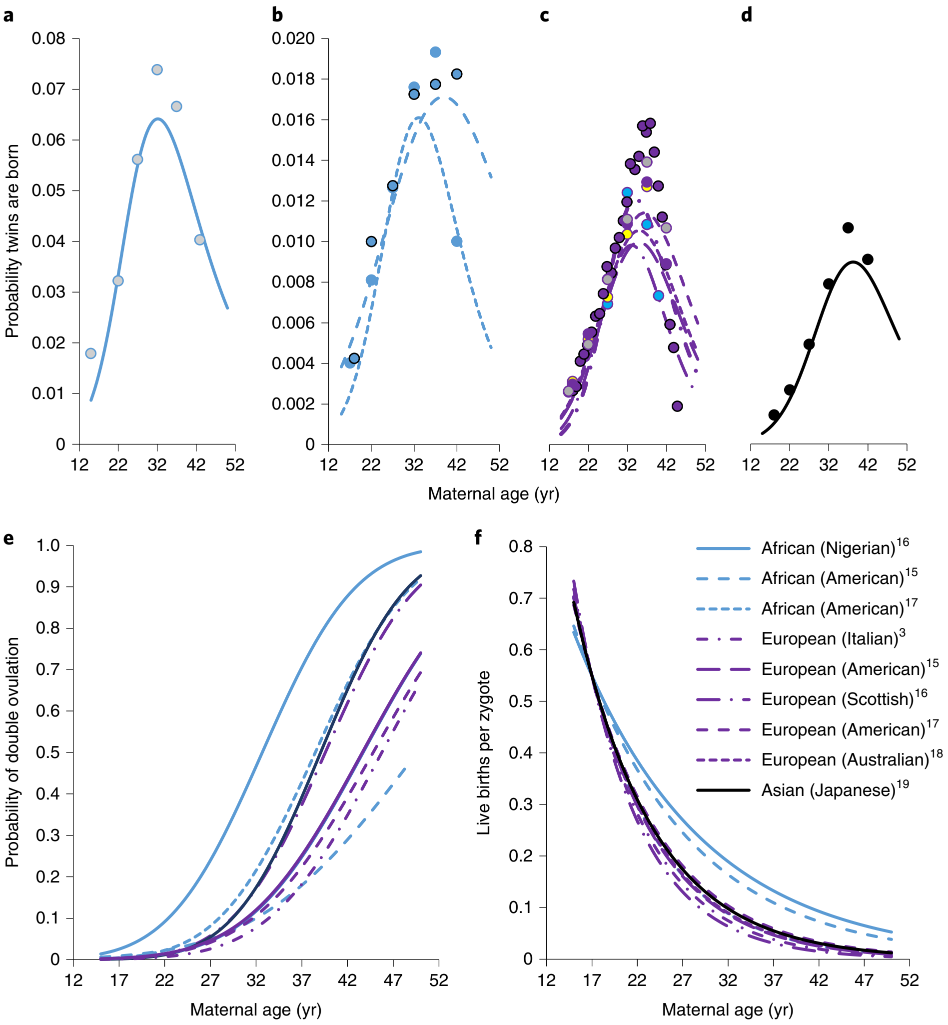


Fig. 1 | Declining prenatal survival and increasing double ovulation rates explain age-dependent twinning rates. a–d, Observed (points) and expected twinning rates (lines) as functions of maternal age in nine populations. **e**,**f**, Increasing probability of double ovulation (**e**) and decreasing rate of live births per zygote (**f**), both as functions of maternal age (equation (1)). The curves in **e** and **f** were chosen for their ability to minimize the squared deviations between the observed and expected twinning rates in **a**–**d** (Table 1).

the combinations of values for the three parameters (the mean and standard deviation of the cumulative normal distribution for the age of switching from single to double ovulation, and the annual rate of decline in p_t) that maximized R^2 (proportion of variation in twinning rate explained by maternal age), allowing us to determine what values of these parameters could best explain the pattern of age-dependent twinning observed in each population.

Our results show that 90% or more of the variation in twinning rates in these populations is explained by a shift from single ovulation to double ovulation with increasing age (Fig. 1 and Table 1), supporting the hypothesis that age-dependent twinning results from a conditional ovulatory strategy. An increase in F_t from near zero at menarche to over 50% prior to menopause (Fig. 1e), coupled with a constant decline in p_t to less than 10% as women approach menopause (Fig. 1f), readily explains the pattern of age-dependent twinning (Fig. 1a–d). Because the decline in prenatal survival ensures that double ovulations increasingly result in only singleton births or reproductive failure, the increased rate of double ovulation does not translate into ever-increasing rates of twin births. Hence, the patterns of age-dependent twinning in human populations are consistent with a conditional strategy that combines an age-dependent switch to double ovulation with the well-established age-dependent decline in prenatal viability[10–12].

Our results suggest that differences in age-dependent twinning rates among populations can be explained by differences in the mean and standard deviation of the age of switching from single to double ovulation and the decline in the probability of live birth per conception with age. For example, the age-dependent twinning rates in a Nigerian population (Fig. 1a), which has the steepest increase and subsequent decline in twinning rate with age, require an average age of switching to double ovulation of 33 years and an annual decline in the probability of live birth of 7% per year, compared with a switching age of 46 years for a Japanese population, which has the lowest twinning rates (Fig. 1e and Table 1), and an annual decline in the probability of live birth of 11% (Fig. 1e and Table 1).

