	J E B	7 0 5	B	Dispatch: 30.1.04	Journal: JEB	CE: Kumar
	Journal Name	Manuscript No.		Author Received:	No. of pages: 12	PE: Sri

doi:10.1111/j.1420-9101.2004.00705.x

Human birthweight evolution across contrasting environments

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Keywords:

birthweight;
chronic diseases;
Homo sapiens;
individual-based agent modelling;
infectious diseases.

Abstract

We explore from both theoretical and empirical perspectives the hypothesis that a significant part of the worldwide variability in human birthweight results from adaptive responses to local selective pressures. We first developed an agent-based model to simulate the process of evolutionary selection on life history strategy, and then we performed a comparative analysis across 89 countries worldwide. The model illustrates that optimal birthweight depends on which fitness-reducing risk locally predominates (somatic diseases, parasitic diseases or adverse environmental conditions). When fitness variations between individuals mainly result from somatic diseases (e.g. industrialized countries), or conversely from infectious and parasitic diseases (e.g. developing countries), selection is expected to favour individuals producing larger children. Conversely, when environmental risks increase in relative importance, selective pressures for producing children with high birthweight are reduced. The comparative analysis supports these theoretical expectations, in particular the finding that birthweight is higher than predicted in highly parasitized countries.

Introduction

Human populations are characterized by important differences in birthweight (Kleinman & Kessel, 1987; Cramer, 1995; Le *et al.*, 1996; Shiono *et al.*, 1997; Bereczkei *et al.*, 2000; Bogin & Smith, 2000; Stinson, 2000; Vangen *et al.*, 2002). Causes for this variation are potentially numerous as many variables have been shown to influence prenatal growth and birthweight in humans (e.g. maternal energy supply, maternal stature, physical work, stress, temperature, disease status, smoking status, gestation length and altitude; see Abell *et al.*, 1991; Brabin, 1991; Emanuel *et al.*, 1992; Zhang & Savitz, 1992; Defo & Partin, 1993; Koupilova *et al.*, 2000; Wells, 2002). Although public health workers traditionally assumed that nongenetic factors predominate (Bogin & Smith, 2000), prenatal growth and birthweight in humans are unlikely to be solely at the mercy of external constraints. Several studies indicated that size and weight at birth in humans are heritable (e.g. Langhoff-Roos *et al.*, 1987; Emanuel, 1992; Towne *et al.*, 1993; Klebanoff *et al.*, 1998). From an evolutionary point of view, human mothers, like other mammals, are expected to maximize their lifetime reproductive success by delivering infants with an optimal birthweight given extant circumstances (Trivers, 1974; Blurton Jones, 1978; Bereczkei, 1993; Bereczkei *et al.*, 2000). Typically, the relationship of birthweight to infant mortality is U-shaped as a result of stabilizing selection (Futuyma, 1998; Stearns & Hoekstra, 2002). However, little is known concerning the short- and long-term fitness consequences of birthweight variation in the different kinds of environments inhabited by human populations across the world (Bereczkei *et al.*, 2000; Lummaa & Clutton-Brock, 2002).

According to evolutionary theory, intra- and interspecific differences in life history traits result for a large part from differences in the characteristics of the

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environment (Roff, 1992; Stearns, 1992). Even if we are far from fully understanding the selective pressures experienced by human populations during the course of evolution, it is safe to consider that anywhere on earth, humans faced (and still face nowadays) three potential risks of major fitness reduction: individuals can die or be severely impaired because of (i) chronic somatic diseases (e.g. cancer, cardiovascular disease), (ii) infectious and parasitic diseases and/or (iii) adverse environmental conditions (e.g. famine, dryness, accidents, disturbances). Health statistics clearly show that these risks strongly vary between human populations in relation to geographic, cultural and economic factors. Interestingly, different predictions can be made on how natural selection should adjust birthweight according to which risk of fitness-reduction predominates. In stable, well-resourced, low-parasite environments (i.e. most modern industrialized countries), somatic diseases are likely to be an important source of fitness variation between individuals. Because infants with a low birthweight are at a higher risk of expressing chronic diseases later in life (e.g. cardiovascular diseases, diabetes, certain cancers, impairment of hearing and vision; see for instance Barker *et al.*, 1989; Kopp, 1990; Robertson *et al.*, 1990; Godfrey & Barker, 2000; Cicognani *et al.*, 2002; Falkner, 2002; Nafstad *et al.*, 2002; Tulassay & Vasarhelyi, 2002), selection in these environments should presumably favour individuals producing larger children (prediction 1). Even if some of these somatic diseases occur late in life (i.e. after reproduction), they are likely to be detrimental to an individual's fitness as they reduce its capacity to deliver grandparental care (inclusive fitness). A second prediction is that in countries where the risks of parasitic infections are extreme (i.e. numerous developing countries), we also expect, all things being equal, women to deliver infants with a high birthweight (prediction 2). Indeed, infants with low birthweight generally have an increased vulnerability to infectious diseases because of impaired immune function (Ferguson, 1978; Victora *et al.*, 1988, 1989, 1990; Cerqueiro *et al.*, 1990; Bukenya *et al.*, 1991; Ittiravivongs *et al.*, 1991; Fonseca *et al.*, 1996; Chandra, 1997, 1999; Moore *et al.*, 1999). Given that offspring mortality (because of infections), more than fertility, is likely to be the primary determinant of fitness variation between reproducing females, human mothers in parasite-rich environments will have a particular reproductive interest in producing larger, more resistant, children. Finally, in environments where adverse environmental conditions predominates (e.g. famine, dryness, accidents, disturbances…), selective pressures for producing large offspring are likely to be relaxed because the negative impacts of environmental factors on individual fitness are largely birthweight-independent. Thus, because in these cases the fitness costs incurred by the maternal organism when producing large children (e.g. reduced survival, lower probability of subsequent reproduction, see Beneczkei *et al.*, 2000) are less well compensated by reproductive advantages, natural selection should favour individuals producing smaller babies (prediction 3).

