REPLY TO LI ET AL.:

Estimate of the association between TB risk and famine intensity is robust to various famine intensity estimators

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We thank Li et al. (1) for their interest in our paper (2) and agree that different approaches to estimating famine intensity, expressed here as the cohort size shrinkage index (CSSI), could affect estimates of its association with tuberculosis (TB) risk in the birth cohort directly impacted by famine. We acknowledge their contention that our published CSSI estimates could be biased upward due to postfamine increases in fertility that suggest delayed births. However, the proposal to use only prefamine (1953 to 1957) births to estimate the counterfactual size of the famine cohort (1958 to 1962) strikes us as ill-advised, since it ignores secular increases in cohort size that are clearly observable in data for Sichuan Province (Fig. 1) and for China as a whole (3). We respond here by examining alternative approaches to estimating the counterfactual cohort size and their impacts on estimates of the association between CSSI and the TB incidence rate ratio in the 1958-to-1962 birth cohort.

We consider seven methods for estimating counterfactual famine cohort sizes (Table 1). These include the method proposed in ref. 1, which assumes cohort size remains fixed at the size of the last 5-y prefamine cohort (termed $CSSI_{pre\_fixed}$). The next six methods utilize both pre- and postfamine cohort data and include our initial approach (2), used also in refs. 4 and 5, in which pre- and postfamine cohort sizes are averaged to estimate the counterfactual ($CSSI_{pre\_post\_mean}$), implicitly accounting for a local secular trend. The $CSSI_{pre\_post\_mean\_adjusted}$ estimator follows the same principle but estimates and removes delayed births from the postfamine cohort. Finally, we use linear and generalized additive models fit to different spans of survival-adjusted pre- and postfamine cohort data to interpolate the counterfactual famine cohort size, including only postfamine cohort data after 1967, after which fertility rates stabilized (6).

The estimated associations between famine intensity and excess TB risk across CSSI estimators reinforce our original conclusions (Table 1). Positive associations at or near 95% significance are observed in all cases, including the model that directly estimates and removes delayed births from the postfamine cohort ($CSSI_{pre\_post\_mean\_adjusted}$). We note that our estimates are made using full 2000 census data (7), in contrast with the household sample (~1%) used by Li et al., which explains the difference between our $CSSI_{pre\_fixed}$ metaregression parameter estimate and the estimate reported in their correspondence (1). While CSSI estimators based on interpolating between prefamine and postfamine cohort sizes may be susceptible to influence by postfamine fertility increases or other changes in population dynamics, estimators ignoring secular trends in cohort size risk underestimating famine intensity. Our explorations of many alternative methods for estimating CSSI suggest that positive associations between TB risk in the famine birth cohort and CSSI are robust to the choice of famine intensity estimator.

Data Availability. Data and code, including technical details of the analysis, are available at https://github.com/qu-cheng/TB_famine/tree/master/Response_to_Li.

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Table 1. Results of metaregression of association between famine cohort (F1) TB incidence rate ratio (IRR) and famine intensity (CSSI) across alternative famine intensity estimators

CSSI estimator	Type	Trend	Data used to fit model	Adjustments	Median CSSI (interquartile range)	Estimated log change TB F1 IRR per 100% increase in CSSI (95% CI)
CSSI$_{\text{pre_fixed}}$	Average	None	1953–1957 cohort	None	0.39 (0.34–0.45)	0.41 (−0.02–0.84)
CSSI$_{\text{pre_post_mean}}$	Average	15 y linear	1953–1957, 1963–1967 cohorts	None	0.49 (0.44–0.52)	0.76 (0.14–1.38)
CSSI$_{\text{pre_post_mean_adjusted}}$	Average	15 y linear	1953–1957, 1963–1967 cohorts, 1952–1970 fertility data	Potential delayed births subtracted from postfamine cohort	0.47 (0.42–0.51)	0.75 (0.14–1.37)
CSSI$_{\text{pre_5_post_5_lm}}$	Linear model	25 y linear	1948–1952, 1968–1972 cohorts	Cohorts adjusted for survival from 1964 to 2000	0.50 (0.46–0.54)	0.95 (0.16–1.73)
CSSI$_{\text{pre_53_post_5_gam}}$	Generalized additive model	Smoothly varying	1900–1952, 1968–1972 cohorts	Cohorts adjusted for survival from 1964 to 2000	0.45 (0.42–0.51)	0.93 (0.17–1.68)
CSSI$_{\text{pre_10_post_10_lm}}$	Linear model	35 y linear	1943–1952, 1968–1977 cohorts	Cohorts adjusted for survival from 1964 to 2000	0.45 (0.40–0.49)	0.82 (−0.03–1.67)
CSSI$_{\text{pre_53_post_10_gam}}$	Generalized additive model	Smoothly varying	1900–1952, 1968–1977 cohorts	Cohorts adjusted for survival from 1964 to 2000	0.43 (0.39–0.46)	0.78 (−0.10–1.67)

