Influence of early-life nutrition on mortality and reproductive success during a subsequent famine in a preindustrial population

Adam D. Hayward[a,1,2], Ian J. Rickard[a,b,1], and Virpi Lummaa[a]

[a]Department of Animal and Plant Sciences, University of Sheffield, Western Bank, Sheffield S10 2TN, United Kingdom; and [b]Department of Anthropology, Durham University, Queen's Campus Stockton, Thornaby, Stockton-on-Tees TS17 6BH, United Kingdom

Edited by Alan Swedlund, University of Massachusetts, Amherst, MA, and accepted by the Editorial Board July 1, 2013 (received for review January 28, 2013)

Individuals with insufficient nutrition during development often experience poorer later-life health and evolutionary fitness. The Predictive Adaptive Response (PAR) hypothesis proposes that poor early-life nutrition induces physiological changes that maximize fitness in similar environments in adulthood and that metabolic diseases result when individuals experiencing poor nutrition during development subsequently encounter good nutrition in adulthood. However, although cohort studies have shown that famine exposure in utero reduces health in favorable later-life conditions, no study on humans has demonstrated the predicted fitness benefit under low later-life nutrition, leaving the evolutionary origins of such plasticity unexplored. Taking advantage of a well-documented famine and unique datasets of individual life histories and crop yields from two preindustrial Finnish populations, we provide a test of key predictions of the PAR hypothesis. Known individuals from fifty cohorts were followed from birth until the famine, where we analyzed their survival and reproductive success in relation to the crop yields around birth. We were also able to test whether the long-term effects of early-life nutrition differed between individuals of varying socioeconomic status. We found that, contrary to predictions of the PAR hypothesis, individuals experiencing low early-life crop yields showed lower survival and fertility during the famine than individuals experiencing high early-life crop yields. These effects were more pronounced among young individuals and those of low socioeconomic status. Our results do not support the hypothesis that PARs should have been favored by natural selection and suggest that alternative models may need to be invoked to explain the epidemiology of metabolic diseases.

developmental plasticity | silver spoon | human life-history | DoHAD

Nutrition during early life may have important long-term health consequences (1–3). In particular, growth restriction in fetal and neonatal life is associated with increased risk of cardiovascular disease (4), diabetes (5), and cancer (6) in later life. Experimental work with animal models strongly supports the conclusion that such relationships are causal and that they are mediated in the developing individual at the physiological, cellular, and epigenetic level (3, 7).

An increasingly cited explanation for such findings is that some of the effects of nutrition on the developing fetus are evolved conditional responses to the environment that only become important in adult life (8, 9). According to this view, individuals tailor their phenotype to maximize their fitness in the environmental conditions experienced during development, predicting that developmental conditions represent the environment that they will experience as adults. This "Predictive Adaptive Response" (PAR) (9) is a form of phenotypic plasticity, whereby individuals modify their phenotype to maximize fitness under a particular set of environmental conditions (10). Genes that promote an appropriate conditional response ("if the environment is *x*, then develop as *a*; if the environment is *y*, then develop as *b*") will be favored by natural selection if the individuals carrying them leave more descendants than individuals not carrying them.

The PAR hypothesis has frequently been invoked to explain associations between intrauterine growth restriction and health outcomes such as type II diabetes and cardiovascular disease (5, 11–14). It is argued that poor growth during early development signals adverse environmental conditions, causing individuals to develop a "thrifty" metabolism, characterized by insulin resistance, slow glucose metabolism, and increased fat deposition, which are adaptations to thriving in nutrient-poor conditions (5, 8, 9, 11). According to this view, only when individuals with thrifty metabolisms experience a nutritionally rich environment does the phenotype lead to disease, i.e., when developmental and later conditions are "mismatched" (9, 15). Metabolic diseases are increasing in prevalence worldwide (16), and the PAR hypothesis has often been used to explain their epidemiological characteristics (15, 17).

In the empirical literature, associations between early-life environmental conditions and health are often interpreted as consistent with the PAR hypothesis (9, 12–14). Understanding the evolutionary processes underlying such associations is deemed to increase our understanding of the health consequences of early-life conditions and guides the development of interventions (18). However, although the PAR hypothesis is frequently alluded to, its novel predictions have rarely been empirically tested (19, 20). One alternative interpretation is that poor early nutrition constrains individual development and long-term health and is more likely to exacerbate the effects of poor nutrition later in life (19, 21), an idea referred to in ecological studies as the "silver spoon" hypothesis (22, 23). The lack of empirical scrutiny of the PAR hypothesis impedes our understanding of the evolutionary reasons for the developmental origins of health and disease, with broad implications for prevention and treatment.

A key prediction of the PAR hypothesis is that individuals experiencing poor nutrition in early life will, via permanent changes to their metabolism, benefit when they experience poor nutrition as adults, relative to individuals who experienced more favorable early-life conditions (9). In evolutionary terms, this prediction suggests that, under poor adult conditions, they will have greater survival and reproductive success (higher fitness) than those who did not experience poor nutrition and develop in accordance with this signal. If the long-term physiological

Author contributions: A.D.H., I.J.R., and V.L. designed research; A.D.H. and I.J.R. performed research; A.D.H. and I.J.R. analyzed data; and A.D.H., I.J.R., and V.L. wrote the paper.

The authors declare no conflict of interest.

This article is a PNAS Direct Submission. A.S. is a guest editor invited by the Editorial Board.

Freely available online through the PNAS open access option.

[1]A.D.H. and I.J.R. contributed equally to this work.

[2]To whom correspondence should be addressed. E-mail: a.hayward@sheffield.ac.uk.

This article contains supporting information online at www.pnas.org/lookup/suppl/doi:10.1073/pnas.1301817110/-/DCSupplemental.

consequence of a poor start in life has any advantage, such benefits should emerge when food is scarce. However, if the long-term effects of early nutrition are more dominated by constraint rather than adaptation, then the reverse is expected, with poor early nutrition being associated with higher mortality and lower fecundity in poor later environments.