The aim of this paper was to evaluate both from a theoretical and an empirical perspective the hypothesis that human birthweight displays regional variation as a consequence of evolutionary adaptation of populations to their environment. We first used an agent-based model to simulate the process of evolutionary selection for the best life history strategy in contrasting environments. Then, we performed a multivariate comparative analysis in which we examined more specifically the role of disease-causing agents on birthweight evolution across 89 countries from around the world.

Materials and methods

Evolutionary modelling

We used an agent-based model to simulate the process of evolutionary selection on life history strategy (see Mangel, 1990). The choice of an agent-based model instead of using more computationally advantageous dynamic optimization models (Mangel & Clark, 1988; Perrin & Sibly, 1993; McNamara & Houston, 1996; Teriokhin, 1998; Kozlowski & Teriokhin, 1999) was made mainly because of the need to optimize birthweight alone. In optimization models, birthweight cannot be optimized directly as it enters into dynamic equations as an initial value (Mangel *et al.*, 1994). Another limitation of optimization modelling, which can be overcome by using agent-based evolutionary models, is that it requires an explicit expression for an optimality criterion. Different optimality criteria (lifetime reproductive success, intrinsic rate of increase etc.) may be adequate for a given modelled situation, depending on the way in which the environment influences individual survival and fertility (Mylius & Diekmann, 1995; Teriokhin, 2002). Thus, the choice of a suitable criterion may be a nontrivial task. On the contrary, the optimality requirement in agent-based models is included implicitly and naturally as the ultimate dominance of a genotype in a population as a result of its competition with other genotypes.

The idea of agent-based modelling consists in simulating iteratively, passing from time step t to $t + 1$, the evolution of a population of individuals (agents), each being eventually able to die or to give birth to new individuals. At any time step t, each individual of the population is characterized by a set of state variables (such as age or body mass), which can change with time, and by its genotype, which cannot change during the individual's lifetime. The descendent inherits the genotype of its parents modified by possible mutations. The environmental setting of a population is characterized by a set of time-independent state-variables. Thus, we assumed that evolution occurs in a fixed environment.

Nevertheless, we could evaluate the impact of the environment on genotype evolution simply by comparing the results of simulations executed for different environments.

The simulated evolution of a population is governed by a set of rules (dynamic equations) which expresses the state of an individual at time $t + 1$ as a function of its state at time t, taking into account its genotype and the state of environment. We assumed that the genotype of an individual defines the parameters of its internal control system, controlling the state-dependent distribution of energy between growth and reproduction.

In the course of simulations under given fixed environmental conditions, the most favourable genotypes spread fastest and ultimately a group of very similar genotypes dominates. Under contrasting environmental conditions other genotypes may dominate, so that the characteristics of the optimal genotype depend critically on the environmental conditions experienced during evolution.

In our model, the variables characterizing the individual's state are its age, $A_i(t)$, and body weight, $W_i(t)$. The dynamic equation for the age of an individual i is quite simple

$$A_i(t+1) = A_i(t) + 1$$

The dynamic equation for body weight is

$$W_i(t+1) = W_i(t) + u_i(t)E_i(t)$$

where $E_i(t)$ is the amount of disposable energy which the individual may spend either on growth or reproduction depending on the value of the single decision variable $u_i(t)$. This variable may take one of only two values: one or zero. If $u_i(t) = 1$ all the energy is allocated to growth and if $u_i(t) = 0$ all the energy is allocated to reproduction. Thus, in the latter case growth is replaced by giving birth to a child j with birthweight B_j equalling

$$B_j = [1 - u_i(t)]E_i(t)$$

The value of $u_i(t)$, in turn, depends on the value of the state variable $W_i(t)$: if $W_i(t)$ is less than some threshold value G_i then $u_i(t) = 1$, otherwise $u_i(t) = 0$. So, we can say that the control system of an individual in our model consists of a single two-state neurone characterized by its threshold G_i which may be also considered as the individual's genotype.

We used the commonly accepted allometric dependence of the energy produced by an individual on its weight (West *et al.*, 1999)

$$E_i(t) = aW_i^b(t)$$

In our simulations we set the parameter b to 0.5 which was estimated using real human data (see Guégan *et al.*, 2000). Our experience shows that this value proves more adequate to models of human life history than the value $b = 0.75$ postulated by Kleiber's law (West *et al.*, 1999).

