Title
Natural selection
in utero
induced by mass layoffs: the hCG evidence

Permalink
https://escholarship.org/uc/item/6332t5qh

Journal
Evolutionary Applications, 5(8)

ISSN
17524571

Authors
Catalano, Ralph
Margerison-Zilko, Claire
Goldman-Mellor, Sidra
et al.

Publication Date
2012-12-01

DOI
10.1111/j.1752-4571.2012.00258.x

Copyright Information
This work is made available under the terms of a Creative Commons Attribution License, availalbe at [https://creativecommons.org/licenses/by/4.0/](https://creativecommons.org/licenses/by/4.0/)

Peer reviewed
**Natural selection in utero induced by mass layoffs: the hCG evidence**

Ralph Catalano, 1 Claire Margerison-Zilko, 1 Sidra Goldman-Mellor, 1 Michelle Pearl, 2 Elizabeth Anderson, 1 Katherine Saxton, 1 Tim Bruckner, 3 Meenakshi Subbaraman, 1 Julia Goodman, 1 Mollie Epstein, 1 Robert Currier 2 and Martin Kharrazi 2

1 School of Public Health, University of California, Berkeley, CA, USA
2 Genetic Disease Screening Program, California Department of Public Health, Richmond, CA, USA
3 Departments of Public Health and Planning, Policy and Design, University of California, Irvine, CA, USA

**Abstract**

Evolutionary theory, when coupled with research from epidemiology, demography, and population endocrinology, suggests that contracting economies affect the fitness and health of human populations via natural selection in utero. We know, for example, that fetal death increases more among males than females when the economy unexpectedly contracts; that unexpected economic contraction predicts low secondary sex ratios; and that males from low sex ratio birth cohorts live, on average, longer than those from high sex ratio cohorts. We also know that low levels of human chorionic gonadotropin (i.e., hCG) measured in the serum of pregnant women predict fetal death. We do not, however, know whether male survivors of conception cohorts subjected to contracting economies exhibit, as theory predicts, higher hCG than those from other cohorts. We show, in 71 monthly conception cohorts including nearly two million California births, that they do. We thereby add to the literature suggesting that the economy, a phenomenon over which we collectively exercise at least some control, affects population health. Our findings imply that the effect arises via natural selection – a mechanism we largely ignore when attempting to explain, or alter, how collective choice affects our biology.

**Introduction**

Natural selection has conserved mechanisms that spontaneously abort gestations that would otherwise yield relatively few grandchildren per unit of maternal investment (Trivers and Willard 1973; Stearns 1987; Forbes 1997; Möller 1997; Baird 2009). This selection in utero presumably contributes to the fitness of the population by keeping women from investing in less fit, while leaving them available to conceive fitter, offspring.

Selection in utero assumes that gestation somehow signals fetal fitness, that this signal must exceed some criterion to avoid spontaneous abortion, and that women autonomically raise that criterion when they encounter stressful environments that threaten their well-being and that of their less hardy children (Trivers and Willard 1973; Forbes 1997; Wells 2000; Catalano and Bruckner 2006). Selection in utero implies, therefore, that gestations just above the criterion in benign times would end in more stressful times.

Few historical data describe fitness of human gestations, but available records show that women who disproportionate bore sons and lived in areas with highly variable weather had fewer grandchildren than women who disproportionately bore daughters (Gabler and Voland 1994; Lummaa 2001). The relatively low fitness of sons in these stressful environments arose, primarily, from the high likelihood of death among young males. The death rate among male infants even now exceeds that of any other male or female age group under reproductive age and has done so in all societies and all years for which we have dependable data (Human Mortality Database 2010). This frailty among male infants persists despite the fact that mothers invest more energy in them...
than in daughters (Clutton-Brock 1991; Helle et al. 2002; Powe et al. 2010). The low return in grandsons on maternal investment in sons would put gestations of males disproportionately near the criterion for spontaneous abortion.

Evidence of male preponderance among fetuses just above the criterion for spontaneous abortion includes that stressful times increase the ratio of male to female fetal deaths (Catalano et al. 2005). The ratio of male to female live births (i.e., the secondary sex ratio), moreover, reportedly falls in stressful times, with few exceptions (e.g., Stein et al. 2003), below that from cohorts in gestation during more benign times (Lyster 1974; Fukuda et al. 1998; Catalano 2003; Kemkes 2006; Catalano et al. 2008, 2009a; Saadat 2008; Helle et al. 2009). And males in low sex ratio birth cohorts exhibit lower infant mortality rates (Catalano et al. 2009b) and live longer (Catalano and Bruckner 2006; Bruckner and Catalano 2007, 2011) than those from other cohorts.

Further evidence of the near-criterion position of male fetuses comes from population endocrinology. As noted above, selection in utero requires that a gestation signal fitness to the mechanisms that spontaneously terminate pregnancy. Research suggests a complex, perhaps redundant, set of signals that vary over the course of gestation (Vigano et al. 2003; Erlebacher 2010; Sales et al. 2011). As noted by Haig (1993), Møller (1997), Forbes (2005), and Baird (2009), however, a relatively low level of gestational human chorionic gonadotropin (hCG) in maternal serum predicts spontaneous abortion better than other candidate signals (Dugoff et al. 2004; Goetzl et al. 2004; Cole 2010; Jelliffe-Pawlowski et al. 2010; Kirkegaard et al. 2011). Consistent with the assumption that male fetuses disproportionately rank low on fitness, gestations of males yield endemically lower hCG levels in maternal serum than those of females (Yaron et al. 2001; Cowans et al. 2009).