Results and discussion

We used two complementary approaches, simulations and probabilistic modelling (Supplementary Methods, Supplementary Figs. 1–3 and Supplementary Tables 1 and 2), to evaluate the prediction that women playing a conditional strategy of switching from single to double ovulation will have greater lifetime reproductive success than women who always single or always double ovulate. Both approaches allowed us to estimate the lifetime reproductive success of women switching from single to double ovulation at different ages. By setting the age of switching to less than what we functionally

Table 1 | Estimates of the parameters that explain age-dependent twinning rates in nine human populations

Population	*n*	drb	dra	spm	spSD	R^2	Reference
African (Nigerian)	18,400	0.93	0.55	32.67	8.02	0.93	16
African (American)	22,100	0.92	0.55	49.62	13.76	0.96	15
African (American)	3,679	0.89	0.55	38.47	8.22	0.91	17
European (American)	21,809	0.89	0.55	44.80	10.27	0.97	17
European (Scottish)	49,000	0.87	0.55	39.56	7.98	0.90	16
European (American)	5,672,228	0.88	0.55	43.70	9.84	0.91	15
European (Italian)	1,817,736	0.88	0.55	39.05	7.53	0.99	3
European (Australian)	45,956	0.89	0.55	43.61	9.89	0.96	18
Asian (Japanese)	72,180	0.89	0.55	45.74	9.64	0.99	19
Mean ±	858,120.89	0.89	0.55	41.91	9.46	0.95	
s.e.m.	633,136.269	0.007		1.664	0.636	0.012	

drb is the annual decline in prenatal survival rate per zygote with increasing maternal age; dra is the live birth rate per zygote at maternal age 18 yr; spm and spSD are the mean and standard deviation, respectively, of the cumulative normal function for the double ovulation rate with increasing maternal age; R^2 is the fraction of the variation in age-dependent twinning explained by these parameters (see Fig. 1).

defined as menarche (age 18, on the basis of the average age of first reproductive attempt in a natural-fertility population[5]), we could estimate the fitness of a strategy of always double ovulating. When the switching age was set to greater than what we functionally defined as menopause (age 40, on the basis of the mean age of last birth in a natural-fertility population[5]), we could estimate the fitness of always single ovulating. Setting the switching age to ages between 18 and 40 allowed us to estimate the fitness of conditional ovulatory strategies that switched from single to double ovulation at different ages. We compared the success of the different strategies using the average number of offspring surviving to age 15. The modelling allowed us to calculate the expected number of zygotes per ovulatory cycle surviving to age 15, and the time between successive cycles for different-aged single- and double-ovulating women (Supplementary Methods). From these data we estimated age-specific reproductive rates for women playing different ovulatory strategies. We treated the survival of individual conceptions resulting from double ovulation as independent events, assumed that each ovum was fertilized, and assumed that women resumed ovulation only after complete brood loss or weaning (Supplementary Methods).

These approaches required data on offspring survival rates between conception and birth, maternal survival rates at the birthing of twins and singletons, singleton and twin survival rates between birth and weaning and to reproductive age (assumed to be 15 years), and the time intervals between successive ovulatory cycles. Such data are unavailable from any single population, so we used multiple sources. Natural-fertility populations in Bangladesh[10] and Gambia[5] provided data for live birth rates per zygote at age 18 (0.55), and maternal childbirth survival rates and postnatal offspring survival rates for twin and singleton births, respectively (Supplementary Table 1). We assumed a decline in live birth rate of 11% which was the average decline rate estimated from our analyses of observed twinning rates (Table 1). The data for determining prenatal survival rates at different times between conception and birth for different-aged women were based on an analysis of the fates of over 1.2 million pregnancies in Denmark[20] (Supplementary Methods, Supplementary Table 3 and Extended Data Fig. 2). The estimates of the time intervals between successive ovulatory cycles were taken from the literature[21].

Both simulations and modelling indicated that fitness was maximized when women switched from single to double ovulation at approximately age 25 (Fig. 2a and Fig. 3a). This result supports the hypothesis that the age-dependent conditional ovulatory strategy we identified as best explaining the observed age-dependent twinning rates is adaptive[1]. The modelling results show why fitness is maximized by switching from single to double ovulation with increasing age. While at all ages the expected per capita number of offspring surviving to 15 per ovulatory cycle was greater for a strategy of double ovulating than for single ovulating (Fig. 3b), this was especially so in older women (91% greater at age 40 versus 26% greater at age 18). However, the lower probability of live birth per ovulatory cycle shortens the time between successive ovulations in single ovulators, while in double ovulators the increased probability of at least one live birth and subsequent lactation lengthens the time between ovulations (Fig. 3c). So, although the per capita offspring per cycle was greater for double ovulations, this was more than compensated by the increased number of ovulations of young single ovulators. Compared with older double ovulators, young double ovulators were also more likely to birth twins (Extended Data Fig. 3), whose poorer postnatal survival depressed fitness and whose birthing incurred greater maternal risks. Hence, double ovulating when young has fitness costs in the investment of time in low-fitness, high-risk pregnancies that produce twins, while double ovulating when older has fitness benefits because twins are rarely produced. These differences in the age-dependent reproductive effects of double and single ovulating results in reproductive rates in young single ovulators that exceed those of young double ovulators, but in older women the reverse is true (Fig. 3d). This age-dependent trade-off in reproductive rates fulfils an important requirement for the maintenance of a conditional strategy, and in the case of conditional double ovulation, produces stabilizing selection on an optimal switching age between menarche and menopause[22].

Our modelling indicates that the optimal switching age is sensitive to differences in the prenatal survival probabilities of embryos resulting from single versus double ovulation. For example, our results are based on the assumption that the prenatal probabilities of survival of embryos resulting from single and double ovulation are the same and are independent (Supplementary Methods). While this assumption is more likely to be valid early in pregnancy, later in development the survival of individual twin fetuses is likely to be less than that of singletons[23,24], and when one of the twin fetuses is lost, the probability of the second fetus being lost increases[25], as do other adverse perinatal outcomes[26]. As a result, the true optimum switching age is probably later than our analyses in Figs. 2 and 3 indicate, and more in line with the switching ages observed in human populations (Fig. 1).