Using detailed longitudinal data on harvest success and individual life histories collected over several decades in two preindustrial Finnish agricultural populations, we examined associations between early-life food availability and subsequent individual survival and fertility during the well-documented famine of 1866–68. These 19th century populations were vulnerable to famine, due to a poor transportation network, little healthcare, an unfavorable growing climate, and their reliance on two principle crops, rye and barley (24). In the late 1860s, several poor harvests, culminating in an almost total failure in 1867, led to catastrophic mortality in late 1867 and early 1868 (25). During this period, excess mortality largely caused by infectious diseases such as typhus, typhoid, and dysentery (25) resulted in at least an 8% reduction in the country's population. A good harvest in 1868 returned mortality levels to within the normal range by 1869. Therefore, 1867 and 1868 represent some of the most extremely adverse environmental conditions, characterized by low nutrition and high disease prevalence, experienced by the population. These data represent a powerful resource for testing hypotheses concerning effects of the early environment on later-life fitness. The longitudinal series of grain data represents a high degree of variation in food availability, allowing characterization of the nutritional conditions around birth for over 50 cohorts. The parish data contain information on socioeconomic status, which is correlated with access to resources, allowing us to control for between-family differences in access to food and to investigate whether wealth affected associations between early conditions and famine fitness. Existing famine cohort studies examine the effects of early experience of famine on health and reproduction in favorable later-life conditions (26) whereas our study analyzes associations between natural variation in early-life environmental conditions and the ability to survive and reproduce in extremely adverse later-life conditions; i.e., the benefits of predicting later-life conditions will be poor. As such, this study is complementary to those investigating the effects of early nutrition on health and fitness in modern obesogenic environments (26), and our findings should contribute to our understanding of the role of developmental conditions in influencing life history, and the evolutionary basis of these associations.

Clear predictions arise from the contrasting hypotheses: PAR models predict that individuals experiencing low food availability around birth should be better able to cope with famine conditions and exhibit higher survival and reproductive success. Meanwhile, the silver spoon model would predict that individuals experiencing low food conditions around birth should experience lower survival and reproductive success during the famine.

Results

Famine Survival. The study populations depended largely on the rye and barley harvests (24), with rye bread providing around 60% of the energy intake of working people and barley also contributing significantly to nutrition (27). Annual harvest success was quantified by relative grain yields, corresponding to the quantity of grain harvested as a multiple of that sown. We quantified early environmental conditions by taking 3-y running means of annual rye and barley yields, centered on the year of birth ("early-life yield" from here on). This method captures variation in food availability before conception, during gestation, and immediately after birth, including variation in maternal and offspring nutritional status during offspring development (28). Our crop yield data reflect conditions experienced by the populations studied because they were taken from an estate within a distance (<50 km) of both of our study parishes over which spatial correlation between crop yields is high (24) and because a previous study has shown these crop data to predict mortality risk in these populations (29). Both rye and barley yields varied considerably across the birth years of our study individuals, the best yields being fourfold higher than the poorest (Fig. S1).

We first analyzed the probability of individuals aged 1–50 y at the end of 1866 surviving to the beginning of 1869 as a function of their early-life rye and barley yields (Fig. 1*A*). This year marked a return to normal crop levels and mortality rates. We used generalized linear mixed-effects models (GLMMs), with a binomial error structure and a logit link function, controlling for several confounding variables (*Materials and Methods*). In the 1860s, the mortality rate in the study populations was around 2% per year, but more than quadrupled in 1867 and 1868 in both sexes (Fig. 1*B*), and was particularly pronounced in the poorest social class (Fig. 1*C*), infants, and postreproductive adults (Fig. 1*D*). Males (n = 1,643) and females (n = 1,593) were analyzed separately because of their different life-history strategies and the documented stronger effects of the famine on male mortality rates (25).

Male survival. In males, higher early-life rye yields were associated with an increased probability of famine survival (GLMM estimate, logit scale ±1 SE: rye = 0.1083 ± 0.0603; Table 1, model 1), equivalent to an increase in survival probability of >8% when experiencing the highest early-life yields compared with the lowest. The statistically best-supported model contained an interaction between early-life rye yield and social class (Table 1, model 9), which suggested that the positive association between early-life rye yield and famine survival was stronger in poor individuals compared with rich and middle class individuals (Fig. 2*A*). Barley yields around birth were not associated with famine survival (Table 1, model 3, estimate = −0.0108 ± 0.0428). We also tested models using the mean of rye and barley yields ("crop" in Table 1) around birth to test the prediction that the total food available was a better predictor of famine survival than the specific crops; however, models with crop did not statistically improve model fit compared to those fitting rye alone.

Female survival. In females, higher early-life yields of both rye and barley were associated with higher famine survival. The association with rye (estimate = 0.1665 ± 0.0734) indicated an increase in survival probability from the lowest to the highest early-life yields of over 7% whereas the effect of barley was slightly weaker (estimate = 0.1326 ± 0.0780), with an increase in survival

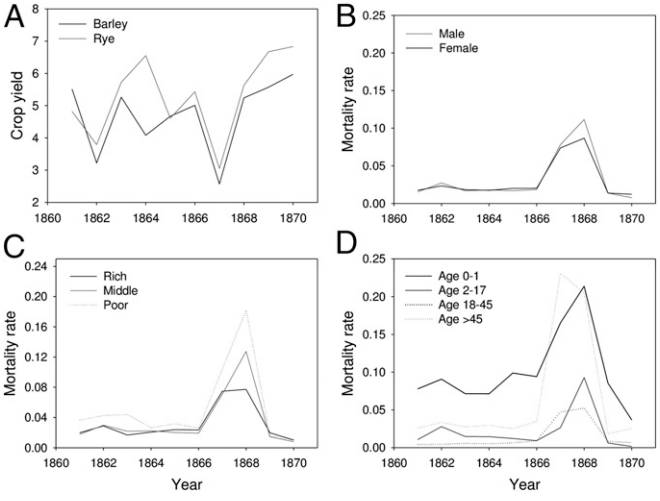

Fig. 1. Crop yields were low and mortality rates exceptionally high during the 1866–68 Finnish famine. (*A*) Variation in rye and barley yields during the 1860s, showing the mean yields from eight localities across Finland. Both rye and barley yields were at their lowest in 1867. (*B–D*) Mortality rates in Ikaalinen and Tyrvää combined through the 1860s, showing the probability of an individual dying in a given year, across (*B*) the sexes, (*C*) social classes, and (*D*) age classes.