The robust correlation between low gestational hCG and spontaneous abortion has led to the suspicion that the hormone plays a role in sustaining pregnancies and may induce, rather than signal, fitness. Clinical trials have not supported this suspicion (Devaseelan et al. 2010).

The epidemiologic literature identifies at least one population stressor that intuition suggests should trigger selection in utero against gestations with low signals of fitness: mass layoffs (Catalano et al. 2010b). The U.S. Department of Labor defines mass layoff events as ‘fifty or more initial claims for unemployment insurance (UI) benefits filed against an employer during a 5-week period’ (Malley and Moutos 1996) and records UI claims resulting from these events as ‘mass layoff UI claims.’

Research reports elevated risk of stress-induced anxiety and subclinical depression among workers who lose their jobs (Dooley and Catalano 1980; Kessler et al. 1987; Conger et al. 1994; Catalano et al. 2010a). These losses appear to increase the risk of job losers and their families experiencing other adverse life events presumed to induce the stress response (Catalano et al. 1987; Rook et al. 1991; Vinokur et al. 1996). The widening ripples induced in the community by unexpected job losses include contagion-like increases in the stress of feared job loss (Leigh 1985; Liem and Liem 1988; Rook et al. 1991; Dua and Smyth 1993; Larson et al. 1994; Minchin 2009).

Consistent with the intuitive connection between the population stress induced by mass layoffs and selection in utero, the sex ratio of fetal deaths reportedly becomes more male biased, and the secondary sex ratio declines, when mass layoffs and joblessness increase above statistically expected levels (Catalano et al. 2005; Catalano et al. 2010b).

In sum, evolutionary theory, as well as empirical evidence from epidemiology, demography, and population endocrinology all lead to the suspicion that contracting economies affect the composition and fitness of contemporary human populations via selection in utero against males with low signals of fitness. We do not, however, know whether male survivors of gestational cohorts subjected to contracting economies exhibit higher hCG than those from other cohorts as we would expect if selection in utero terminated more low than high hCG gestations. We contribute to the literature by testing this expectation.

Our test requires that we specify which conception cohorts would most likely lose male fetuses when monthly mass layoffs exceed expected levels. The literature on fetal loss suggests that selection against less fit male fetuses may extend later in gestation than that against females. An estimated 25% of implanted (i.e., hCG-producing) gestations end within 6 weeks of implantation (Wilcox et al. 1999; Jukic et al. 2011). Female fetuses with chromosomal abnormalities predominate among these early abortuses (Evdokimova et al. 2000; Boklage 2005). At least 20% of the remaining pregnancies spontaneously abort even among young, healthy women in high-income societies with universal health care (Buss et al. 2006). Males predominate among these later losses (Evdokimova et al. 2000; Boklage 2005) in which chromosomal abnormalities appear less frequently than in the earlier losses.

Gestation, particularly of males, exhibits a critical window for selection between the 18th and 24th week when the risk of spontaneous abortion rises above the generally downward trend that begins after the 6th week of pregnancy (Goldhaber and Fireman 1991; Baird 2009). Consistent with selection in utero, males with low hCG and less robust reaction to exogenous stimuli predominate.
among these later losses. Clinical research reports that fetuses begin to exhibit the stress response to invasive therapeutic procedures at approximately the 18th week of gestation (Giannakouloupolos et al. 1994, 1999; Marcus et al. 1999; Gitau et al. 2001; Myers et al. 2004). Basic research reports, moreover, that maturation of sensory mechanisms allows fetal cardiac response to, for example, sound in the mother’s environment around the 24th week of gestation (Lecanuet and Schaal 1996). Yet more research finds that motor activity appears greater among male than female fetuses but peaks for both in our critical period (i.e., late 2nd and early 3rd trimesters) and then decreases (Almli et al. 2001).

The literature described above suggests, and we test, the hypothesis that male infants in the 18th to 24th weeks of gestation when mass layoffs exceed expected values will exhibit levels of gestational hCG greater than expected from potentially confounding characteristics of their conception cohort, from levels among female infants in the same conception cohort, and from levels among male infants in earlier cohorts. The test uses data describing approximately 2 million infants conceived in California from May 2001 through March 2007.

Materials and methods

Data

hCG Data

All women in prenatal care by the 140th day of gestation have, by law, the opportunity to participate in California’s Genetic Disease Screening Program (GDSP). The program assesses the risk of chromosomal abnormalities using several blood analytes, including maternal serum hCG. GDSP contracts with regional laboratories to analyze blood samples from women who opt for testing. The laboratories follow a uniform assay protocol that uses an automated analytical system (Cunningham and Tompkinson 1999; Kazerouni et al. 2009).

We linked the hCG scores from the prenatal screening program with data from the California Department of Public Health birth registry for the years 2001–2007. The probabilistic linking procedure used combinations of mother’s/father’s/child’s names (first two letters, NYSIIS phonetic codes, and whole names), mother’s social security number, street address, phone numbers, residential ZIP code, mother’s birth date (year only and whole dates), date and time of birth, and birth facility.