Finally, we asked whether twinning is a maladaptive by-product of an otherwise adaptive conditional ovulatory strategy[9]. This hypothesis predicts that if women who double ovulate throughout their lives could avoid birthing twins (for example, via the reabsorption of one fetus), then their lifetime reproductive success should exceed that of women who switch from single to double ovulation

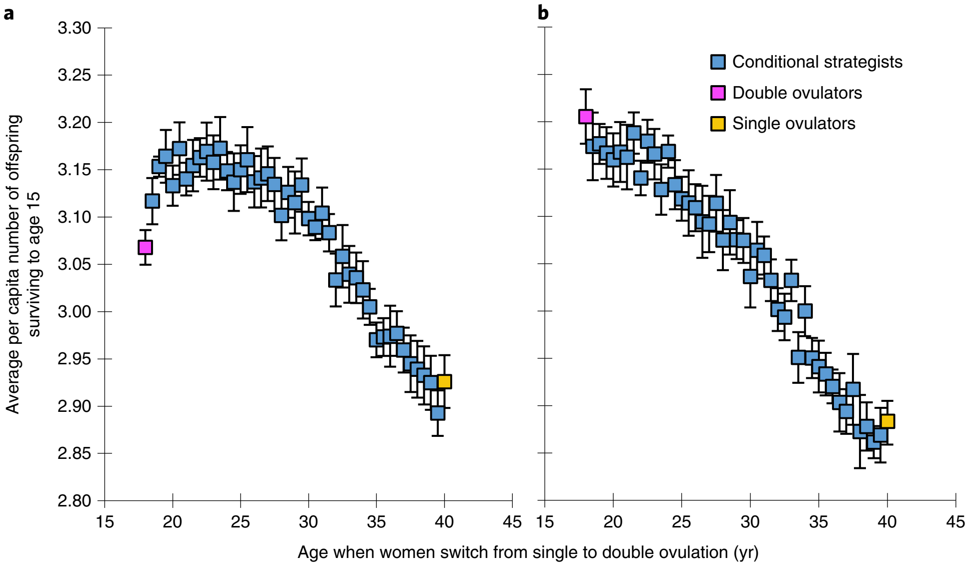


Fig. 2 | Average per capita numbers of offspring surviving to 15 years (95% confidence intervals, $n = 10$) from simulations of the reproductive lives of 1,000 women. a,**b**, When the age of switch is 18, women always double ovulate throughout their reproductive lives; when it is 40 (the age of menopause), they always single ovulate throughout their reproductive lives. When the switch age is between 18 and 40, women are playing different conditional strategies defined by the switch age. In **a**, women that double ovulated could give birth to twins. In **b**, women that double ovulated carried only one offspring to term.

with increasing age and occasionally produce twins. We repeated the simulations, but now women who double ovulated were allowed to give birth only to singletons even if they were expected to carry twins to term. Hence, they received the fertility benefits of double ovulation without incurring the costs of twin births. In these simulations, lifetime reproductive success was maximized at switching ages less than or equal to the age of menarche (Fig. 2b). Since these women double ovulated during each ovulatory cycle, this result supports the by-product hypothesis[9].

Our results potentially shed light on why mothers who have produced twins often have greater fitness than mothers who never do so[4,5,7,8]. Follicle development and ovulation are controlled by the hypothalamic–pituitary axis, which is able to integrate an adaptive response to cues associated with maternal condition and age[27]. Mothers who produce twins often do so at higher parities (independent of maternal age)[3] and often possess physical characteristics, such as height and body mass indices, that potentially increase the probability of double ovulation, lifetime reproductive success and prenatal survival[5,28]. In this study, we have only attempted to explain the evolution of age-dependent double ovulation. However, if double ovulation and prenatal survival are conditional on these other factors, in addition to maternal age, then it would not be surprising if women who have produced twins often have greater fitness than those who have not.

Our findings indicate that the ultimate cause (sensu Mayr[29]) of the pattern of age-dependent twinning in human populations is natural selection favouring double ovulation with increasing age in response to declining fertility. These results suggest that in human populations in which increasing numbers of women delay first reproduction[30], a substantial fraction of singleton births will result from double ovulation with the subsequent prenatal loss of one of the siblings. For example, if the probability of double ovulation and probability of live birth per ovum for women at age 27 are 0.05 and 0.2 (Fig. 1e,f), respectively, approximately 8% of all singletons will have been produced following double ovulation. In contrast, at age 37, when the probability of double ovulation and probability of live birth per ovum are 0.4 and 0.05 (Fig. 1e,f), respectively, the fraction of singletons produced by double ovulation rises to approximately 56%. Alongside this, when reproduction is delayed, we also expect a population-level increase in the incidence of twin births, a phenomenon already seen in developed countries[31].

Methods

Estimating expected age-dependent twinning rates from the decline in live birth rate and increase in double ovulation rate. Using the formula that calculates twinning rate as a function of the rates of live births per zygote and double ovulation, we used the Solver add-in in Microsoft Excel to determine the rates of age-dependent decline in live births per zygote and age-dependent increase in double ovulation that provided the best fit to the observed age-dependent twinning rates (that is, maximized the R^2 with the observed twinning rates) in large samples from populations with African, European and Asian ancestries (Table 1). The models were fitted subject to several constraints. We fixed the probability of live birth at age 18 (dra) at 0.55 on the basis of the best estimate of which we are aware, coming from a natural-fertility population in Bangladesh[10]. The probability of live births per zygote declines with maternal age[10,12], and we assumed an exponential decline, where the annual decline was constrained to be less than 0.99 and greater than 0.55 (no model approached either boundary; see Supplementary Information). On the basis of quantitative genetic models for conditional strategies[22,32] (Supplementary Discussion), we assumed that the increase in probability of double ovulation per ovulatory cycle with maternal age was best described by an increasing cumulative normal function, with the mean (spm) and standard deviation (spSD) constrained in our Solver searches to be greater than two years.