The value of parameter a reflects several aspects. First, a evidently depends on the units chosen for measuring energy. Here, we measured energy in units of mass, as can be seen from the above dynamic equation for body weight. In principle, the value of a may vary for different individuals, however we considered that all individuals were identical. The value of a also reflects the fact that we only model the allocation of energy to growth and reproduction, and thus it is weighted to ignore contributions to other energetic requirements, e.g. maintenance, defence. Finally, we supposed that the value of a depends on the availability of food. Hence, we made simulations for different values of a to mimic differences in food availability across environments.

We supposed that at any time step any individual i may possibly die with a probability

$$P_i(t) = \mathrm{e}^{-Q_i(t)}$$

where $Q_i(t)$ is the overall mortality rate composed of four components

$$Q_i(t) = q_e + c\mathrm{e}^{dA(t)} + \frac{q_s}{B_i} + \frac{q_p}{B_i}$$

The first two components do not depend on individual birthweight and are, in fact, two components of the Gompertz–Makeham equation (Gompertz, 1825; Makeham, 1860). More specifically, while q_e does not depend on individual age, the second parameter $c\mathrm{e}^{dA(t)}$ increases exponentially with age. In our model we interpreted q_e as the individual-independent (more precisely, birthweight-independent) component of environmental stress (e.g. because of injuries). It was varied from $q_e = 0$ to 0.008 to imitate aggravation of environmental conditions. In addition, in order to imitate the simultaneous aggravation of alimentary conditions, we tied the increase of q_e from 0 to 0.008 with a linearly dependent decreasing function with a varying from 0.57 to 0.47. Henceforth, we will refer to q_e as to '(birthweight-independent) environmental stress'.

The coefficients c and d of the age-dependent component were taken as constant for all individuals and environmental conditions. We set $c = 0.000005$ and $d = 0.1$, corresponding to typical values of these parameters estimated from real data (Gavrilov & Gavrilova, 1991). The third component of mortality rate, q_s/B_i, was interpreted as somatic malfunctions (somatic diseases) caused by insufficient birthweight. The parameter q_s was set equal to 0.015 for all individuals and environmental conditions. In the following sections, q_s will be referred to as (birthweight-dependent) somatic stress.

The fourth component, q_p/B_i, is the most interesting in our model. It represents the negative effect of parasitic stress (i.e. infectious and parasitic diseases) which becomes stronger for insufficient birthweight. We varied q_p from $q_p = 0$ to 0.02 to imitate the aggravation of

Table 1 Assumptions made on the values of the model parameters.

Parameter	Symbol	Lower value	Upper value	Step
Coefficient in the equation of energy production	a	0.47	0.57	0.011
Power in the equation of energy production	b	0.5	0.5	–
Coefficient in the Gompertz component of mortality	c	0.000005	0.000005	–
Power in the Gompertz component of mortality	d	0.1	0.1	–
Environmental birthweight-independent component of mortality	q_e	0	0.008	0.001
Environmental birthweight-dependent component of mortality	q_p	0	0.2	0.002
Somatic birthweight-dependent component of mortality	q_s	0.015	0.015	–

parasitic conditions. Further, we will refer to q_p as (birthweight-dependent) parasite stress. In addition to $Q_i(t)$, two further components of mortality, acting only during the first year of life and so reflecting the effect of infant mortality, were taken into account in the model

$$Q_{i0} = \frac{10q_s}{B_i} + \frac{10q_p}{B_i}$$

They are similar to the already considered birthweight-dependent components of mortality rate q_s/B_i and q_p/B_i but are magnified 10 times, corresponding to relative magnitudes of newborn and later-life mortalities as estimated from data (Thomas *et al.*, 2000).

The ranges of values for a, q_0,q_e, as well as the value of q_s, were chosen expressly so as to provide realistic values for human life history traits (birthweight, adult weight, age at maturity, life expectancy). Table 1 summarizes the assumptions made for the values of the model parameters. The flowchart in Fig. 1 illustrates the processes underlying the life functioning of an individual.

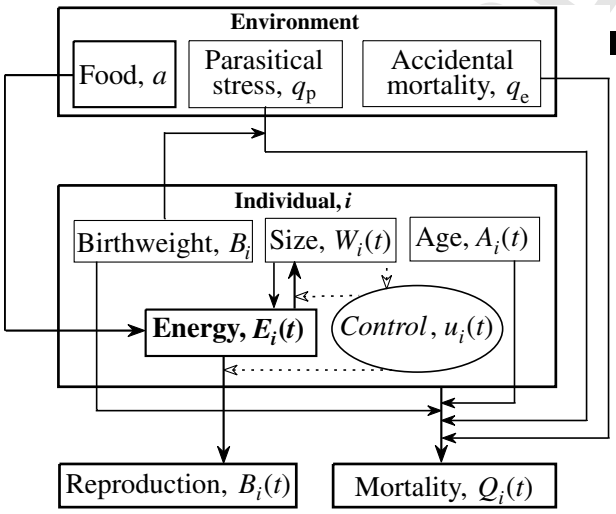

Fig. 1 Flowchart illustrating the processes underlying the life functioning of an individual. The dashed arrows represent information flows, the fine arrows indicate direct biological influences and the thick arrows denote the energy flows.