For our dependent variable, we calculated median levels of maternal serum hCG (measured in international units per liter), assayed in the 14th through 21st weeks of gestation, among live born males from each of the 71 monthly cohorts conceived from May 2001 through March 2007. We used gestational age, derived primarily from ultrasound tests, to assign pregnancies to month of conception. If ultrasound results were not available, gestational age was estimated from the date of last menstrual period or physical exam (Dietz et al. 2007; Pearl et al. 2007). We included only singleton gestations in the study because conventions for assigning gestational hCG to survivors of multiple gestations have not been set, maternal serum screening of multiple gestations appears much less common than for singleton gestations (53% compared to 65%), and sex-specific selection in utero among twins appears different than that among singletons (Catalano et al. 2009a).

Mass Layoffs

We retrieved the number of UI claims resulting from mass layoffs in California for our test period from the US Department of Labor website (Unites States Department of Labor 2011). We assume, based on the literature (Cobb and Kasl 1977; Malley and Moutos 1996; Carroll 2003), that the announcement of intended mass layoffs gauges the degree to which the larger population perceives a threat to its economic security. Firms are legally required to notify workers of mass layoffs 60 days before the layoff occurs. We therefore consider mass layoff UI claims as indicators of stress on the population 2 months prior to the actual claims.

We needed 9 months of UI claims from mass layoffs for each conception cohort to estimate coefficients for exposure through 9 months of gestation. Our first cohort was conceived in May 2001 and our last in March 2007. We, therefore, retrieved mass layoffs for 79 months (i.e., from May 2001 through November 2007) to cover gestation of our 71 conception cohorts.

Covariates

Our test equation included nine covariates. First, we included the median female hCG score for each of the 71 cohorts. Including this covariate ensures that no measurement artifact (e.g., changes in assay kits) or any confounder that similarly affects both male and female gestations will induce inferential errors in test. Because hCG levels vary over gestation, we also included mean gestational age, in days, at time of maternal blood draw for each conception cohort. We included percentage of insulin-dependent mothers of male fetuses in each cohort because the literature reports correlations between maternal diabetes and hCG (Merviel et al. 2001). We, in addition, included mean maternal weight at time of the hCG test and mean maternal age at birth for mothers of males in each cohort. The test equation also included cohort percentage of mothers reporting Hispanic, non-Hispanic white, non-Hispanic African American, and Asian American race or ethnicity.
Analyses

Consistent with the literature alluded to in the Introduction, we argue that cohorts of male infants exposed to greater-than-expected mass layoff announcements in approximately the 18th through 24th weeks of gestation will exhibit higher levels of gestational hCG than other cohorts. Because of the 2 month delay between mass layoff announcements and mass layoff UI claims, and because we cannot know when in a month conceptions began, or when layoffs were announced, we define exposed cohorts as those conceived 7 or 8 months before unexpectedly high levels of monthly mass layoff UI claims. We arrive at this window by adding 8.6 weeks (i.e., 60 days divided by 7) to the 18 weeks that start the critical period and the 24 weeks that end it. This leaves the span of 26.6–32.6 weeks. Dividing these by the 4.2 weeks in a typical month yields the window of 6.33–7.76 months. Our exposure period, therefore, starts approximately the second week of the 7th month of gestation and ends approximately in the last week of the 8th month.

Statistical tests of association essentially measure the degree to which two variables differ from their expected values in the same cases. The tests typically assume that the expected value of any observation is the mean of all observations. Variables measured over time, however, often violate this assumption because they exhibit ‘autocorrelation’ in the form of secular trends, cycles, or the tendency to remain elevated or depressed, or to oscillate, after high or low values. The expected value of an observation in such a series is not the mean of all observations but rather the value predicted by autocorrelation.

We used Box-Jenkins modeling to detect and model autocorrelation in our independent and, after adjusting for covariates, dependent variable (Box et al. 1994). More specifically, we tested our hypotheses through the following steps.

1. We used Box-Jenkins routines to decompose the number of mass layoff UI claims, measured in 1,000s, in California from March 2001 through December 2007 into statistically expected and residual (i.e., observed minus expected) values.

2. We regressed median male hCG scores among live births in each of the 71 conception cohorts on the nine covariates described above.

3. We applied Box-Jenkins routines to the residuals of the model estimated in Step 2 to detect autocorrelation. We added autoregressive and moving average parameters as needed to the model estimated in step 2 to ensure that the final residuals had a constant mean of 0, constant variance, and exhibited no autocorrelation.

4. We estimated the equation formed by adding, as a predictor variable, the residual values derived in Step 1 to the model developed in Steps 2 and 3. We aligned the data such that male cohort hCG was predicted from the UI claim residuals at the first through ninth month of gestation. Our theory predicts the coefficient for exposure at either or both the 7th or 8th month of gestation will be significantly ($P < 0.05$, 2-tailed test) < 0.

Results

Approximately 65% of live births linked to prenatal screening records, yielding 2,057,433 singleton births. Table I compares live births from the screened gestations with all births in the test years. The groups appear similar although the screened group had a lower proportion of older women and a higher proportion of privately insured women. These differences probably result from older women being referred directly for amniocentesis rather than for the blood screening test, and uninsured women less frequently obtaining prenatal care and therefore less likely receiving any screening.