Simulations. The simulation model, which was written in the language R[33], estimates lifetime reproduction in a cohort of (nominally 1,000) women by simulating ovulatory cycles from the first reproductive attempt until reproduction stops owing to death or menopause (Supplementary Table 1 and Supplementary Figs. 1–3). Dependent on inputs governing the probability of prenatal loss, these cycles can result in early loss, abortion, late fetal loss (miscarriage) or live birth (Supplementary Table 1). The failure of a pregnancy to proceed to term delays the commencement of cycling after the event by a variable amount depending on when the pregnancy ends (Supplementary Table 1). The simulation allows women to either single or double ovulate on the basis of their age at ovulation relative to a double-ovulation switch point that determines the age at which they switch from single to double ovulation (spm in Supplementary Table 1). We were able to simulate different conditional ovulatory strategies by setting the ovulation switch point to values between the age of menarche (age 18) and the age of menopause (age 40). Women could also be constrained to double or single ovulate throughout their reproductive lives by setting the switch to ages less than 18 or greater than 40, respectively. Depending on the number of ova released and the probabilities of surviving the prenatal period (considered to be independent where there are two zygotes), none, one or twin offspring are born. Subject to inputs governing the probabilities of still-birth, background adult death rate, and maternal death in childbirth, successful live births occur (Supplementary Table 1). Contingent on inputs controlling postnatal mortality, children survive for periods

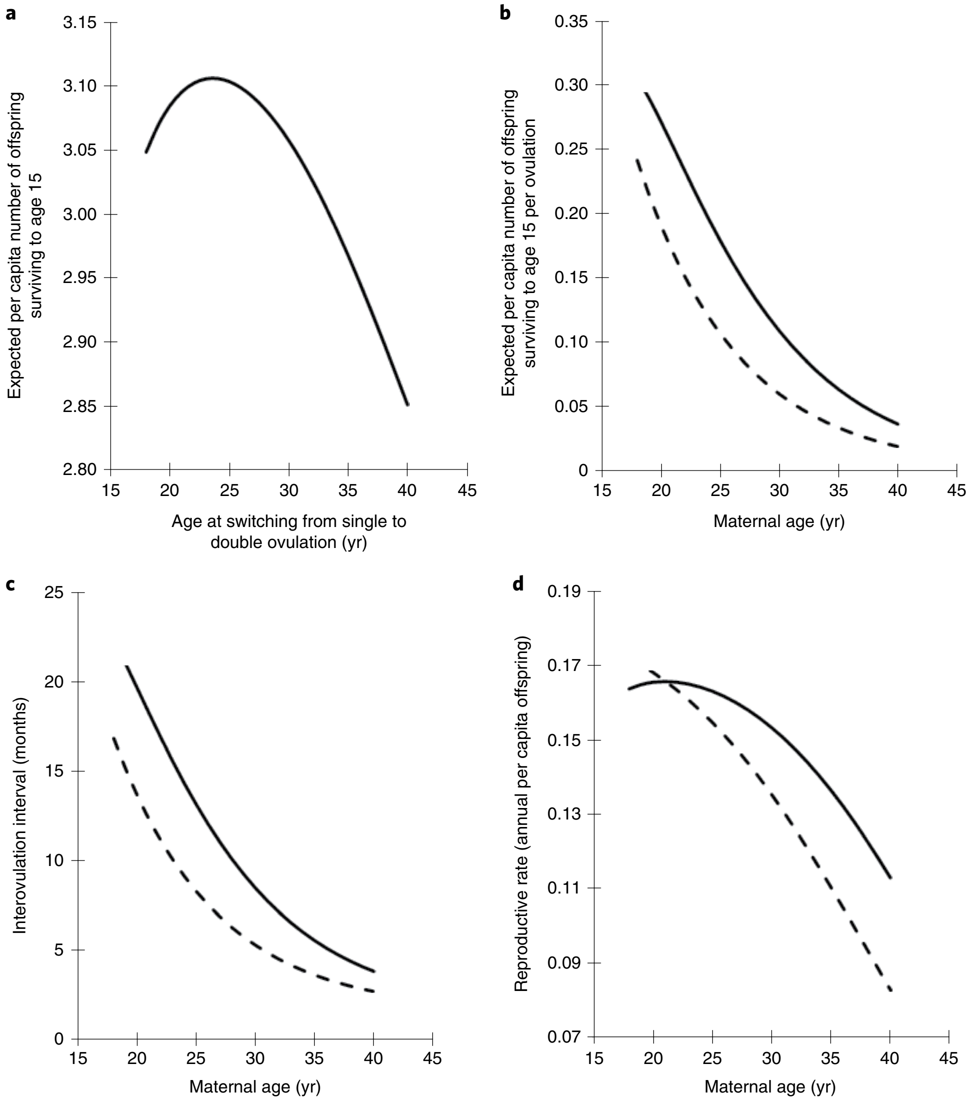


Fig. 3 | Results of mathematical modelling of the reproductive characteristics of different ovulatory strategies. a, Expected lifetime reproductive success for women switching from single to double ovulation at different ages. **b**, Per capita number of offspring surviving to age 15 per ovulation for double (solid line) and single ovulators (dashed line) at different ages. **c**, Time between successive ovulations for double (solid line) and single ovulators (dashed line) of different ages. **d**, Expected annual reproductive rates for double (solid line) and single ovulators (dashed line) of different ages.

of 1 month, 1 year, 2 years (weaning) or 15 years (Supplementary Table 1). The duration of offspring survival influences the duration of time that the female stops cycling (Supplementary Table 1). Survival to 15 years is considered a successful reproductive event for the mother, and the per capita number of offspring surviving to 15 years was our measure of maternal fitness. Women are continually subject to the probability of death, including when pregnant and weaning (Supplementary Table 1). When women died during childbirth, the children they were birthing also died. The simulation allows for up to 20 parities; however, a woman's reproductive longevity is curtailed by declining ova quality (Supplementary Table 3 and Extended Data Fig. 2d). Women older than the user-defined age at menopause at the time that they are due to begin cycling again after a pregnancy attempt or child bearing (Supplementary Table 1) do not continue cycling, but women that are not pregnant and younger than this age can cycle beyond that age.

The simulation assumes that women are not sperm limited and make no socially driven decisions to delay or reduce the number of children they attempt to have, so successful pregnancy was a function only of embryo survival to live birth. The simulation makes no provision for siblings, grandparents or males assisting in the care of offspring. The estimates of the demographic parameters used in the simulation come from multiple sources. The probability of live birth at age 18 comes from a natural-fertility population in Bangladesh[10]. The decline in the probability of live birth with increasing age was based on the decline in live birth probability needed to explain the observed twinning rate averaged over all the populations summarized in Table 1. The probabilities associated with different prenatal fates of zygotes (early losses, spontaneous abortions and late losses) were estimated in over 1.2 million pregnancies in Danish women of different ages[20] on the basis of the ratios of spontaneous abortions and stillbirths (late-pregnancy losses) to live births, given the assumption, on the basis of the average of our estimates in Table 1, that the live birth rate declines with maternal age at 11% per year from 0.55 at age 18 (Supplementary Methods, Supplementary Table 3 and Extended Data Fig. 2).