Table 1. Statistical comparison of models investigating famine survival

	Males		Females	
Model/structure	AIC	ΔAIC	AIC	ΔAIC
0/BASE	1,362.10	0.00	1,170.33	0.00
1/BASE + Rye	1,360.67	−1.43	1,166.54	−3.79
2/BASE + Rye^2	1,361.80	−0.30	1,168.41	−1.92
3/BASE + Barley	1,364.08	1.98	1,168.68	−1.65
4/BASE + Barley^2	1,365.30	3.20	1,169.52	−0.81
5/BASE + Crop	1,362.64	0.54	***1,163.58***	***−6.75***
6/BASE + Crop^2	1,361.02	−1.08	1,165.40	−4.93
7/BASE + Rye + Barley	1,366.03	3.93	1,165.46	−4.87
8/BASE + Rye:Barley	1,363.42	1.32	1,167.11	−3.22
9/BASE + Rye:Social	***1,352.63***	***−9.47***	1,170.33	0.00
10/BASE + Rye:Age	1,362.11	0.01	**1,164.53**	**−5.80**
11/BASE + Barley:Social	1,367.91	5.81	1,170.89	0.56
12/BASE + Barley:Age	1,365.76	3.66	1,170.55	0.22
13/BASE + Crop:Social	1,359.10	−3.00	1,165.95	−4.38
14/BASE + Crop:Age	1,364.63	2.53	1,164.47	−5.86

A comparison of the generalized linear mixed-effects models (GLMMs) investigating famine survival in males and females. All models include the fixed and random effects listed in Table 2, as well as the terms shown under "structure." All ΔAIC values are shown relative to the base model (model 0), which is described in Table 2. The best-supported models for males and females are shown in bold italic type; nonnested models that also significantly improve model fit are shown in bold type.

probability of 5% in the highest versus the lowest yields. The positive associations with both crops were reflected in the positive association between survival and the combined mean crop yield, which provided the statistically best-supported model (Table 1, model 5; estimate = 0.2808 ± 0.0970), equivalent to an increase in famine survival probability from the poorest to the most favorable early conditions of over 10%. An interaction between age and rye yield statistically improved the fit of the model (Table 1, model 10 versus model 1), suggesting that higher early-life rye yield was associated with higher survival in children, but not in older age classes (Fig. 2*B*). In contrast to the results from males, there was no evidence that the effects of early-life crop yields differed between the social classes.

Famine Reproduction. Second, we investigated associations between early-life crop yields and the probability of an individual reproducing during the famine ("fertility"). Males aged 16–50 (n = 314) and females aged 16–45 (n = 275) were analyzed separately; all included individuals were married at the start of the famine because reproduction was rare outside wedlock (28). We analyzed whether or not an individual produced a child during 1867–68 using generalized linear models (GLMs) with binomial errors and a logit link function, controlling for confounding variables (*Materials and Methods*, Table S1). During the famine, fertility was markedly lower than throughout the rest of the 1860s (Fig. 3).

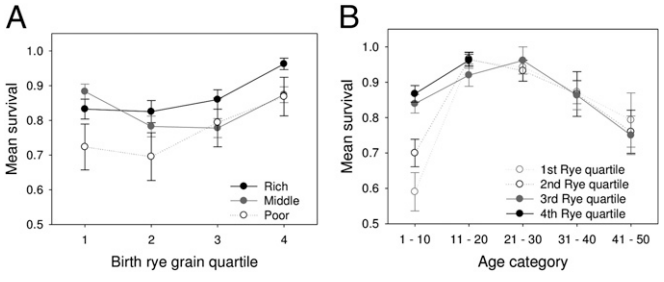

Fig. 2. The associations between natal rye grain yields and famine survival varied with social class and age in males and females, respectively. (*A*) Males in the rich and middle classes show relatively high famine survival at all levels of birth year rye yield whereas poor individuals show low famine survival at low birth year yields but relatively high survival at high yields. (*B*) In females, famine survival was independent of birth year rye yield across most ages. However, at younger ages, there was progressively higher famine survival of individuals with increasing birth year rye yield. Both age and rye yield were analyzed as continuous covariates, but data were binned for ease of interpretation. Symbols show mean survival ±1 SE.

We found no support for the prediction of the PAR hypothesis that individuals experiencing low early-life crop yields should be better able to reproduce during the famine compared to individuals experiencing high early-life crop yields. In males, none of the early-life crop effects or interactions statistically improved model fit (Table S2). The lack of an effect in males is perhaps not surprising, given the likely diminished role of nutrition in mediating male fertility, compared with the more intuitive link to female reproduction. In females, the main effect of barley yield statistically improved model fit (Table S2, model 3), and the quadratic effect of barley was a marginal statistical improvement on this (Table S2, model 4). Overall, the results suggested that higher early-life barley yield was associated with higher famine reproductive success, consistent with the prediction of the silver spoon hypothesis that later-life fitness should be positively associated with nutrition around birth (estimates: barley = 3.0481 ± 1.5083; barley^2 = −0.2476 ± 0.1345).

Discussion

In this study, we have provided an empirical test of a key prediction of the PAR hypothesis in a human population, namely, that poor early-life nutrition should be associated with higher fitness in adverse later-life conditions, compared with individuals experiencing more favorable early-life conditions (9, 19, 20). Contrary to this prediction, our results show that low early-life crop yields were associated with lower survival and reproductive success during the 1866–1868 Finnish famine, and thus our results are more consistent with silver spoon models that predict that development is constrained by poor early nutrition (22, 23). Our findings suggest that, rather than inducing the adaptive development of a phenotype suited to maximizing fitness in poor nutritional conditions in later life, poor nutritional conditions during development may limit future survival and reproduction. As such, they provide the most definitive test yet of one of the strongest predictions that can be derived from the PAR hypothesis, adding to the evidence that poor early nutrition constrains development to compromise individual fitness (21, 28, 30, 31). Our results do not support the hypothesis that developmental changes resulting from poor early nutrition are due to evolved PARs that increase individual prospects in nutrient-poor environments.