Step 1 above, using Box-Jenkins routines to decompose mass layoff UI claims into statistically expected and residual components, yielded the values plotted in Fig. 1. The following Box-Jenkins model best fits the UI series.

$$\nabla_3 Y_t = \left( \frac{1}{1 - \phi B^3} \right) \epsilon$$

$Y_t$ is the number of mass layoff UI claims in month t. $\nabla_3$ is the difference operator indicating that $Y$ at month t was subtracted from $Y$ at month t + 3 to remove strong quarterly autocorrelation (i.e., high or low values at month t followed by similarly high or low values 3 months later). $\phi B^3$ is an autoregressive parameter indicating that a quarterly ‘memory’ remained in the series even after difference at 3 months. The estimated value of $\phi$ (i.e., .57; SE = 0.0998) suggested that this memory decreased geometrically by about 50% with the passage of each quarter.

Steps 2 and 3, regressing the median male hCG scores in the 71 conception cohorts on the nine covariates and adjusting residuals for autocorrelation, yielded the expected values shown in Fig. 2. The covariates model in Table I shows the coefficients estimated in this adjustment and their standard errors. Table I also shows that we detected and modeled autocorrelation in which high or low median levels of hCG among males repeated, adjusting for covariates, with similar, but smaller, high or low values 16 months later. This pattern implies that we could not predict hCG for cohorts conceived before
Our final test, therefore, used 55 cohorts conceived from September 2002 through March 2007.

Step 4, adding the unexpected mass layoff UI claims derived in step 1 to the model resulting from step 3, yielded the results shown in Table 2. Consistent with our argument, the cohorts of male infants conceived 8 months prior to unexpectedly high levels of claims exhibited higher median hCG levels than expected from history and from the specified covariates. Figure 3 shows a scatter plot and regression line for male cohort hCG, adjusted for covariates and autocorrelation, and unexpected mass layoff claims in the 8th month of gestation.

We conducted several additional tests to estimate the robustness of our findings. First, we transformed the dependent variable to natural logarithms to determine whether variability in variation could have induced our results. The findings did not change. In a related test, we applied the routines that detect and control outliers in the dependent variable (Chang et al. 1988). We detected no outliers. We also used the routines that iteratively ‘pare’ statistically nonsignificant ($P > 0.05$; 2-tailed test) covariates from the final model (Liu and Hudak 1992). This routine left only median female hCG, mean maternal weight, and mean gestational age at blood draw among covariates in the final estimation but mass layoff UI claims remained significantly and positively related to median male hCG scores.

We also tested our hypothesis with three other configurations of our dependent variable. First, we estimated an equation with the male hCG deficit (i.e., median male hCG subtracted from median female hCG) as the dependent variable. This specification reflects the argument that
the endemic difference in gestational hCG will shrink when stressors on the population induce selection against less fit fetuses. The coefficient for mass layoff UI claims remained significantly and, consistent with theory, inversely related to the males hCG deficit. Second, we used the ratio of male to female median hCG (i.e., the hCG sex ratio) as the dependent variable. The coefficient for mass layoff UI claims, consistent with the other results, again remained significantly >0. Third, we estimated an equation using only data for males (i.e., male median hCG as the dependent variable, female scores not among covariates). Because excluding median female hCG scores from the test leaves confounders shared by both sexes uncontrollable, we detected and controlled ‘level shifts,’ induced by changes over time in assay methods, in the residuals from the Box-Jenkins model. We assigned a variable to a binary exposure. We followed the convention for creating such exposure variables by using a simple median split of months in which mass layoffs exceeded their expected values (i.e., had positively signed residuals from the Box-Jenkins model). We assigned a score of 1 to the 14 months with residual mass layoffs (in 1000s) above the median (i.e., 5.7909) and scored the remaining 57 months 0. Second, we estimated an equation with all the covariates shown in Table 1 and the

Table 1. Comparison of study sample to all California births, 2002–2007.

| Study sample (May 2001–March 2007) | California births 2002–2007 |
|------------------------------------|----------------------------|
| Singletons                        | 2 057 443                  |
| % Male                            | 51.1                       |
| Maternal age (years), %            |                            |
| <20                                | 8.8                        |
| 20–24                             | 22.9                       |
| 25–34                             | 55.4                       |
| >34                               | 12.9                       |
| Payment source (delivery), %      |                            |
| Public                            | 45.5                       |
| Private                           | 51.4                       |
| Uninsured                         | 1.1                        |
| Other/Unknown                     | 2.0                        |
| Month prenatal care began, %      |                            |
| 1–2                               | 72.1                       |
| 3–4                               | 23.5                       |

Table 2. Coefficients from covariates-only and full model predicting median gestational hCG among male infants for 71 monthly California conception cohorts starting May 2001.

| Variable                          | Covariates model | Full model |
|-----------------------------------|------------------|------------|
| Mean age mothers of males         | −0.0748          | −0.0975    |
| Mean weight mothers of males      | −0.0773          | −0.0863    |
| Mean male gestational age % male  | 0.9984**         | 1.0773**   |
| % white male                      | 0.1079           | 0.4665     |
| % African                         | 10.3345          | 14.9893    |
| % Hispanic male                   | −1.9895          | −2.2170    |
| % Asian male                      | −0.9091          | −1.7212    |
| % Insulin using mothers of males  | 68.4463*         | 62.4579    |
| UI Claims in month 8              | 0.0024           | 0.0036     |
| UI Claims in month 7              | 0.0037           | 0.0040     |
| UI Claims in month 6              | 0.0030           | 0.0039     |
| UI Claims in month 5              | 0.0020           | 0.0041     |
| UI Claims in month 4              | 0.0058           | 0.0036     |
| UI Claims in month 3              | 0.0027           | 0.0040     |
| UI Claims in month 2              | 0.0004           | 0.0036     |
| UI Claims in month 1              | 0.0030           | 0.0039     |
| Autoregression at 16th month      | −0.5706**        | −0.6232**  |

*P < 0.05; two-tailed test.
**P < 0.01; two-tailed test.