Postnatal survival rates were based on those taken from a Gambian natural-fertility population[5]. We assumed prenatal survival probabilities to be the same for twins and singletons and independent for zygotes produced by double ovulation (that is, if the probability of survival per zygote is p, then in double ovulations, the probability of both zygotes surviving is p^2, one surviving is $2p(1-p)$ and neither surviving is $(1-p)^2$). Other than parameters such as the age of switching from single to double ovulation and whether double ovulation could result in twin births, which defined the strategy, all ovulatory strategies had the same set of parameters of the simulated biological background and so represented a comparison only of the differences that arise from the changes in strategy.

In replicate simulations (see Supplementary Figs. 1–3 and Supplementary Table 2 for further details), we estimated fitness by tallying the number of offspring surviving to age 15 produced by cohorts of 1,000 women playing different ovulatory strategies, each defined by the age at which women switched from single to double ovulation. Simulations designated as 'Twins not produced' were identical to those previously described, except that whenever two offspring survived to birth, twin births were replaced with a singleton birth. In each simulation, we followed women from their first ovulation, through each ovulatory cycle to either death or menopause and tabulated the number of offspring surviving to age 15.

Probabilistic model comparing the fitness of single versus double ovulation strategies. We used the same inputs and assumptions as in the simulations. We have defined the fitness of a woman at age x as $\sum_{k=x}^{M} C(k)$ where $C(k)$ is the number of children conceived when the woman is age k that survive to age 15, and M is the age of menopause. Our model estimates the expected value of this expression as

$$F(x) = \sum_{k=x}^{M} N(k)S(k|x)$$

where $N(k)$ is the average number of offspring conceived by a woman of age k that survive to age 15, and $S(k|x)$ is the probability that a woman alive at age x has not died before age k. We determine $N(k)$ by

$$N(k) = \frac{12V(k)}{T(k)}$$

where $V(k)$ is the expected number of offspring per ovulation that survive to age 15 when a woman is age k, and $T(k)$ is the expected time between ovulations (in months) when a woman is age k. $S(k|x)$ is determined by the recurrence relation

$$S(x|x) = 1$$

$$S(x+1|x) = R(x) \cdot \mathrm{asr}$$

$$S(x+2|x) = S(x+1|x) \cdot R(x+1) \cdot \mathrm{asr}$$

$$\vdots$$

$$S(k|x) = S(k-1|x) \cdot R(k-1) \cdot \mathrm{asr}$$

where $R(t)$ is the probability a woman age t does not die in childbirth and asr is the annual survival rate of the adult population. See Supplementary Methods and Supplementary Table 2 for details regarding the constructions of the functions V, T, and R for single and double ovulators.

Reporting Summary. Further information on research design is available in the Nature Research Reporting Summary linked to this article.

Data availability

The data have been uploaded to Dyad and are available at https://doi.org/10.5061/dryad.h70rxwdfw.

Code availability

The computer code has been uploaded to Dyad and is available at https://doi.org/10.5061/dryad.h70rxwdfw. This code is supplied by the authors with the request that future users of the code are aware that it represents an ongoing research programme and that they contact the authors in a collaborative spirit.