These results are robust to the inclusion of a number of confounding variables, the most important of which are differences across the social classes and age. We specifically tested the interaction between social class and crop yields to determine how the social classes may have differed in their response to famine. The lower famine survival of the poor (Table 2) and greater benefit of a high early-life crop yield to the poor (Fig. 2*A*) suggest that rich and middle class individuals were better able to avoid the adverse effects of the famine or poor early-life nutrition. Richer individuals may have maintained their health and survival by obtaining foods such as meat and fish rarely eaten by the working population (27), ensuring that those born in low-crop years experienced only a slight survival penalty. An interaction between early-life rye yield and age revealed that, whereas young females experienced a survival advantage of high early-life yields, there was no association in older females (Fig. 2*B*). This interaction could be due to the short-lived effects of low nutrition around birth, or a decrease in the frailty of the population as fewer individuals survive in the later cohorts. The fact that higher early-life rye yields were associated with higher

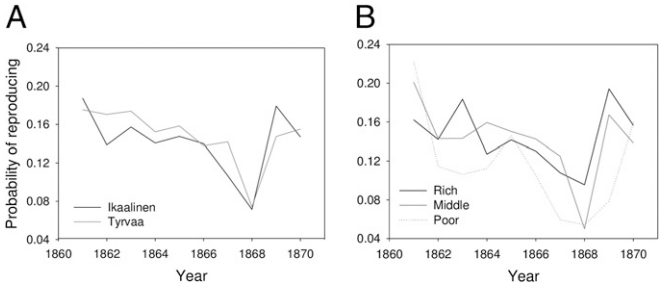

Fig. 3. Individuals in Ikaalinen and Tyrvää were less likely to produce children during the famine (1867–1868). (*A*) In both parishes, individuals were less likely to reproduce during 1868 especially. (*B*) This was particularly pronounced in the poorest social class, individuals of which also experienced lower reproductive rates during 1867.

survival of the 1- to10-y age group (Fig. 2*B*) suggests that experiencing poor early nutrition may not confer adaptive benefits for survival in poor childhood environments, as suggested by notable alternatives to the PAR model (8, 32). It has also been suggested that developing individuals may derive information about the external environment as a long-term signal that integrates many years of maternal experience, through the environment in utero (33). Finally, selection for developmental plasticity may be driven by an immediate survival advantage during early postnatal life. Results consistent with plasticity providing an early-life survival advantage were reported by a study of infants (mean age 12 mo) admitted to Jamaican hospitals with kwashiorkor, a symptom of malnutrition associated with edema but retention of some fat and protein reserves, and marasmus, a symptom characterized by a lack of edema and wasting. Individuals who responded to malnutrition with kwashiorkor experienced higher mortality and were significantly heavier at birth than those displaying marasmus, suggesting that lighter-born individuals used their energy reserves more efficiently to survive a period of malnutrition (34). These results were interpreted as evidence consistent with a short-term PAR. Our annual-based data were unable to test for such short-lived effects, and so such studies are a welcome addition to the debate (33).

Table 2. Parameter estimates for fixed and random effects in the base models of survival for males and females

	Males		Females	
Variable	Estimate	SE	Estimate	SE
Fixed effects				
Intercept	1.5791	0.2927	2.2346	0.5873
Parish (Ikaalinen)	0.0000	0.0000	—	—
Parish (Tyrvää)	0.5665	0.2287	—	—
Social class (rich)	0.0000	0.0000	0.0000	0.0000
Social class (middle)	−0.3317	0.1974	−0.7369	0.2412
Social class (poor)	−0.9035	0.2902	−0.9986	0.3296
Birth order	−0.0778	0.0332	—	—
Maternal age	—	—	−0.0265	0.0155
Age	0.1594	0.0219	0.2466	0.0269
Age^2	−0.0037	0.0005	−0.0052	0.0006
Variance components				
Maternal ID	1.0727	0.0347	1.8136	0.0453

The table lists the fixed and random effects included in the base model for famine survival of males and females. The parameter estimates are from generalized linear mixed-effects models (GLMMs) of survival with binomial errors and a logit link function; parameter estimates and SEs (SE) are on the logit scale. Nonsignificant terms are not shown and include birth status and quadratic effects of maternal age and birth order. —, indicates that a variable was not supported for either sex.

Several evolutionary arguments suggest why developmental changes in response to poor nutrition during early life are unlikely to have been favored by natural selection during human evolution. Although adaptive prediction should bestow benefits when correct, it must also incur costs when early and later conditions are mismatched (19, 20), and, in order for adaptive plasticity to be favored by selection, the benefits of correct prediction should exceed the costs of incorrect prediction. Is early-life nutrition likely to be informative about the nutritional environment several years later? This is a key question because the evolution of developmental plasticity should be favored only where there is a strong relationship between early- and late-life environments (35). It is also arguable that developmental plasticity is dependent on environmental factors that operate over specific developmental windows (26). It is for our understanding of the evolutionary origins of these effects that we consider this study to be most relevant, and about which our study raises even more questions. If we are to conclude that individuals do not make adaptations in line with a predicted adult environment, then why are effects of the developmental environment so profound? Some effects of poor nutrition may be explained as the adverse consequence of shortfalls in the basic building blocks of life (23), but the potential importance of more complex epigenetic effects such as changes in DNA methylation patterns has only recently become widely appreciated (36). They appear to be good examples of potential "programming" and the likely result of positive selection. These ideas require considerable empirical research before a definitive answer is reached, yet even without these our results suggest that the dominant evolutionary explanation that is used to account for effects of the early adverse environment (12–14) may be inappropriate. It would therefore be inadvisable to design treatments or interventions that seek to mimic the benefits of the purportedly desirable "match" between phenotype and adult environment. In the absence of strong evidence that such matches have shaped development and life history, such efforts could be detrimental to health.

In this study, the chronology of events and the extrinsic nature of the putative causal variable (early-life crop yield) suggest that it is likely that the variables measured are independent and that the associations uncovered represent causal effects on survival and reproduction during the famine. These associations may have resulted from indirect effects on maternal condition and direct effects on the availability of gruel fed to infants (37). An alternative is selection effects: cohorts suffering high mortality in their first year are subsequently comprised of only a subset of the original individuals (30), which have shown greater survival and which may be more "robust" and not representative of the original cohort. However, greater resilience of these individuals means that it is unlikely that such selection effects would have caused spurious positive associations between early-life food availability and survival. As well as within-cohort selection effects, between-cohort differences may create selection bias. Fewer individuals from older cohorts will have survived to the famine and so these individuals will be less representative of the range of variation within their cohort than are individuals from younger cohorts. In addition, there may be bias toward including individuals who experienced higher early-life crop yields if they are more likely to have survived to the famine so, once again, more robust individuals are likely to be present. Thus, both within- and between-cohort differences in frailty and potential selection bias may have reduced the magnitude of the positive associations found, and thus, if anything, our estimates of the positive effects of natal crop yields on famine survival may be conservative and the strength of silver spoon effects revealed may be underestimated.