American) that prior literature suggests could confound the association between the economy and the sex ratio. Results showed that, as expected from earlier research, the sex ratio of survivors of the conception cohorts declined as the number of mass layoffs increased above levels expected from autocorrelation. While the results shown in Table 2 allow us to reject the null hypothesis, they convey little about the strength of association. We, therefore, made additional calculations to determine whether the discovered effect could actually change the ranking of conception cohorts on male hCG levels. First, we converted our continuous mass layoffs variable to a binary exposure. We followed the convention for creating such exposure variables by using a simple median split of months in which mass layoffs exceeded their expected values (i.e., had positively signed residuals from the Box-Jenkins model). We assigned a score of 1 to the 14 months with residual mass layoffs (in 1000s) above the median (i.e., 5.7909) and scored the remaining 57 months 0. Second, we estimated an equation with all the covariates shown in Table 1 and the
binary exposure variable for the 8th month of gestation (i.e., mass layoffs announced in the 6th month of gestation). Results showed that male median hCG rose by 0.1985 IU/L in the exposed cohorts. Third, we estimated the implications of this finding for two intuitively informative unexposed conception cohorts. First, the lowest of the 71 median male hCG scores was 19.1200 IU/L and came, as expected, from an unexposed cohort. Our findings imply that exposing this cohort to stressful levels of mass layoff announcements would cull enough less fit male fetuses to raise its score to 19.3185 IU/L (i.e., 19.1200 + 0.1985). This increase means that the effect we estimated has sufficient strength to move the cohort from rank 71 (i.e., lowest) to 64th among all cohorts. Second, the cohort, also unexposed, at the median (i.e., 19.900) of all cohorts would rise from 36th to 19th (i.e., 20.0985) if exposed to these announcements.

**Discussion**

We contribute to the literature by offering the first test of an important link in the suspected causal chain connecting population stressors to the secondary sex ratio. We find that male infants in the 18th to 24th weeks of gestation when mass layoffs exceed expected values exhibit levels of gestational hCG greater than expected from potentially confounding characteristics of their conception cohort, from levels among female infants in the same conception cohort, and from levels among male infants in earlier cohorts. This finding suggests, consistent with theory, both that the maternal stress response includes raising the level of fetal fitness needed to avoid spontaneous abortion and that hCG signals that fitness.

Contributions of this finding to basic science include mechanistic evidence of natural selection in utero responding to a stressor of contemporary human populations. Although earlier work offers indirect demographic and epidemiologic evidence of the effects of such selection, none provides evidence of suspected mechanisms responding to known populations stressors. We show that more-than-expected mass layoff announcements, predict, if not cause, a population array of hCG consistent with natural selection in utero.

Epidemiology has only recently acknowledged (e.g., Catalano and Bruckner 2005) the connection, long suspected by evolutionary theorists (e.g., Trivers and Willard 1973), between natural selection and fetal loss. Our work uses data and methods familiar to both groups to demonstrate that a known risk factor for fetal loss, low gestational hCG, may play an important role in natural selection. We further demonstrate that population stressors apparently sufficient to induce fetal loss and natural selection in utero include one already studied by epidemiologists – declining economies (Catalano et al. 2010a).

Our data do not allow us to determine whether, as implied by selection in utero, conception cohorts with higher levels of gestational hCG exhibit lower morbidity early in life than those with lower hCG. Linking pregnancy-screening data with infant health records would allow estimating the yield of cohort morbidity and mortality predictable from gestational hCG. These estimates might be useful for anticipating temporal variation in the need for preventive and treatment services in infant populations.

Our use of state-level data leaves unclear whether the labor markets that accounted for most of the mass layoffs also yielded most of the high gestational hCG cohorts.
Using sub-state regions will require access to unpublished mass layoff data but would allow more inferential certainty. We used median hCG scores in part because we wanted a conventional dependent variable for what readers might find an otherwise unconventional test. This choice, however, also made our test conservative in that a shifting criterion for spontaneous abortion affects only a small population of fetuses at the far left tail of the hCG distribution. Unrelated changes elsewhere in the distribution could, therefore, dilute the effect of selection in utero on median hCG scores. Future research should explore more sensitive measures of selection (e.g., the value defining the 10th percentile of hCG among males in each cohort) than cohort median hCG.

The strengths of our analyses include the number, size, and diversity of birth cohorts we analyzed. We know of no other data describing gestational hCG in as many as two million births from 71 monthly birth cohorts that include a broad array of racial and ethnic groups. This wealth of data allowed us to use time-series methods to detect selection in utero in the phenomenon to which it most logically applies—temporal variation in a signal of fitness among survivors of large, naturally occurring, conception cohorts exposed in gestation to varying doses of an ambient stressor.