Received: 3 December 2019; Accepted: 6 March 2020;
Published online: 11 May 2020

References

1. Maynard Smith, J. *Evolution and the Theory of Games* (Cambridge Univ. Press, 1982).
2. Mbarek, H. et al. Identification of common genetic variants influencing spontaneous dizygotic twinning and female fertility. *Am. J. Hum. Genet.* **98**, 898–908 (2016).
3. Bulmer, M. G. *The Biology of Twinning in Man* (Clarendon, 1970).
4. Lummaa, V., Haukioja, E., Lemmetyinen, R. & Pikkola, M. Natural selection on human twinning. *Nature* **394**, 533–534 (1998).
5. Sear, R., Shanley, D., McGregor, I. A. & Mace, R. The fitness of twin mothers: evidence from rural Gambia. *J. Evol. Biol.* **14**, 433–443 (2001).
6. Forbes, S. *A Natural History of Families* (Princeton Univ. Press, 2005).
7. Robson, S. L. & Smith, K. R. Twinning in humans: maternal heterogeneity in reproduction and survival. *Proc. R. Soc. B* **278**, 3755–3761 (2011).
8. Rickard, I. J., Courtiol, A. & Lummaa, V. Why is lifetime fertility higher in twinning women? *Proc. R. Soc. B* **279**, 2510–2511 (2012).
9. Anderson, D. J. On the evolution of human brood size. *Evolution* **44**, 438–440 (1990).
10. O'Connor, K. A., Holman, D. J. & Wood, J. W. Declining fecundity and ovarian ageing in natural fertility populations. *Maturitas* **30**, 127–136 (1998).
11. Centers for Disease Control and Prevention, American Society for Reproductive Medicine & Society for Assisted Reproductive Technology *2011 Assisted Reproductive Technology National Summary Report* (US Dept of Health and Human Services, 2013).
12. McCoy, R. C. et al. Common variants spanning PLK4 are associated with mitotic-origin aneuploidy in human embryos. *Science* **348**, 235–238 (2015).
13. Atkinson, D. E. Frequency of dizygotic twinning. *Nature* **322**, 780–780 (1985).
14. Buzatto, B. A., Buoro, M., Hazel, W. N. & Tomkins, J. L. Investigating the genetic architecture of conditional strategies using the environmental threshold model. *Proc. R. Soc. B* **282**, 20152075 (2015).
15. Shipley, P. W., Wray, J. A., Hechter, H. H., Arellano, M. G. & Borhani, N. O. Frequency of twinning in California: its relationship to maternal age, parity and race. *Am. J. Epidemiol.* **85**, 147–156 (1967).
16. Nylander, P. P. S. Ethnic differences in twinning rates in Nigeria. *J. Biosoc. Sci.* **3**, 151–158 (1971).
17. Enders, T. & Stern, C. The frequency of twins, relative to age of mothers in American populations. *Genetics* **33**, 263–272 (1948).
18. Pollard, G. N. Multiple births in Australia, 1944–63. *J. Biosoc. Sci.* **1**, 389–404 (1969).
19. Imaizumi, Y. & Hayakawa, K. Infant mortality among singletons and twins in Japan during 1999–2008 on the basis of risk factors. *Twin Res. Hum. Genet.* **16**, 639–644 (2013).
20. Nybo Andersen, A. M., Wohlfahrt, J., Christens, P., Olsen, J. & Melbye, M. Maternal age and fetal loss: population based register linkage study. *Brit. Med. J.* **320**, 1708–1712 (2000).
21. Donnet, M. L., Howie, P. W., Marnie, M., Cooper, W. & Lewis, M. Return of ovarian function following spontaneous abortion. *Clin. Endocrinol.* **33**, 13–20 (1990).
22. Hazel, W., Smock, R. & Johnson, M. A polygenic model for the evolution and maintenance of conditional strategies. *Proc. R. Soc. Lond. B* **242**, 181–187 (1990).
23. Hall, J. G. Twinning. *Lancet* **362**, 735–743 (2003).
24. Fellman, J. & Eriksson, A. W. Stillbirths in multiple births: test of independence. *Twin Res. Hum. Genet.* **9**, 677–684 (2006).
25. Johnson, C. D. & Zhang, J. Survival of other fetuses after a fetal death in twin or triplet pregnancies. *Obstet. Gynecol.* **99**, 698–703 (2002).
26. Evron, E., Sheiner, E., Friger, M., Sergienko, R. & Harlev, A. Vanishing twin syndrome: is it associated with adverse perinatal outcome? *Fertil. Steril.* **103**, 1209–1214 (2015).
27. Scaramuzzi, R. J. et al. Regulation of folliculogenesis and the determination of ovulation rate in ruminants. *Reprod. Fertil. Dev.* **23**, 444–467 (2011).
28. Hoekstra, C. et al. Dizygotic twinning. *Hum. Reprod. Update* **14**, 37–47 (2008).
29. Mayr, E. Cause and effect in biology. *Science* **134**, 1501–1506 (1961).
30. Jean-Paul, S. & Tomas, F. First birth trends in developed countries: persisting parenthood postponement. *Demogr. Res.* **15**, 147–180 (2006).
31. Pison, G., Monden, C. & Smits, J. Twinning rates in developed countries: trends and explanations. *Popul. Dev. Rev.* **41**, 629–649 (2015).
32. Tomkins, J. L. & Hazel, W. The status of the conditional evolutionarily stable strategy. *Trends Ecol. Evol.* **22**, 522–528 (2007).
33. *R: A language and environment for statistical computing* (R Foundation for Statistical Computing, 2018).

Acknowledgements

C. Lively, D. Dudle, L. Simmons, C. Smock and D. Hruschka provided comments on the manuscript drafts. We thank N. LeBas for detailed discussions of these ideas. J.L.T. was supported by a Future Fellowship (grant no. FT110100500) from the Australian Research Council. R.C.S. and W.N.H. were funded by DePauw University Faculty Development Grants.

Author contributions

J.L.T. proposed the study. W.N.H. and J.L.T. began developing the approaches. R.S. provided the demographic data and background on the biology of twinning. R.C.S. and W.N.H. finalized the mathematical model. J.L.T. and R.B. finalized the simulation model. W.N.H. wrote the first draft of the manuscript, and all authors contributed to the completed manuscript.

Competing interests

The authors declare no competing interests.