The model results illustrated in Figs 2 and 3 are based on 99 simulation variants corresponding to 99 combinations of values of q_p (from 0 to 0.02 with step 0.002) and q_e (from 0 to 0.008 with a step of 0.001). For each simulation, 25 000 iterations were carried out for each of 20 independently and randomly chosen initial populations of 500 individuals each. The threshold G for each newborn differed from the value of its parent by a random number having a standard normal distribution. The population size was limited by its initial number of 500 via the stochastic elimination of sufficient newborns to ensure a constant population size of 500. The results, for each simulation, were the median values of the four life history traits, i.e. birthweight, adult weight, age at maturity and life expectancy, of 10 000 individuals obtained by the end of 25 000 iterations.

Comparative analysis

Data

International data on mean birthweight and percentage of preterm birth (i.e. below 37 weeks) were obtained from a database available from the World Health Organization (WHO) (2000). These data come from various sources (e.g. scientific journals, reports from ministries of health…) and combine male and female data. When several values were given for the same country (i.e. several cities), we used the mean of these values. In other situations, data refer to a limited part of a population (e.g. a given city), and thus an important assumption we made is that they are representative of the country. It is frequently argued that comparative analyses using information from different sources may be inappropriate because data have been collected with different methods, or they come from different sources. Although the argument is always applicable when no significant result is detected (i.e. data are not precise enough to detect a potentially significant result), it is unlikely to be relevant when significant trends are found, as a biological tendency has no *a priori* reason to be correlated to background noise in the data set (Møller, 1997; Lawton, 1999). Because alimentary conditions are known to strongly affect birthweight, we also considered the mean calorie consumption per person per day. This information

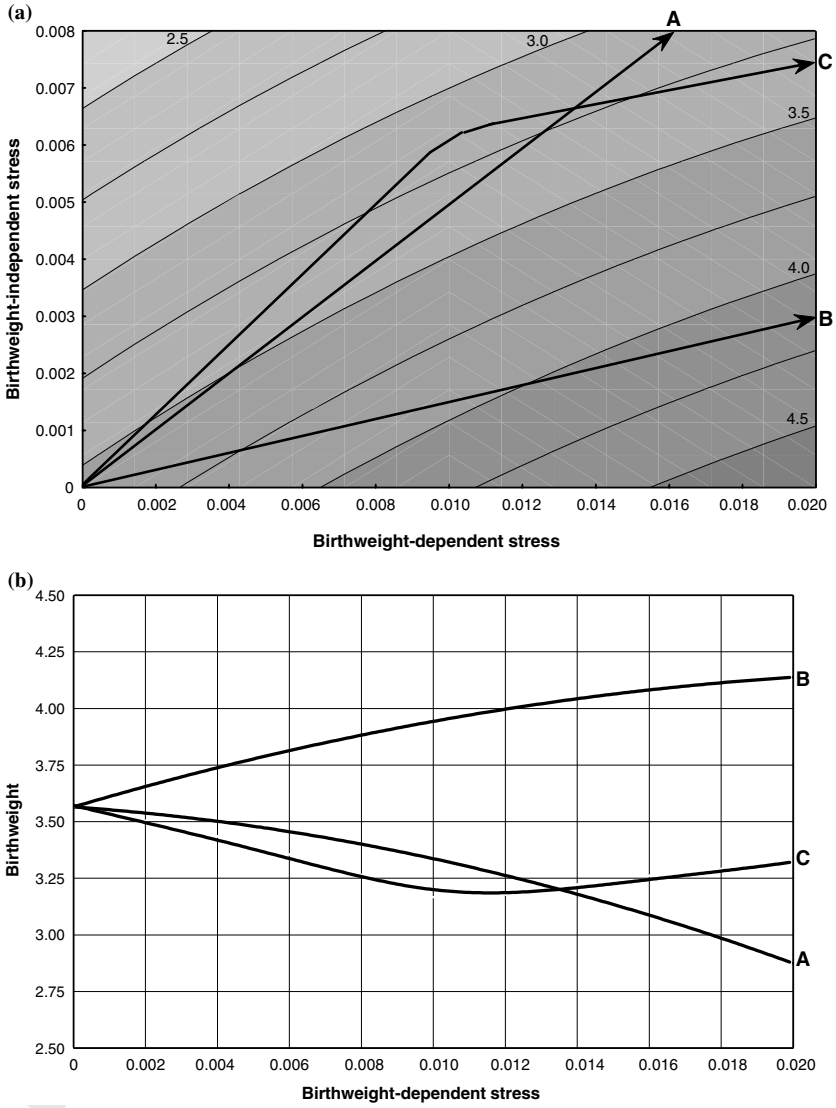

Fig. 2 (a) The contour plot of modelled optimal birthweight against birthweight-dependent and birthweight-independent components of environmental stress. The values of birthweight are shown by the numbers near contour lines and by the saturation of contour areas. The bold curves A, B, and C correspond to different scenarios of simultaneous increase of two components (see text). (b) The dependencies of birthweight on birthweight-dependent component of stress corresponding to three scenarios A, B, and C of joint increase of two components of stress shown in (a).