Our findings add to the literature suggesting that the economy, a phenomenon over which we collectively exercise at least some control, affects human biology and population health (Catalano et al. 2010b). We contribute to the literature by showing that the effect arises, at least in part, from natural selection—a mechanism we largely ignore when attempting to explain, or alter, how collective choice affects our biology (Ness and Stearns 2008).

Acknowledgements

The authors acknowledge the Robert Wood Johnson Health and Society Scholars Program, the Berkeley Population Center Grant R21 HD056581 and NIH grant R24 MH081797-01 for supporting the preparation of this manuscript. The authors declare no competing financial interests.

Data archiving statement

Data deposited in the Dryad repository: doi:10.5061/dryad.h4j28d1n

Literature cited

Almli, C., R. Ball, and M. Wheeler 2001. Human fetal and neonatal movement patterns: gender differences and fetal-to-neonatal continuity. Developmental Psychobiology 38:252–273.

Alwan, L. C., and H. V. Roberts 1988. Time-series modeling for statistical process control. Journal of Business and Economic Statistics 6:87–95.

Baird, D. D. 2009. The gestational timing of pregnancy loss: adaptive strategy? American Journal of Human Biology 21:725–727.

Boklage, C. E. 2005. The epigenetic environment: secondary sex ratio depends on differential survival in embryogenesis. Human Reproduction 20:583–587.

Box, G., G. Jenkins, and G. Reinsel 1994. Time Series Analysis: Forecasting and Control, 3rd edn. Prentice Hall, London, UK.

Bruckner, T., and R. Catalano 2007. The sex ratio and age-specific male mortality: evidence for culling in utero. American Journal of Human Biology 19:763–773.

Buss, L., J. Tolstrup, C. Munk, T. Bergholt, B. Ottesen, M. Gronbaek, and S. K. Kjaer 2006. Spontaneous abortion: a prospective cohort study of younger women from the general population in Denmark. Validation, occurrence and risk determinants. Acta Obstetricia et Gynecologica Scandinavica 85:467–475.

Carroll, C. D. 2003. Macroeconomic expectations of households and professional forecasters. Quarterly Journal of Economics 118:269–298.

Catalano, R. A. 2003. Sex ratios in the two Germanies: a test of the economic stress hypothesis. Human Reproduction 18:1972–1975.

Catalano, R. 2011. Selection in utero contributes to the male longevity deficit. Social Science & Medicine 72:999–1003.

Catalano, R. A., and T. Bruckner 2005. Economic antecedents of the Swedish sex ratio. Social Science & Medicine 60:537–543.

Catalano, R., and T. Bruckner 2006. Secondary sex ratios and male life-span: damaged or culled cohorts. Proceedings of the National Academy of Sciences of the United States of America 103:1639–1643.

Catalano, R., D. Dooley, and K. Rook 1987. A test of reciprocal risk between undesirable economic and noneconomic life events. American Journal of Community Psychology 15:633–651.

Catalano, R., T. Bruckner, E. Anderson, and J. B. Gould 2005. Fetal death sex ratios: a test of the economic stress hypothesis. International Journal of Epidemiology 34:944–948.

Catalano, R., T. Bruckner, and K. R. Smith 2008. Ambient temperature predicts sex ratios and male longevity. Proceedings of the National Academy of Sciences of the United States of America 105:2244–2247.

Catalano, R., J. Ahern, T. Bruckner, E. Anderson, and K. Saxton 2009a. Gender-specific selection in utero among contemporary human birth cohorts. Paediatric and Perinatal Epidemiology 23:273–278.

Catalano, R. K., T. Bruckner, S. Goldman, and E. Anderson 2009b. A sex-specific test of selection in utero. Journal of Theoretical Biology 257:475–479.

Catalano, R., S. Goldman-Mellor, K. Saxton, C. E. Margerison-Zilklo, M. Subbaraman, K. Lewinn, and E. Anderson 2010a. The Health Effects of Economic Decline. Annual Review of Public Health 32:431–450.

Catalano, R., C. E. Margerison-Zilklo, K. B. Saxton, and T. Bruckner 2010b. Selection in utero: a biological response to mass layoffs. American Journal of Human Biology 22:396–400.

Chang, L., G. C. Tiao, and C. Chen 1988. Estimation of time series parameters in the presence of outliers. Technometrics 30:193–204.

Clutton-Brock, T. 1991. The Evolution of Parental Care. Princeton University Press, Princeton, NJ.

Cobb, S., and S. V. Kasl 1977. Termination: the Consequences of Job Loss. U.S. Department of Health, Education and Welfare, HEW (NI-
OSH) Publication No. 77-224. U.S. Government Printing Office, Washington DC.

Cole, L. A. 2010. Biological functions of hCG and hCG-related molecules. Reproductive Biology and Endocrinology 8:102.

Conger, R. D., X. J. Ge, G. H. Elder, F. O. Lorenz, and R. L. Simons 1994. Economic stress, coercive family process, and developmental problems of adolescents. Child Development 65:541–561.

Cowans, N. J., A. Stamatopoulou, N. Maiz, K. Spencer, and K. H. Nicolaides 2009. The impact of fetal gender on first trimester nuchal translucency and maternal serum free β-hCG and PAPP-A MoM in normal and trisomy 21 pregnancies. Prenatal Diagnosis 29:578–581.

Cunningham, G. C., and D. G. Tombokson 1999. Cost and effectiveness of the California triple marker prenatal screening program. Genetics in Medicine 1:199–206.