There are several further potential caveats that must be considered when evaluating these results. The first is to ask whether crop yields are a relevant measure of nutrition. Rye and barley contributed around 80% of the energy intake of the study populations (27), and the poor transport network limited the population to food produced locally (24). Previous studies on these

populations confirm that crop yields are associated with mortality risk (29) and that early-life yields are associated with variation in fitness (28), suggesting that they have direct relevance to our study individuals. Second, some areas of the country were more adversely affected by the famine than others, and death rates were skewed by the mortality of migrants. However, our populations are in a region that experienced among the highest mortality rates (25), and our results cannot be affected by migrants because we included only individuals born in the study parishes, excluding those who migrated before 1869. The famine may also have disrupted recording of births and deaths, but it is unlikely that mistakes would be biased with respect to early-life crop yields and affect our conclusions. Third, it is necessary to consider whether the patterns observed here would apply to other populations experiencing different levels of environmental variation. Adaptive developmental plasticity may not be apparent in preindustrial Finland because of the large and unpredictable interannual variation but may be more apparent in a population in a more stable environment. As discussed above, the balance between variability and stability would need to allow accurate prediction to confer higher benefits than costs, which is unlikely in long-lived animals such as humans (19) although a fluctuating environment does not preclude the evolution of such plasticity in shorter-lived animals (38, 39).

Finally, much of the mortality during this famine and others was due to diseases rather than starvation (40). However, the synergistic negative influences of infection and poor nutritional status on morbidity and mortality (41, 42) mean that deaths from disease are inextricably linked to and modified by nutrition. The high mortality rates in the most vulnerable parts of our population (the poorest, youngest, and oldest; Fig. 1) suggest that access to resources was crucial in determining mortality risk, whether or not it was related to infectious disease. In addition, if nutrition did not contribute to mortality, the potential role of disease is an awkward issue for the PAR hypothesis more generally, aside from the results of this study. Pathogen pressure will have always been present throughout human evolution and will have mediated the effects of nutrition on mortality in all of our mammalian ancestors in whom PARs are suggested to operate and to have evolved (9).

This study uses detailed long-term data collected in a natural fertility and mortality context to investigate a neglected question in the study of the developmental origins of health and disease. By examining the evolutionary fitness consequences of variation in the developmental environment, our results provide a valuable perspective on the reasons for long-term effects of early nutritional adversity. To fully understand the epidemiology of early environmental effects on individual development, it has become increasingly recognized that we must consider exactly how evolution has shaped the human genome to respond to such circumstances (8, 12–14). Our results do not support the prediction that individuals who experience poor nutrition in early life adapt their metabolism in such a way that they are prepared for such conditions in adult life. Instead, we find that they are even less well-adapted to harsh later-life conditions. These results reinforce the findings of previous studies in pointing toward an overriding role of developmental constraint, as predicted by silver spoon models derived from evolutionary life-history theory. We urge that further consideration of the PAR hypothesis integrates the possibility of adaptation to the environment with the constraining effects that it appears to impose on survival and reproduction, the outcomes that are important in an evolutionary context. The details behind how humans and their ancestors have evolved to respond to environmental conditions are not trivial in the context of understanding the global epidemic of metabolic diseases, and even designing interventions (17, 18). Improved resolution of these details may not only give rise to more testable predictions, but also improve strategies for prevention and management of metabolic disease and other emerging health concerns.

Materials and Methods

Study Population and Data Collection. We investigated associations between food availability around birth and survival and reproductive success in a subsequent famine using a longitudinal individual-based dataset from 19th century Finnish church records. Life histories were constructed for individuals from more than 10 rural "parishes" previously used in analysis of life-history variation (43). We used data collected from the parishes of Ikaalinen and Tyrvää in Southwest Finland.

The preindustrial period in Finland ended around the 1870s; before this, the population was characterized by high birth and death rates, poor transportation, primitive agricultural technology (24), and unreliable healthcare and contraception (44). The chief causes of mortality were diseases such as smallpox, typhus, typhoid, and whooping cough (45), epidemics of which were largely independent of food availability, only coinciding occasionally (46). The populations were strictly monogamous, divorce was forbidden, and adultery punishable (47), suggesting that a very low proportion of children were born outside marriage. Women generally married in their midtwenties, and 99% of women finished reproducing by age 45 (28). Individuals were divided into three social classes, based on occupations: "wealthy" included farm owners and merchants; "middle-class" included craftsmen and tenant farmers; and "poor" included crofters and laborers (48).

Crop Yield Data. Available grain figure data series for the historical period often span only a few decades, and the spatial correlation of grain figures between locations is low beyond 100 km (24). We chose parish and crop data that maximized the range of ages included in our analyses and that were collected from proximate locations. The parishes of Ikaalinen and Tyrvää are located <50 km from Valkila, from where annual grain yield data were collected from 1804 to 1874. The short distance between our study parishes and the estates where crop data were collected ensures that our grain figures accurately reflect conditions experienced by our study population (24), as does the established association between variation in crop yields and immediate individual mortality risk (29).

Statistical Analysis. ***Famine survival.*** We analyzed the probability of an individual alive at the end of 1866 surviving to the start of 1869, which marked a return to normal crop levels and mortality rates (Fig. 1), as a function of rye and barley yields around their birth. We took 3-y running means of crop yields centered on the year of birth, capturing variation in food availability before conception, during gestation, and immediately postpartum (28). Previous studies have shown associations between conditions in specific trimesters of pregnancy and later-life health (26). Using our annual data, we were unable to separate out these periods or pre- from postnatal conditions and therefore chose to capture both pre- and postnatal variation simultaneously. Although this method may miss adaptations to conditions occurring at specific sensitive periods, it is unlikely that this lack of precision would lead to biased estimates of the association between early nutrition and subsequent fitness.