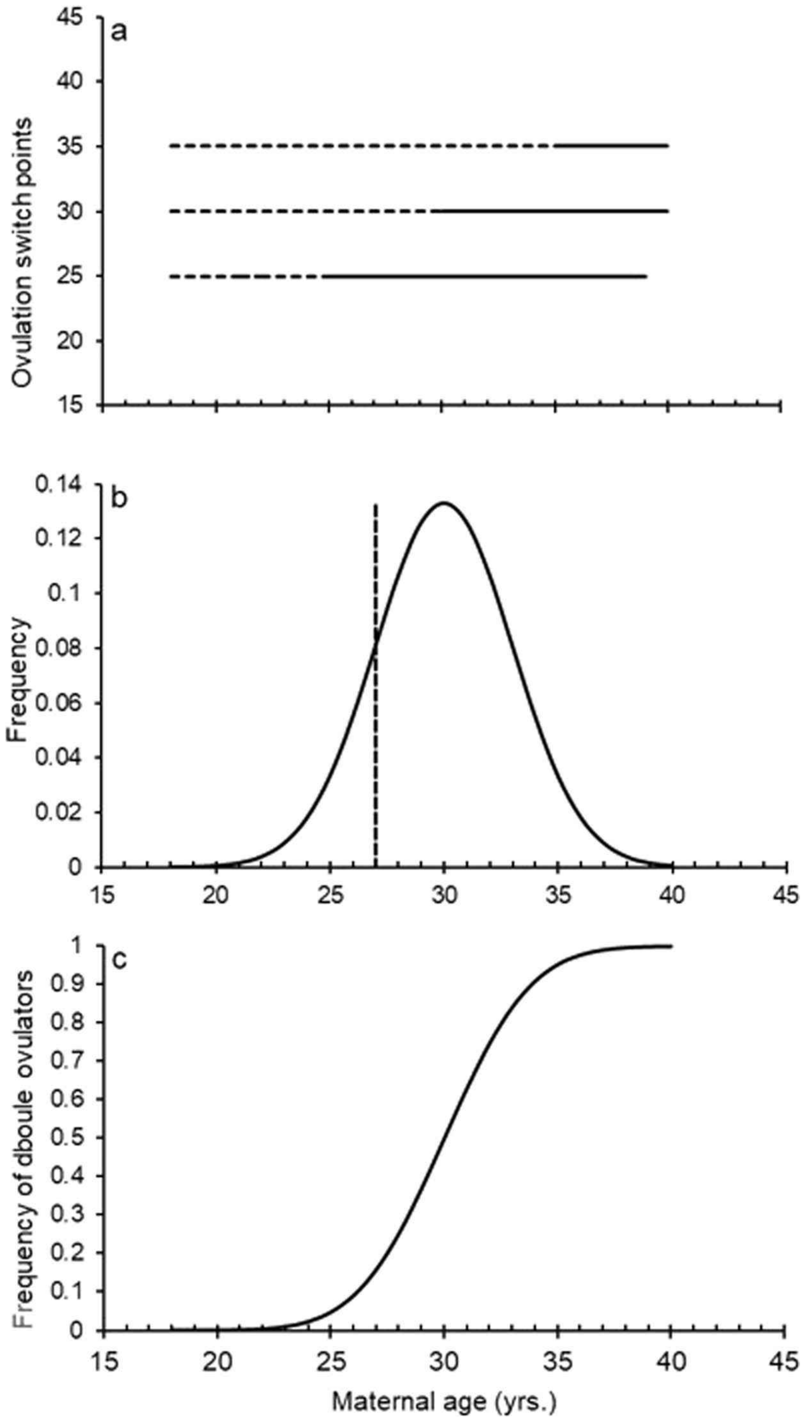
Additional information

Extended data is available for this paper at https://doi.org/10.1038/s41559-020-1173-y.

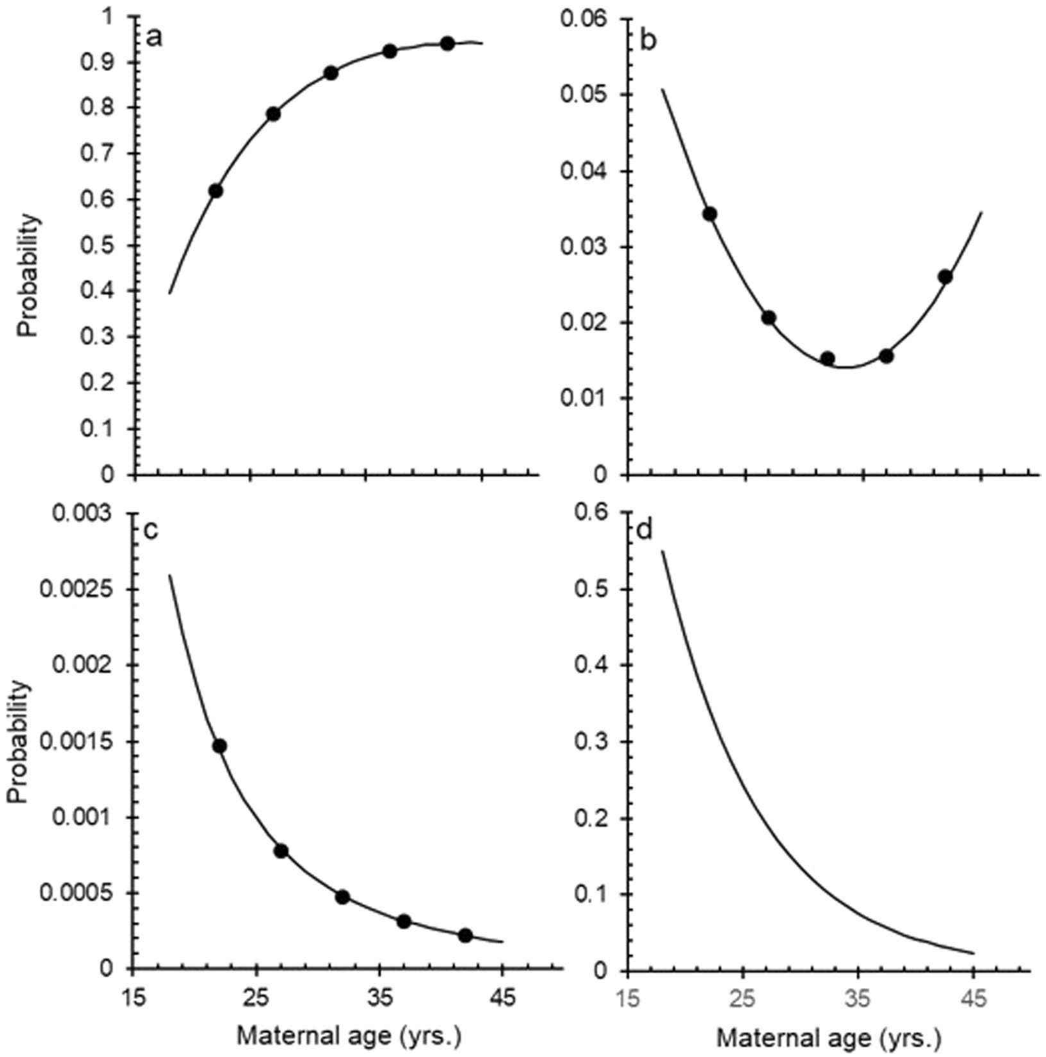
Supplementary information is available for this paper at https://doi.org/10.1038/s41559-020-1173-y.

Correspondence and requests for materials should be addressed to W.N.H. or J.L.T.