Devesaean, P., P. Fogarty, and L. Regan 2010. Human chorionic gonadotrophin for threatened miscarriage. Cochrane Database of Systematic Reviews 1–22. Art. No.: CD007422. DOI: 10.1002/14651858.CD007422.pub2.

Dietz, P. M., L. J. England, W. M. Callaghan, M. Pearl, M. L. Wier, and M. Kharaazi 2007. A comparison of LMP-based and ultrasound-based estimates of gestational age using linked California livebirth and prenatal screening records. Paediatric and Perinatal Epidemiology 21:62–71.

Dooley, D., and R. Catalano 1980. Economic change as a cause of behavioral disorder. Psychological Bulletin 87:450–468.

Dua, P., and D. J. Smyth 1993. Survey evidence on excessive public pessimism about the future behavior of unemployment. Public Opinion Quarterly 57:566–574.

Dugoff, L., J. C. Hobbins, F. D. Malone, T. F. Porter, D. Luthy, C. H. Comstock, G. Hankins et al. 2004. First-trimester maternal serum PAPP-A and free-beta subunit human chorionic gonadotropin concentrations and nuchal translucency are associated with obstetric complications: a population-based screening study (the FASTER Trial). American Journal of Obstetrics and Gynecology 191:1446–1451.

Erlebacher, A. 2010. Immune surveillance of the maternal/fetal interface: controversies and implications. Trends in Endocrinology and Metabolism 7:428–434.

Evdokimova, V. N., T. V. Nikitina, I. N. Lebedev, N. N. Sukhanova, and S. A. Nazarenko 2000. About the sex ratio in connection with early embryonic mortality in man. Ontogenesis 31:251–257.

Forbes, S. 1997. The evolutionary biology of spontaneous abortion in humans. Trends in Ecology & Evolution 12:446–450.

Forbes, S. 2005. A Natural History of Families. Princeton University Press, Princeton, NJ.

Fukuda, M., K. Fukuda, T. Shimizu, and H. Möller 1998 Decline in sex ratio at birth after Kobe earthquake. Human Reproduction 13:2321–2322.

Gabler, S., and E. Voland 1994. Fitness of twinning. Human Biology 66:699–713.

Giannakoulopoulos, X., W. Sepulveda, P. Kourtis, V. Glover, and N. M. Fisk 1994. Fetal plasma cortisol and beta-endorphin response to intrauterine needling. Lancet 344:77–81.

Giannakoulopoulos, X., J. Teixeira, N. Fisk, and V. Glover 1999. Human fetal and maternal noradrenaline responses to invasive procedures. Pediatric Research 45:494–499.

Gitau, R., N. M. Fisk, J. M. Teixeira, A. Cameron, and V. Glover 2001. Fetal hypothalamic-pituitary-adrenal stress responses to invasive procedures are independent of maternal responses. Journal of Clinical Endocrinology and Metabolism 86:104–109.

Goetzl, L., D. Krantz, J. L. Simpson, R. K. Silver, J. M. Zachary, E. Per- gament, L. D. Platt et al. 2004. Pregnancy-associated plasma protein A, free beta-hCG, nuchal translucency, and risk of pregnancy loss. Obstetrics and Gynecology 104:30–36.

Goldhaber, M. K., and B. H. Fireman 1991. The fetal life table revisited: spontaneous abortion rates in three Kaiser Permanente cohorts. Epidemiology 2:33–39.

Haig, D. 1993. Genetic conflicts in human pregnancy. The Quarterly Review of Biology 68:495–532.

Helle, S., V. Lummaa, and J. Jokela. 2002 Sons reduced maternal longevity in preindustrial humans. Science 296:1085.

Helle, S., S. Helama, and K. Lertola 2009. Evolutionary ecology of human birth sex ratio under the compound influence of climate change, famine, economic crises and wars. Journal of Animal Ecology 78:1226–1233.

Human Mortality Database. 2010. University of California, Berkeley (USA) and Max Planck Institute for Demographic Research (Germany) 2010 [cited 2010]. Available from Available at http://www.mortality.org or http://www.humanmortality.de.

Jelliffe-Pawloski, L. L., R. J. Baer, and R. J. Currie 2010. Second trimester serum predictors of preterm birth in a population-based sample of low-risk pregnancies. Prenatal Diagnosis 30:727–733.

Jukic, A. M., C. R. Weinberg, D. D. Baird, and A. J. Wilcox 2011. The association of maternal factors with delayed implantation and the initial rise of urinary human chorionic gonadotrophin. Human Reproduction 26:920–926.

Kazernou, N. N., B. Carrier, L. Malm, S. Riggle, C. Hodgkinson, S. Smith, C. Templeis et al. 2009. Triple-marker prenatal screening program for chromosomal defects. Obstetrics and Gynecology 114:50–58.

Kemkes, A. 2006. Secondary sex ratio variation during stressful times: the impact of the French revolutionary wars on a German parish (1787–1802). American Journal of Human Biology 18:806–821.

Kessler, R. C., J. S. House, and J. B. Turner 1987. Unemployment and health in a community sample. Journal of Health and Social Behavior 28:51–59.

Kirkegaard, I., T. B. Henriksen, and N. Uldbjerg. 2011. Early fetal growth, PAPP-A and free beta-hCG in relation to the risk of delivering a small-for-gestational age infant. Ultrasound in Obstetrics and Gynecology 37:341–347.