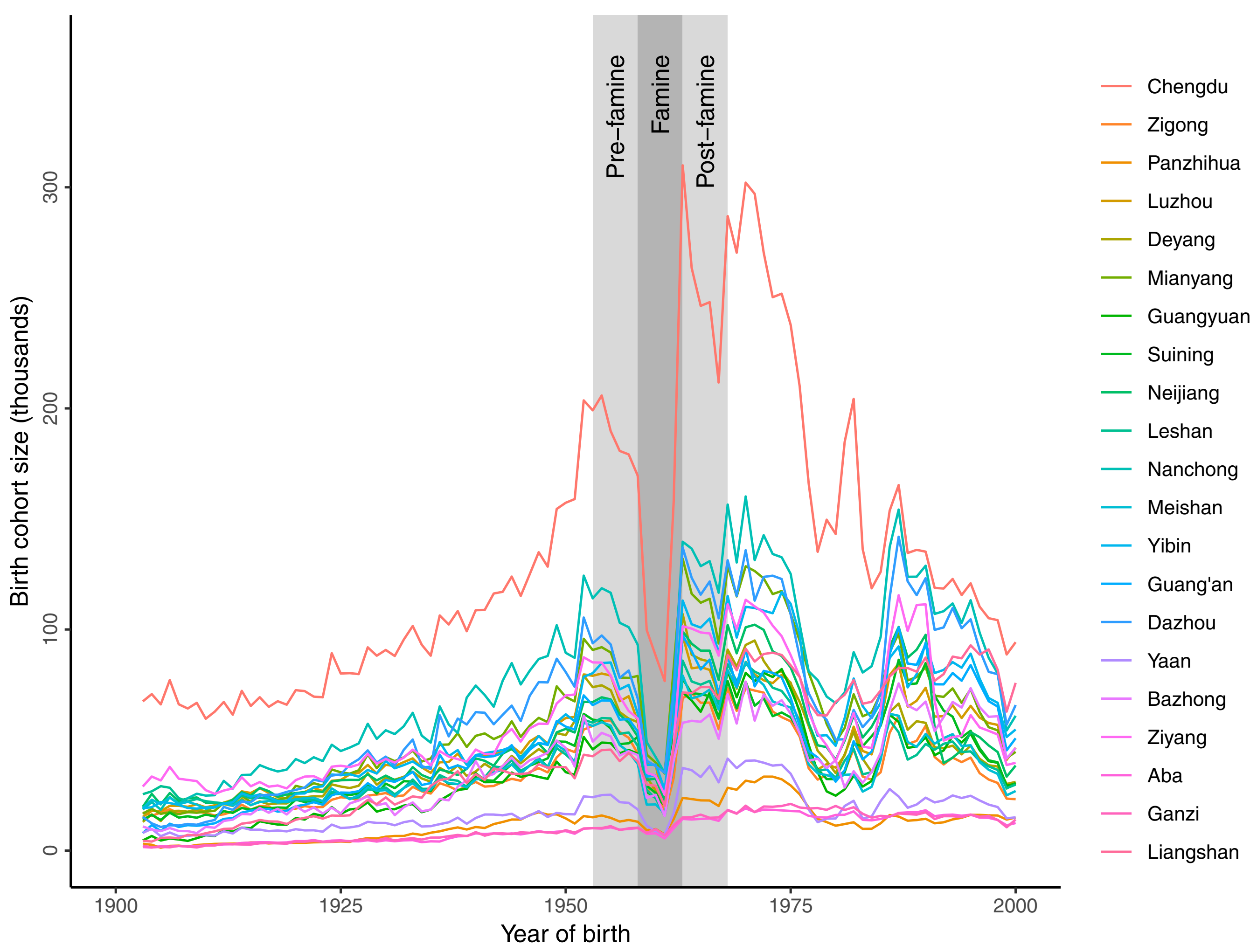

Fig. 1. Birth cohort size by year of birth and by prefecture (colors) in Sichuan Province, People's Republic of China estimated from the 2000 census data (7), adjusted for survival rates estimated from national census data collected in 1964, 1982, and 2000 (8, 9). Shaded areas represent the famine birth cohort (1958 to 1962, dark gray) and the prefamine (1953 to 1957) and postfamine (1963 to 1967) cohorts (light gray).

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