was obtained from food balance sheets from the World Atlas© (1992). Data on female stature were taken from Guégan *et al.* (2001). As in previous papers (Guégan *et al.*, 2000, 2001; Thomas *et al.*, 2000, 2001), disease occurrence in the different countries were compiled from two international health care databases, i.e. the Centres for Disease Control and Prevention (Atlanta, USA at http://www.cdc.gov/) and the World Health Organization (Geneva, Switzerland at http://www.who.int/). We collected data for a set of 16 categories of human parasitic and infectious diseases known to affect human survival (typhoid, hepatitis A, hepatitis B, malaria, schistosomiasis, filariosis, meningococcosis, yellow fever, dengue fever, cholera, trypanosomiasis, dracunculosis, chagas disease, Lyme disease, cutaneous leishmaniosis and visceral leishmaniosis). Based on this information, we calculated the disease load as the total number of diseases for each country with a maximum disease load equal to 13. Because data on all variables were not always available, our study was based on different numbers of countries for different analyses – from 51 to 130 (the most complete list included 19 European countries, 37 countries from Asia, 40 from Africa and 37 from America).

Statistical analyses

To analyse the relationship between birthweight and parasitic/infectious diseases, we first performed polynomial regressions of crude values of birthweight on the number of infections to capture nonlinearity, and retained the regression which was the most significant. In a second step, we performed the same analyses using birthweight corrected for both the percentage of preterm children and for the mean number of calories per person

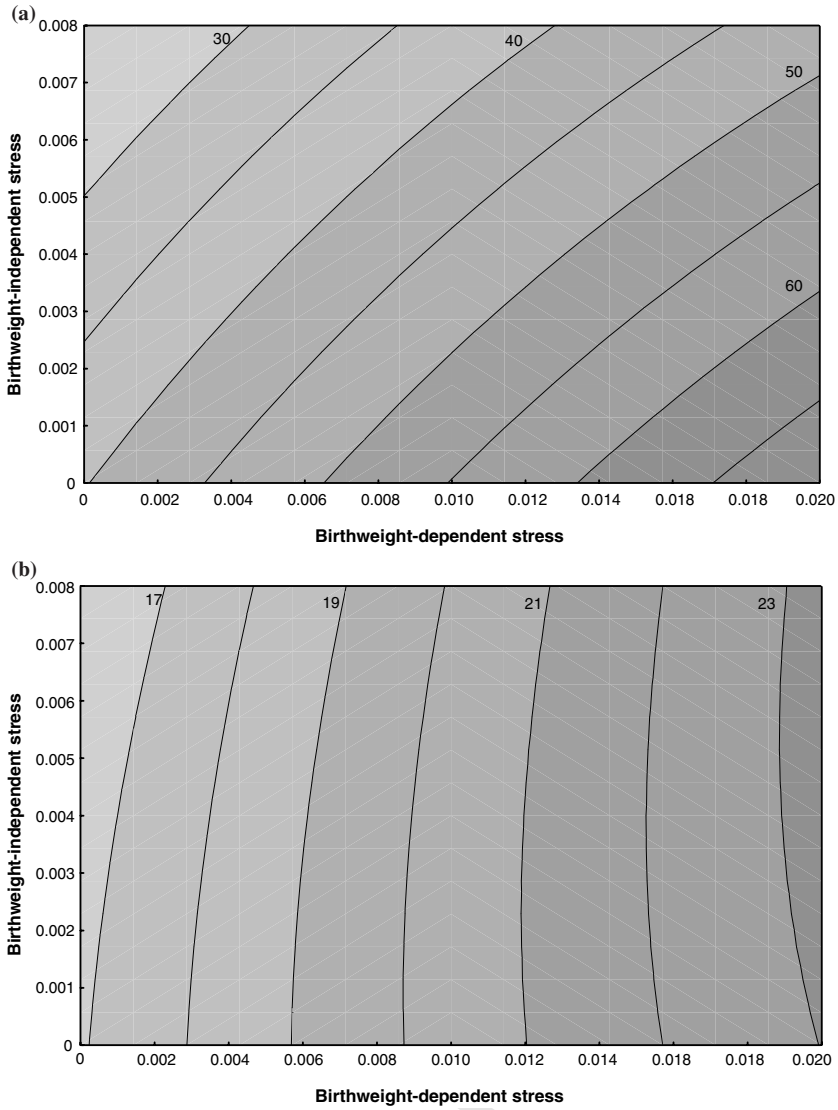

Fig. 3 (a) The contour plot of modelled optimal adult weight against birthweight-dependent and birthweight-independent components of environmental stress. The values of adult weight are shown by the numbers near contour lines and by the saturation of contour areas. (b) The contour plot of modelled optimal age at maturity against birthweight-dependent and birthweight-independent components of environmental stress. The values of age at maturity are shown by the numbers near contour lines and by the saturation of contour areas.

per day using residual values from multiple regressions. Because female stature and obstetrical performance are usually linked (see Guégan *et al.*, 2001), we also examined the relationship between mean female stature and parasitic/infectious diseases by performing polynomial regressions. To find confidence limits for the position of the minimum of the quadratic regression, we used a bootstrap method (Efron, 1979) by calculating estimates of this position for 1000 random re-samples from the original data.