Larson, J. H., S. M. Wilson, and R. Beley 1994. The impact of job insecurity on marital and family relationships. Family Relations 43:138–143.

Lecanuet, J. P., and B. Schaal 1996. Fetal sensory competencies. European Journal of Obstetrics, Gynecology, and Reproductive Biology 68:1–23.

Leigh, J. 1985. The effects of unemployment and the business cycle on absenteeism. Journal of Economics and Business 37:159–170.

Liem, R., and J. H. Liem 1988. Psychological effects of unemployment on workers and their families. Journal of Social Issues 44:87–105.

Liu, L. M., and G. B. Hudak 1992. Forecasting and Time Series Analysis Using the SCA Statistical System. Scientific Computing Associates, Oak Brook, IL.

Lummaa, V. 2001. Reproductive investment in pre-industrial humans: the consequences of offspring number, gender and survival. Proceedings of the Royal Society of London: Biological Sciences 268:1977–1983.

Lyster, W. R.. 1974. Altered sex ratio after the London smog of 1952 and the Brisbane flood of 1965. Journal of Obstetrics and Gynaecology of the British Commonwealth 81:626–631.
Malley, J., and T. Moutos 1996. Unemployment and consumption. Oxford Economic Papers-New Series 48:584–600.

Marcus, M. A. E., W. Gogarten, F. Louwen, R. Wusten, and H. Van Aken 1999. Remifentanil for fetal intrauterine microendoscopic procedures. Anesthesia and Analgesia 88:5257.

Merviel, P., F. Müller, J. Guibourdenche, N. Berkane, R. Gaudet, G. Bréart, and S. Uzan 2001. Correlations between serum assays of human chorionic gonadotrophin (hCG) and humanplacental lactogen (hPL) and pre-eclampsia or intrauterine growth restriction (IUGR) among nulliparas younger than 38 years. European Journal of Obstetrics & Gynecology and Reproductive Biology 95:59–67.

Minchin, T. 2009. ‘It knocked this city to its knees’: the closure of Pillowtex Mills in Kannapolis, North Carolina and the decline of the US textile industry. Labor History 50:287–311.

Møller, A. P. 1997. Developmental selection against developmentally unstable offspring and sexual selection. Journal of Theoretical Biology 185:415–422.

Myers, L. B., L. A. Bulich, P. Hess, and N. M. Miller 2004. Fetal endoscopic surgery: indications and anaesthetic management. Best Practices & Research in Clinical Anaesthesiology 18:231–258.

Ness, R. M., and S. C. Stearns 2008. The great opportunity: evolutionary applications to medicine and public health. Evolutionary Applications 1:28–48.

Pearl, M., M. L. Wier, and M. Kharrazi 2007. Assessing the quality of last menstrual period date on California birth records. Paediatric and Perinatal Epidemiology 21:50–61.

Powe, C. E., C. D. Knott, and N. Conklin-Brittain 2010. Infant sex predicts breast milk energy content. American Journal Human Biology 22:50–54.

Rook, K., D. Dooley, and R. Catalano 1991. Stress transmission: the effects of husbands’ job stressors on the emotional health of their wives. Journal of Marriage and the Family 53:163–177.

Saadat, M. 2008. Decline in sex ratio at birth after Bam (Kerman Province, Southern Iran) earthquake. Journal of Biosocial Science 40:935–937.

Sales, K. J., V. Grant, R. D. Catalano, and H. N. Jabbour. 2011. Chorionic gonadotrophin regulates CXCR4 expression in human endometrium via E-series prostanoid receptor 2 signalling to PI3K-ERK1/2: implications for fetal-maternal crosstalk for embryo implantation. Molecular Human Reproduction 1:22–32.

Stearns, S. C. 1987. The selection-arena hypothesis. In S. C. Stearns, ed. The Evolution of Sex and its Consequences, pp. 337–386. Birkhauser Verlag, Basel.

Stein, A., P. Zybert, and L. Lumey 2003. Acute undernutrition is not associated with excess of females in humans: the Dutch Hunger Winter. Proceedings of the Royal Society B Biological Sciences 271:S138–S141.

Trivers, R. L., and D. E. Willard 1973. Natural selection of parental ability to vary sex ratio of offspring. Science 179:90–92.

United States Department of Labor. Mass Layoffs Statistics. 2011. http://www.bls.gov/mls/#data (accessed on 16 May, 2011).

Vignano, P., S. Mangioni, F. Pompei, and I. Chiodo. 2003. Maternal-conceptus cross talk: a review. Placenta S56–S61.

Vinokur, A. D., R. H. Price, and R. D. Caplan 1996. Hard times and hurtful partners: how financial strain affects depression and relationship satisfaction of unemployed persons and their spouses. Journal of Personality and Social Psychology 71:166–179.

Wells, J. C. 2000. Natural selection and sex differences in morbidity and mortality in early life. Journal of Theoretical Biology 212:65–76.

Wilcox, A. J., D. D. Baird, and C. R. Weinberg 1999. Time of implantation of the conceptus and loss of pregnancy. New England Journal of Medicine 340:1796–1799.

Yaron, Y., I. Wolman, M. J. Kupferminc, Y. Ochshorn, A. Many, and A. Orr-Urtreger 2001. Effect of fetal gender on first trimester markers and on Down syndrome screening. Prenatal Diagnosis 21:1027–1030.