All individuals were born in Ikaalinen or Tyrvää between1816 and 1865 and were 1–50 y old in 1866. Individuals who migrated to another parish before 1869 were excluded from analysis, but individuals migrating in 1869 or later were retained. We analyzed the survival of 1,643 males and 1,593 females alive in 1866 to the beginning of 1869 as a binomial trait (1 = survived, 0 = died) using generalized linear mixed-effects models (GLMMs) with a logit link function in the R package "lme4." We included maternal identity as a random effect to account for family-level variation in survival rates. We added fixed effects potentially associated with survival, including study parish and father's social class (rich, middle, and poor), as fixed factors, measured at the same time as crop yield around birth. We also included birth status (singleton or twin) as a fixed factor, because twins show lower survival rates (44), and birth order, maternal age (49), and individual age at the end of 1866 as linear and quadratic covariates. We tested the significance of these variables by dropping them sequentially from GLMMs of survival and comparing them using Akaike's Information Criterion (AIC) values, retaining only those terms that increased model AIC by >2 when dropped.

Significant terms were retained in "base models" for males and females separately. We then added rye and barley yields around birth and interactions with age and social class. We also tested models including the mean of rye and barley yields (referred to as "crop"), to test whether overall food availability, rather than a specific crop, was the strongest predictor of famine survival. We tested interactions between grain yields and age, to investigate whether effects were stronger in young individuals, and between grain yields and social class, to test the prediction that the poorest

individuals were most strongly affected by early conditions. Once again, we selected the best models for males and females by comparing model AIC values. Separate analysis of males and females was performed, due to biological and social differences outlined above and to allow us to fit these interactions in both sexes, avoiding fitting three-way interactions including sex.

We also repeated the survival models in adults only because the PAR hypothesis explicitly suggests that prediction should be selected for through adult fitness (9). Our main analysis, which included all ages, tested for benefits across life, including childhood, as predicted by alternative versions of the PAR (8). Analysis of adults revealed no evidence in support of higher famine survival in those experiencing lower early-life crop yields (Table S3, Fig. S2). There were fewer significant associations between early-life crop yields and famine survival in adults compared with where all ages were analyzed simultaneously, potentially because the fitness benefits of adaptations to poor early conditions were stronger in childhood, or potentially because of reduced ability to detect significant associations due to our smaller sample size when analyzing adults only (Table S3).

Reproductive success. We also analyzed the probability of 314 males and 275 females reproducing during the famine as a function of early-life crop yields. Males (up to age 50) and females (up to age 45) were analyzed separately: at these ages, most individuals have finished reproducing. All individuals were married at the start of the famine. Social class was assigned to males based on their occupation, and in females on the basis of their husband's occupation (48).

For both males and females, we constructed a base model including the same fixed effects as for survival, adding a factor indicating whether or not an individual had produced a child in the 2 y before the famine and a covariate indicating the number of live children produced by 1866. We analyzed whether or not an individual produced a child during 1867 or 1868 as a binomial trait using generalized linear models (GLMs) with a logit link function (0 = did not reproduce; 1 = produced at least one child; only 12 females and 17 males produced more than one). We initially ran GLMMs including maternal identity as a random effect, but the maternal effect accounted for almost zero variance in fertility and so was dropped from all models. The base model was selected as described above. The same grain yield models were compared, with the best model selected using AIC values.

ACKNOWLEDGMENTS. We thank the editor and three anonymous reviewers for comments that greatly improved the quality of the manuscript; Kimmo Pokkinen, Lasse Iso-Iivari, and Jenni Pettay for collecting parish data; and Jari Holopainen for collating crop yield data. This research was funded by the European Research Council, the Natural Environment Research Council, and a Royal Society University Research Fellowship (to V.L.).