Results

Evolutionary modelling

The essence of the results is presented in Fig. 2a in the form of the dependence of optimal birthweight, w_b, on birthweight-dependent parasitic and birthweight-independent environmental components of mortality, q_P and q_e. This dependence is fairly well approximated by a quadratic polynomial function of the form:

$$w_b = 3.56 + 71.90q_p - 166.16q_e - 743.95q_p^2 - 1286.26q_Pq_e + 877.20q_e^2$$

The contour lines in Fig. 2a are contour lines of this polynomial.

The general tendency consists of an increase in the optimal birthweight with increasing parasite stress and decreasing environmental stress. However, as q_P and q_e are positively correlated in reality (Thomas *et al.*, 2000), it is important to consider the evolution of birthweight along curves on the plane (q_p, q_e) corresponding to simultaneous increases of q_p and q_e.

We considered three scenarios of correlated increases in q_p and q_e, illustrated by the three bold curves in Fig. 2a. First, (A), the optimal birthweight monotonically declines if the rate of increase of the parasite stress component is inferior to the rate of increase of the environmental stress component. Then, (B), the optimal birthweight monotonically rises if the rate of increase of the parasite stress component is superior. Finally, (C), the optimal birthweight first declines and then rises if the rate of increase of the environmental stress component is first superior and then inferior compared with the rate of increase of the parasite stress component.

The change of birthweight along these three curves is shown on Fig. 2b. We see indeed that in case (A) the optimal birthweight monotonically declines with increasing q_p, in the second case, (B), it rises, and in the third case, (C), it first declines and then rises. The patterns of change of evolutionary optimal values of adult weight and age at maturity as dependent on q_p and q_e are shown on Fig. 3a and b, respectively.

Comparative analysis

From data collected for 130 countries, birthweight, w_b, appears to depend nonmonotonically on the number of infections, i (Fig. 4a). This dependency is well fitted by a quadratic parabola function

$$w_b = 3.744 - 0.163i + 0.00885i^2$$

Both the coefficients of i and i^2 are significant at the levels $P < 0.000001$ and $P = 0.000001$, respectively, illustrating that the dependency between birthweight and infection is significantly nonlinear.

The minimum for this parabola is attained at the number of infections equalling $i_{\min} = -0.5 \times (-0.163/0.00885) \approx 9.2$ that is less than the greatest numbers of infections, i.e. $i = 12$, encountered in real data. We calculated the 95% bootstrap confidence interval for $i_{\min}$,$[8.7 < i_{\min} < 10.1]$, which falls inside the range of observed number of infections, i.e. between 3 and 12.

To exclude the possibility that the dependence of birthweight on infections is not quadratic but simply asymptotically decreasing, we estimated the significance of linear regression of birthweight on infections for the most parasitized countries (with more than nine infections). We obtained the following equation based on the data for 30 countries

$$w_b = 2.404 + 0.056i$$

which is statistically significant at the level $P = 0.037$.

We eliminated the negative effect of birth prematurity and the positive effect of food supply on birthweight (Matsuda *et al.*, 1995; Albertsson-Wikland *et al.*, 1998) by repeating the same analysis for the residuals, r_b, of birthweight from the linear regression between the percentage of children incubated for <37 weeks and the mean number of calories per person per day. The

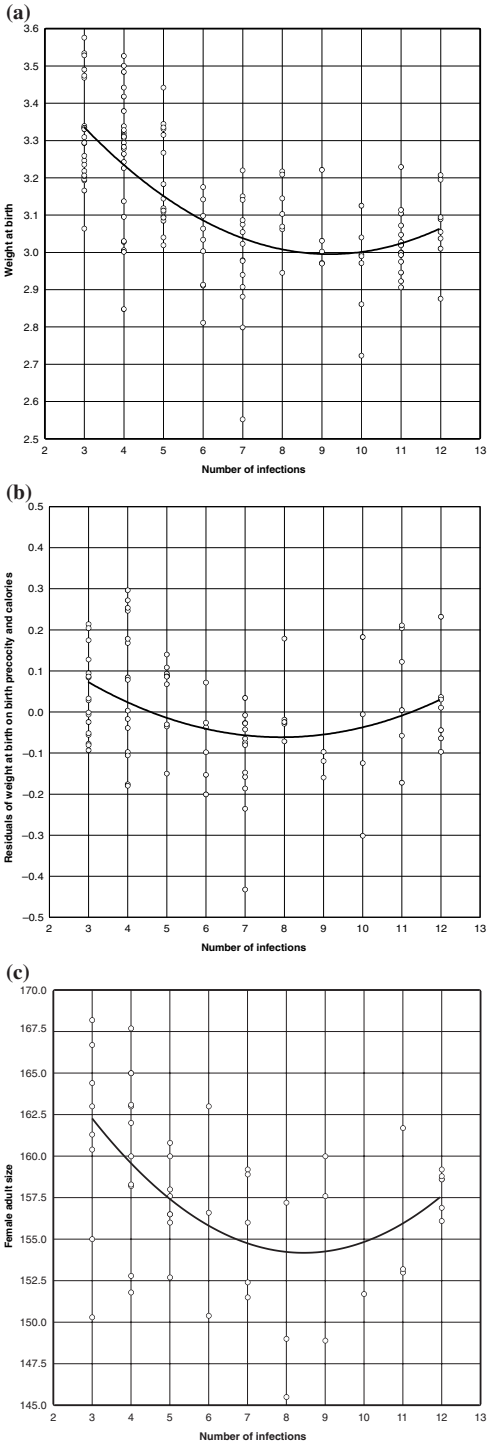

Fig. 4 (a) The observed dependency of birthweight on number of infections. (b) The observed dependency of the residuals of birthweight from its linear regression on the per cent of children incubated <37 weeks and the number of calories per person per day on the number of infections. (c) The observed dependency of adult female stature on number of infections.