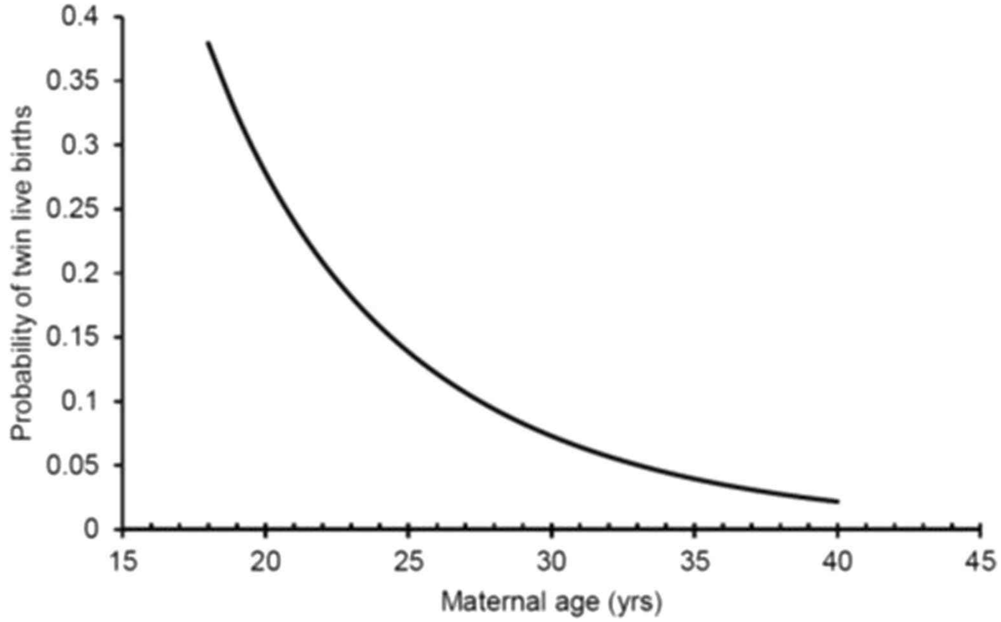
Peer review information Peer reviewer reports are available.



Extended Data Fig. 1 | Double ovulation as a threshold trait. a, Three conditional (age-dependent) ovulatory strategies that differ in age of switching from single (dashed line) to double ovulation (solid line). **b**, Threshold trait depiction of a cohort of population with normally distributed variation in age at switching (mean age at switching from single to double ovulation is 30 yrs., SD of 3 yrs.). At age 27, the threshold (vertical line positioned at age 27) divides the population into individuals that double ovulate (those with switching ages less than 27) and single ovulate (those with switching ages greater than 27). **c**, As age increases, the fraction of double ovulators increases as a cumulative normal function as the threshold in **b** shifts to the right, increasing the fraction of the distribution of switching ages that is less than the threshold.



Extended Data Fig. 2 | Age-dependent probabilities of live birth, and prenatal death from early losses, spontaneous abortion, and late losses. a-c, points from Supplementary Table 3; lines are best fitting curves from least squared regression. **a**, Early loss of pregnancy (variable r in Supplementary Table 1); **b**. Spontaneous abortion (variable s in Supplementary Table 1); **c**, Late loss of pregnancy (variable t in Supplementary Table 1); **d**, Live birth (line from average of results in Fig. 1f; variable u in Supplementary Table 1).



Extended Data Fig. 3 | Age-dependent probability of twin live births in double ovulators. Probability of twin live births was calculated using equation 1, assuming declining probability of live birth with increasing maternal age as depicted in Extended Data Fig. 2d.

nature research

Corresponding author(s): Hazel and Tomkins

Last updated by author(s): 03/03/2020

Reporting Summary

Nature Research wishes to improve the reproducibility of the work that we publish. This form provides structure for consistency and transparency in reporting. For further information on Nature Research policies, see Authors & Referees and the Editorial Policy Checklist.

Statistics

For all statistical analyses, confirm that the following items are present in the figure legend, table legend, main text, or Methods section.

n/a	Confirmed	
☐	☒	The exact sample size (*n*) for each experimental group/condition, given as a discrete number and unit of measurement
☒	☐	A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
☒	☐	The statistical test(s) used AND whether they are one- or two-sided *Only common tests should be described solely by name; describe more complex techniques in the Methods section.*
☒	☐	A description of all covariates tested
☒	☐	A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons
☐	☒	A full description of the statistical parameters including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals)
☐	☒	For null hypothesis testing, the test statistic (e.g. *F*, *t*, *r*) with confidence intervals, effect sizes, degrees of freedom and *P* value noted *Give P values as exact values whenever suitable.*
☒	☐	For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
☒	☐	For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes
☒	☐	Estimates of effect sizes (e.g. Cohen's *d*, Pearson's *r*), indicating how they were calculated

Our web collection on statistics for biologists contains articles on many of the points above.

Software and code

Policy information about availability of computer code

Data collection	We used R 3.6.1 and our own package called TwinSim, Microsoft Excel and the Microsoft excel add-in Solver for the analysis. This is detailed in the ms. The distinction between analysis and collection is blurred.
Data analysis	We used R 3.6.1, Microsoft Excel and the Microsoft excel add-in Solver for the analysis. This is detailed in the ms.

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors/reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Research guidelines for submitting code & software for further information.

Data

Policy information about availability of data

All manuscripts must include a data availability statement. This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A list of figures that have associated raw data
- A description of any restrictions on data availability

Fig 1 & Fig 2, and Table 1 have associated data. The mathematical model is available in the manuscript, while the twin simulation package in R is available upon request from the authors, with the caveat that it cannot be used for further publications or distribution without the authors permission. This is because we are currently using the simulation to prepare further manuscripts.

Field-specific reporting

Please select the one below that is the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

☐ Life sciences ☐ Behavioural & social sciences ☒ Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see nature.com/documents/nr-reporting-summary-flat.pdf

Ecological, evolutionary & environmental sciences study design

All studies must disclose on these points even when the disclosure is negative.

Study description	An analytical model and a simulation model
Research sample	All of our data comes from the literature except for those generated by the simulation. From the literature we have sourced twinning rates for populations of different origin as well as specific life-history data from the Gambia, Bangladesh and Denmark.
Sampling strategy	Sample sizes were sufficient to ensure the publication of the original works.
Data collection	We used simulations and equations to collect our data.
Timing and spatial scale	NA
Data exclusions	There were no data exclusions
Reproducibility	NA
Randomization	NA
Blinding	NA

Did the study involve field work? ☐ Yes ☒ No

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

n/a	Involved in the study
☒	☐ Antibodies
☒	☐ Eukaryotic cell lines
☒	☐ Palaeontology
☒	☐ Animals and other organisms
☒	☐ Human research participants
☒	☐ Clinical data

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☒	☐ MRI-based neuroimaging