1. Barker DJP (1998) *Mothers, Babies and Health in Later Life* (Churchill Livingston, Edinburgh).
2. Bateson P, et al. (2004) Developmental plasticity and human health. *Nature* 430(6998):419–421.
3. McMillen IC, Robinson JS (2005) Developmental origins of the metabolic syndrome: Prediction, plasticity, and programming. *Physiol Rev* 85(2):571–633.
4. Barker DJP, et al. (1993) Fetal nutrition and cardiovascular disease in adult life. *Lancet* 341(8850):938–941.
5. Hales CN, Barker DJ (1992) Type 2 (non-insulin-dependent) diabetes mellitus: The thrifty phenotype hypothesis. *Diabetologia* 35(7):595–601.
6. Michels KB, et al. (1996) Birthweight as a risk factor for breast cancer. *Lancet* 348(9041):1542–1546.
7. Gluckman PD, Hanson MA, Buklijas T, Low FM, Beedle AS (2009) Epigenetic mechanisms that underpin metabolic and cardiovascular diseases. *Nat Rev Endocrinol* 5(7): 401–408.
8. Bateson P (2001) Fetal experience and good adult design. *Int J Epidemiol* 30(5): 928–934.
9. Gluckman PD, Hanson MA (2004) Living with the past: Evolution, development, and patterns of disease. *Science* 305(5691):1733–1736.
10. West-Eberhard MJ (2003) *Developmental Plasticity and Evolution* (Oxford Univ Press, Oxford).
11. Hales CN, Barker DJP (2001) The thrifty phenotype hypothesis. *Br Med Bull* 60(1):5–20.
12. Khan I, Dekou V, Hanson M, Poston L, Taylor P (2004) Predictive adaptive responses to maternal high-fat diet prevent endothelial dysfunction but not hypertension in adult rat offspring. *Circulation* 110(9):1097–1102.
13. Bol V, Desjardins F, Reusens B, Balligand J-L, Remacle C (2010) Does early mismatched nutrition predispose to hypertension and atherosclerosis, in male mice? *PLoS ONE* 5(9):e12656.
14. Kemp MW, Kallapur SG, Jobe AH, Newnham JP (2012) Obesity and the developmental origins of health and disease. *J Paediatr Child Health* 48(2):86–90.
15. Gluckman PD, Hanson MA (2006) *Mismatch: Why Our World No Longer Fits Our Bodies* (Oxford Univ Press, Oxford).
16. Eckel RH, Grundy SM, Zimmet PZ (2005) The metabolic syndrome. *Lancet* 365(9468): 1415–1428.
17. Popkin BM, Adair LS, Ng SW (2012) Global nutrition transition and the pandemic of obesity in developing countries. *Nutr Rev* 70(1):3–21.
18. Vickers MH (2011) Developmental programming of the metabolic syndrome: Critical windows for intervention. *World J Diabetes* 2(9):137–148.
19. Rickard IJ, Lummaa V (2007) The predictive adaptive response and metabolic syndrome: Challenges for the hypothesis. *Trends Endocrinol Metab* 18(3):94–99.
20. Wells JC (2012) A critical appraisal of the predictive adaptive response hypothesis. *Int J Epidemiol* 41(1):229–235.
21. Krause ET, Honarmand M, Wetzel J, Naguib M (2009) Early fasting is long lasting: Differences in early nutritional conditions reappear under stressful conditions in adult female zebra finches. *PLoS ONE* 4(3):e5015.
22. Grafen A (1988) On the uses of data on lifetime reproductive success. *Reproductive Success*, ed Clutton-Brock TH (Univ of Chicago Press, Chicago), pp 454–471.
23. Monaghan P (2008) Early growth conditions, phenotypic development and environmental change. *Philos Trans R Soc Lond B Biol Sci* 363(1497):1635–1645.
24. Holopainen J, Helama S (2009) Little Ice Age farming in Finland: Preindustrial agriculture on the edge of the Grim Reaper's scythe. *Hum Ecol* 37(2):213–225.
25. Pitkänen KJ, Mielke JH (1993) Age and sex differentials in mortality during two nineteenth century population crises. *Eur J Popul/Rev Eur Démogr* 9(1):1–32.
26. Painter RC, Roseboom TJ, Bleker OP (2005) Prenatal exposure to the Dutch famine and disease in later life: An overview. *Reprod Toxicol* 20(3):345–352.
27. Vihola T (1994) Mitä ihminen tarvitsi elääkseen [What man needed to stay alive]. *Pane Leipään Puolet Petäjäistä: Nälkä ja Pulavuodet Suomen Historiassa* [*Mix Half of Bread with Pine Bark: Hunger and the Years of Crisis in the History of Finland*], ed Karonen P (Univ of Jyväskylä, Jyväskylä, Finland), pp 83–92.
28. Rickard IJ, et al. (2010) Food availability at birth limited reproductive success in historical humans. *Ecology* 91(12):3515–3525.
29. Hayward AD, Holopainen J, Pettay JE, Lummaa V (2012) Food and fitness: Associations between crop yields and life-history traits in a longitudinally monitored preindustrial human population. *Proc R Soc Lond B* 279(1745):4165–4173.
30. Doblhammer-Reiter G, van den Berg GJ, Lumey LH (2011) Long-term effects of famine on life expectancy: A re-analysis of the Great Finnish Famine of 1866–1868 (Institute for the Study of Labor, Bonn, Germany), IZA Discussion Paper No. 5534.
31. Hayward AD, Lummaa V (2013) Testing the evolutionary basis of the predictive adaptive response hypothesis in a preindustrial human population. *Evolution, Medicine and Public Health* 1:106–117.
32. Wells JCK (2003) The thrifty phenotype hypothesis: Thrifty offspring or thrifty mother? *J Theor Biol* 221(1):143–161.
33. Kuzawa CW, Quinn EA (2009) Developmental origins of adult function and health: Evolutionary hypotheses. *Annu Rev Anthropol* 38(1):131–147.
34. Forrester TE, et al. (2012) Prenatal factors contribute to the emergence of kwashiorkor or marasmus in severe undernutrition: Evidence for the predictive adaptation model. *PLoS ONE* 7(4):e35907.
35. Nettle D, Frankenhuis WE, Rickard IJ (2013) The evolution of predictive adaptive responses in human life history. *Proc R Soc Lond B* 280:20131343.
36. Beldade P, Mateus ARA, Keller RA (2011) Evolution and molecular mechanisms of adaptive developmental plasticity. *Mol Ecol* 20(7):1347–1363.
37. Moring B (1998) Motherhood, milk, and money: Infant mortality in pre-industrial Finland. *Soc Hist Med* 11(2):177–196.
38. Lee TM, Zucker I (1988) Vole infant development is influenced perinatally by maternal photoperiodic history. *Am J Physiol* 255(5 Pt 2):R831–R838.
39. van den Heuvel J, et al. (2013) The predictive adaptive response: Modeling the life-history evolution of the butterfly *Bicyclus anynana* in seasonal environments. *Am Nat* 181(2):E28–E42.
40. Anderson TJC, Zizza CA, Leche GM, Scott ME, Solomons NW (1993) The distribution of intestinal helminth infections in a rural village in Guatemala. *Mem Inst Oswaldo Cruz* 88(1):53–65.
41. Scrimshaw NS (2000) Infection and nutrition: synergistic interactions. *The Cambridge World History Of Food*, eds Kiple KF, Ornelas KC (Cambridge Univ Press, Cambridge, UK), pp 1397–1411.
42. Beldomenico PM, et al. (2008) Poor condition and infection: A vicious circle in natural populations. *Proc Biol Sci* 275(1644):1753–1759.
43. Lummaa V, Lemmetyinen R, Haukioja E, Pikkola M (1998) Seasonality of births in Homo sapiens in pre-industrial Finland: Maximisation of offspring survivorship? *J Evol Biol* 11(2):147–157.
44. Lummaa V, Jokela J, Haukioja E (2001) Gender difference in benefits of twinning in pre-industrial humans: Boys did not pay. *J Anim Ecol* 70(5):739–746.
45. Turpeinen O (1978) Infectious diseases and regional differences in Finnish death rates, 1749-1773. *Popul Stud (Camb)* 32(3):523–533.
46. Turpeinen O (1973) Regional differentials in Finnish mortality rates 1816–1865. *Scand Econ Hist Rev* 21(2):145–163.
47. Sundin J (1992) Sinful sex: Legal prosecution of extramarital sex in preindustrial Sweden. *Soc Sci Hist* 16(1):99–128.
48. Pettay JE, Helle S, Jokela J, Lummaa V (2007) Natural selection on female life-history traits in relation to socio-economic class in pre-industrial human populations. *PLoS ONE* 2(7):e606.
49. Gillespie DOS, Russell AF, Lummaa V (2013) The effect of maternal age and reproductive history on offspring survival and lifetime reproduction in preindustrial humans. *Evolution* 67(7):1964–1974, 10.1111/evo.12078.