dependency of these residuals on the number of infections can be fitted by a quadratic regression based on the data for 89 countries

$$r_b = 0.286 - 0.0878i + 0.00554i^2$$

with the coefficients of i and i^2 being significant at the levels $P < 0.0018$ and $P = 0.0037$ respectively and with $i_{\min} \approx 7.9$. The nonmonotonic nature of the dependence on the number of infections is again well expressed (see Fig. 4b) and the bounds of the 95% confidence limit for $i_{\min}$, $[7.2 < i_{\min} < 9.0]$, again do not exceed the range of observed numbers of infections.

Secondly, taking into account that the birthweight is significantly correlated with adult female stature ($R = 0.50$, $P = 0.00068$), we analysed the dependency of adult female stature on the number of infections. As a result, we obtained for adult female stature a nonmonotonous dependency on the number of infections based on the data for 51 countries

$$w_a = 173.63 - 4.604i + 0.272i^2$$

with $i_{\min} \approx 8.5$ (see Fig. 4c).

The coefficients of i and i^2 in this equation are significant at $P = 0.00079$ and 0.0025 respectively, and the bounds of the 95% confidence limit for $i_{\min}$, $[8.0 < i_{\min} < 9.2]$, do not exceed the range of observed numbers of infections, which confirms indirectly the existence of a minimum in the dependence of birthweight on infection.

Discussion

Investigating the evolution of behavioural and/or life history traits in humans is often limited by the fact that one must assume that current environmental conditions provide, at least partially, a reliable picture of the selective landscape experienced by human populations in the past (Barret *et al.*, 2002). Numerous countries have recently (some 300 years ago in some developed countries and in less developed countries about 1920) undergone what are known as the demographic- and the epidemiologic-transitions (see Coale & Treadway, 1986). These transitions correspond to major changes whereby both fertility and mortality (including infectious and parasitic disease mortality) decreased whereas at the same time, we have seen an increase in the relative prevalence of degenerative diseases in countries where mortality has declined. A major assumption made in this study is that both current human life history traits and major environmental characteristics (i.e. the data we used) are reliable for testing our evolutionary predictions on birthweight.

Although parasites are often harmful to their hosts, relatively few studies have illustrated how selection has favoured parental responses improving offspring resistance to infections, beyond selection for responses which alleviate the direct impact of parasites on infected hosts (Brambell, 1970; Sorci *et al.*, 1994; Carlier & Truyens, 1995; Buechler *et al.*, 2002). Parasitic and infectious diseases have been and continue to be a major cause of human mortality in the world, most particularly in tropical areas where many different agents are dreadful killers (Jackson, 2000). Because children with low birthweight are usually more susceptible to infections than others (see references in Introduction), we here predicted that natural selection should have operated on mechanisms (e.g. physiology, psychology, behaviour…) that enable human females to produce larger children when infection risks are extreme. Our study apparently supports this hypothesis since, once a threshold in the infection risk is reached (nine diseases in our study), birthweights significantly increase with the number of diseases present. Further studies are necessary to determine whether the simple accumulation of harmful diseases is, *per se*, responsible for this pattern, or whether it results from the particular effects of some diseases among those that appear in communities beyond the eight to nine diseases point.

The two most important variables known to influence birthweight in the modern literature (i.e. gestation length and nutritive conditions) do not confound this result as the same pattern is observed after controlling statistically for these effects. However, other potential confounding variables do remain. For instance, available birthweight data records only live births, hence differential mortality of smaller foetuses in parasitically-diverse countries could bias birthweight towards larger babies. Further information would be necessary to clarify the exact links between birthweight and resistance/susceptibility to parasitic and infectious diseases. Indeed, many components of the immune system develop early in foetal life (Good & Gabrielsen, 1964) and maternal malnutrition is generally observed to have greater effect on thymic and lymphoid tissue growth than on other organs (Owens *et al.*, 1989; Moore *et al.*, 1999). In this context, a higher birthweight *per se* may not directly confer a higher capacity to resist infections, instead it would simply correlate with nutritive conditions met by the foetus when developing his/her immune organs.

In a previous study considering 150 different countries, Guégan *et al.* (2001) showed that human fertility increases with the diversity of parasitic and infectious diseases. The present work suggests that improving the chance of offspring survival is also likely to be a crucial component of individual fitness when parasitic pressures increase. Because fertility in heavily parasitized countries is usually very high for most women, fitness variation between mothers are more likely to result from variation in the survival of the offspring produced than on their number (Strassmann & Gillespie, 2002). In summary, these results and those of Guégan *et al.* (2001) suggest that in human populations living under severe parasitic constraints, natural selection has favoured increased reproductive investment, represented by increases in

both the size and number of offspring (all things being equal). An increase in reproductive investment in response to raised (parasite-driven) mortality is in keeping with basic tenets of life history theory (Stearns, 1992). Furthermore our data points to a partition of increased investment into both number and size of offspring. Here, we argue that the increase in size is a direct selective response to the dependency of parasite-linked fitness losses on birthweight. However our results cannot exclude an alternative hypothesis that the global increase in reproductive budget is invested in multiple dimensions of reproductive output (size, number and potentially other dimensions such as lactation) to counter diminishing returns in any one dimension of investment (Stearns, 1992; Mangel *et al.*, 1994). Further theoretical studies would be necessary to understand the trade-offs retained by selection between offspring number and offspring size for different scenarios of infection exposure (e.g. kinds of parasitic and infectious diseases, synergic effects among parasite groups, virulence, periodicity of the exposures).