Supporting Information

Hayward et al. 10.1073/pnas.1301817110

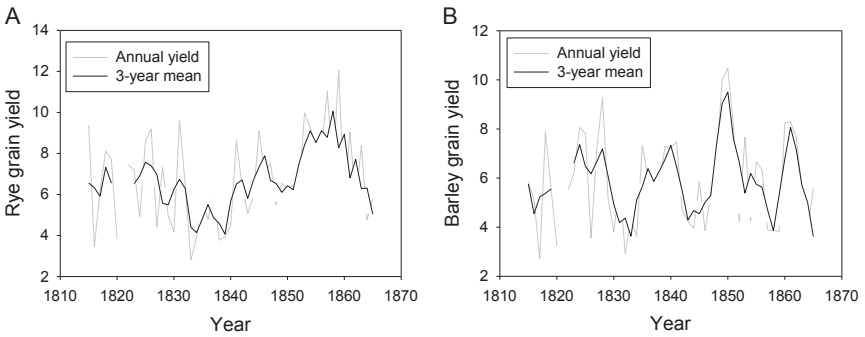

Fig. S1. Annual variation in crop grain yields at Valkila, 1815–1865. The yields of rye and barley varied considerably during the years in which individuals in the data used for the study were born. *A* and *B* show rye and barley yields, respectively, with the 3-y mean used in the analyses (black lines) calculated from the annual yields (gray lines).

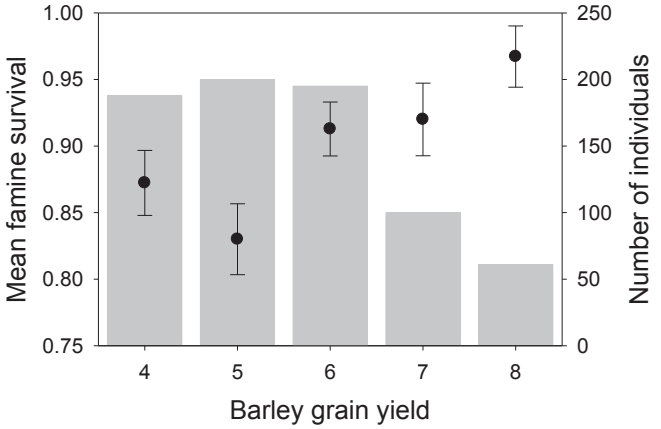

Fig. S2. Association between birth year barley yield and famine survival in adult females. When considered separately from females aged 15 and under, there was a positive association between birth year barley yield and survival of the famine in adult females (Table S2). Note that this effect was also present when all females were analyzed together (model 3 in Table 2). Filled circles show mean famine survival across barley yield ±1 SE; gray columns show the sample size in each bin of barley yield.

Table S1. Parameter estimates for fixed effects in the base models of reproductive success

	Males		Females	
Variable	Estimate	SE	Estimate	SE
Intercept	−0.6383	3.4010	4.1233	0.7439
Maternal age	−0.0672	0.0282	—	—
Birth order	0.1563	0.0761	—	—
Previous reproduction	—	—	−0.8332	0.2940
Children alive	0.3977	0.1213	0.3687	0.1149
Age	0.2257	0.1958	−0.1256	0.0219
Age^2	−0.0048	0.0027	—	—

The table lists the fixed and random effects included in the base model for famine reproductive success of both sexes. The parameter estimates are from generalized linear mixed-effects models (GLMMs) of reproductive success with binomial errors and a logit link function; parameter estimates and SEs are shown on the logit scale. Terms that were not supported for either sex are not shown. —, indicates that a variable was not supported in a given sex.

Table S2. Statistical comparison of models investigating famine reproductive success

		Males		Females	
Model	Structure	AIC	ΔAIC	AIC	ΔAIC
0	BASE	***379.89***	***0.00***	345.23	0.00
1	BASE + rye	381.85	1.96	347.20	1.97
2	BASE + rye^2	383.63	3.74	348.79	3.56
3	BASE + barley	381.57	1.68	**342.68**	**−2.55**
4	BASE + barley^2	381.17	1.28	***341.21***	***−4.02***
5	BASE + crop	381.81	1.92	345.06	−0.17
6	BASE + crop^2	382.37	2.48	346.91	1.68
7	BASE + rye + barley	383.46	3.57	344.68	−0.55
8	BASE + rye:barley	384.79	4.90	346.66	1.43
9	BASE + rye:social	—	—	350.54	5.31
10	BASE + rye:age	383.85	3.96	348.55	3.32
11	BASE + barley:social	—	—	346.37	1.14
12	BASE + barley:age	383.18	3.29	344.64	−0.59
13	BASE + crop:social	—	—	348.50	3.27
14	BASE + crop:age	383.57	3.68	347.06	1.83

A comparison of the generalized linear models (GLMs) investigating famine reproductive success in males and females. All models include the fixed effects listed in Table S1, as well as the terms shown under "Structure." ΔAIC values are shown relative to the base model (model 0) described in Table S1. The best-supported models for males and females are shown in bold italic type; the model shown in bold type for females is a more parsimonious model because the ΔAIC between the model with barley^2 and barley is 1.47.

Table S3. Statistical comparison of models investigating famine survival of adult males and females

		Males		Females	
Model	Structure	AIC	ΔAIC	AIC	ΔAIC
0	BASE	***644.43***	***0.00***	501.64	1.79
1	BASE + rye	646.12	1.69	501.65	1.80
2	BASE + rye^2	647.81	3.38	502.38	2.53
3	BASE + barley	646.27	1.84	***499.85***	***0.00***
4	BASE + barley^2	647.91	3.48	501.61	1.76
5	BASE + crop	646.02	1.59	503.1	3.25
6	BASE + crop^2	644.87	0.44	504.24	4.39
7	BASE + rye + barley	647.99	3.56	499.92	0.07
8	BASE + rye:barley	644.04	−0.39	501.52	1.67
9	BASE + rye:social	649.16	4.73	505.64	5.79
10	BASE + rye:age	646.77	2.34	503.65	3.80
11	BASE + barley:social	648.88	4.45	502.66	2.81
12	BASE + barley:age	648.1	3.67	501.08	1.23
13	BASE + crop:social	648.16	3.73	506.39	6.54
14	BASE + crop:age	647.82	3.39	502.66	2.81

A comparison of the generalized linear models (GLMs) investigating survival of the famine in adult males (n = 768) and females (n = 744) aged >15. All models include the fixed effects listed in Table 2 of the main text, as well as the terms shown under "Structure." ΔAIC values are shown relative to the base model (model 0). The best-supported model for each sex is shown in bold italic type. These results are discussed in relation to the results for males and females of all ages in the main text.