Interestingly female stature is positively correlated to birthweight, displaying the same pattern with regard to parasitic and infectious diseases, in particular it also increases after the threshold of eight to nine diseases is reached. These correlations are observed both in the data (compare Fig. 4a with Fig. 4c) and in the model (compare Fig. 2a with Fig. 3a). The simplest explanation for this correlation is that conditions that influence foetal growth also influence subsequent growth later in life. However, as we can see in Fig. 3b, increasing parasitic stress is accompanied with increasing age of maturity that allows to bear children of greater birthweight in severe conditions (see also Restif *et al.*, 2001). In fact, there may be different explanations for this correlation between female stature and birthweight. We assumed in the model that increasing birthweight decreases the risk of death from infections. In our model, the selection for an increased adult size is rather secondary: larger adult sizes are necessary for obtaining higher birthweights. Alternatively, we could assume that higher adult sizes decrease the risk of death from infections. We would expect in this case a selection for a larger adult size in the most infected areas. This could be achieved by producing children with higher birthweights. Although we prefer the first hypothesis, both are theoretically possible.

Also other phenomena are likely to occur. Indeed, knowing that there is a strong correlation between female height and risks of difficult childbirth (Camilleri, 1981; Parsons *et al.*, 1989; Tsu, 1992; Van Roosmalem & Brand, 1992; Kwawukume *et al.*, 1993; Moller & Lindmark, 1997), this correlation may result from adaptive adjustments of female morphology to the size of the children they produce. Thus, in heavily parasitized countries, not only high fecundities would exert selective pressures for large stature in women (see Guégan *et al.*, 2001), but the need for producing larger children would also influence positively the evolution of this trait. Alternatively, we cannot exclude that selection in parasitized countries favours (for reasons that remain to be determined) adult individuals with large statures. Because of the positive relationship between the stature of females and the birthweight of their children (see references in Introduction), higher birthweights in parasitized areas could be a consequence of the former selection without the need to invoke an advantage of large babies over smaller one. Further studies are thus necessary to determine which trait(s) are the target(s) of the selection. Irrespectively of what is the main target of selection (birthweight or adult size), our modelling predicts that the observed tendency for the increase of both these parameters in the countries with highest infections can occur only if in the most dangerous conditions the importance of accidents as compared with infections becomes relatively less important. Additional data and their analysis are necessary to confirm or refute this prediction, as well as information on the role played by the age at first reproduction in these processes.

Another important result of this study is that the largest birthweights are observed in countries with no or few harmful parasites. We predicted this result because of two interacting phenomena. First, knowing that these countries usually correspond to industrialized countries, it can be first argued that large amounts of nutritive resources are available to pregnant women. A second reason is that natural selection should have favoured individuals producing larger children because of their reduced probability of developing a chronic disease later in life compared with individuals who had a lower birthweight (see references in Introduction). Knowing that in rich countries, most deaths occur as a result of somatic diseases, such as cancer, strokes and heart disease (40% of all deaths in developing countries vs. 75% in industrialized countries, WHO, 1996 estimates), these causes of mortality/morbidity appear likely to be a major source of fitness variation between individuals. Thus, as both selective and environmental pressures lead in the same direction, it is unsurprising that birthweights reach the highest values in the most economically developed countries. Further investigations are however needed to valid our conclusions since, as far as we know, the mechanism of the relationship of birthweight to later susceptibility to chronic disease is unclear and still debated. If for instance mutations cause both the low birthweight and the later susceptibility to chronic diseases, maternal manipulation of birthweight would have no effect.

Interestingly, once we correct birthweight for the influence of nutrition and of prematurity, mean birthweights in low- and in highly-infected countries become on average similar, confirming the preponderant role of environmental (nongenetic) variables in generating birthweight variation between industrialized and developing countries. However, other parameters undoubtedly

intervene since significant birthweight variations (total data set) remain after controlling for the previous effects. In accordance with our predictions, peak values are observed for low- and for highly-parasitized countries, respectively.

In conclusion, and to summarize, although a large number of nongenetic variables certainly contribute to explaining variability in birthweight worldwide, our study suggests that a significant part of the variability on this trait results from adaptive responses to local selective pressures. In such a context, parasitic pressures apparently played a significant role. Further analyses that include other kinds of pathogen (e.g. viruses) are necessary to confirm our findings.

Acknowledgments

We thank M. Raymond, H. Harpending and one anonymous referee for comments on an earlier version of the manuscript. F. Thomas is supported by an 'ACI jeunes Chercheurs'.

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Received 16 September 2003; revised 18 December 2003; accepted 19 December 2003

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