Reply to 'Early-life exposure to the Chinese Famine and subsequent T2DM'

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Such differences in ages of assessment will undoubtedly have affected the likelihood of receiving a diagnosis.

Equally important, Chinese Famine exposure varied substantially, indicated by very different mortality across provinces[6]. Such differences in exposure will have effects on the association with T2DM[4,7,8]. In the severely affected famine areas in the CNNHS study, fetal-exposed participants had a clear increased risk of hyperglycaemia (OR 3.92; 95% CI 1.64–9.39), but no risk was apparent in less severely affected areas (OR 0.57; 95% CI 0.25–1.31)[4]. Similarly, in the SPECT study in Shandong and Anhui provinces, we again found that severe fetal exposure to famine resulted in an increased risk of T2DM (OR 1.59; 95% CI 1.11–2.30) but found no association in less severely affected areas[8].

Moreover, in our 2017 report from the China Health and Retirement Longitudinal Survey (CHARLS), fetal exposure to famine also resulted in an increased risk of T2DM after participants were age-matched (combination of the non-exposed cohort 1962–1964 and pre-famine cohort 1956–1958) (OR 1.37; 95% CI 1.07–1.75)[9]. Given that CHARLS is a nationally representative sample of those >45 years of age, we were surprised that it was not included in the meta-analysis.

In this context, we re-analysed six studies (five that were also included in the Review by Zimmet et al. and one from the CHARLS) with age-matched controls[1,8,9], taking into account severity of famine exposure. The summary estimate showed small but significant overall effects on the risk of T2DM (OR 1.25; 95% CI 1.15–1.37). However, we found a clearer association in severely affected areas (OR 1.38; 95% CI 1.11–1.72) and no association in less severely affected areas (OR 0.94; 95% CI 0.57–1.57) (Supplementary Tables).

Based on these findings, we conclude that the severity of antenatal exposure to the Chinese Famine determined heightened risk for later T2DM. Given that severe exposure was widespread in China (15 of 28 provinces had an over 50.0% higher mortality than the 3 years (1956–1958) immediately preceding the famine (1959–1961)[6,9]), it seems likely that the Chinese Famine has indeed substantially contributed to the current T2DM epidemic. We agree with Li and his colleagues that, regardless of earlier famine exposure, healthy lifestyles will reduce the burden of T2DM, but this does not diminish the significance of the Chinese Famine effects.

There is a reply to this letter by Li, C. et al. *Nat. Rev. Endocrinol.* https://doi.org/10.1038/s41574-019-0302-7 (2019).

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The authors declare no competing interests.

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We thank Zou et al. (Early-life exposure to the Chinese Famine and subsequent T2DM. *Nat. Rev. Endocrinol.* https://doi.org/10.1038/s41574-019-0299-y (2019)[1] for their interest in our Comment (Li, C. et al. The effect of the Chinese Famine on type 2 diabetes mellitus epidemics. *Nat. Rev. Endocrinol.* **15**, 313–314 (2019))[2] and welcome the opportunity to address their concerns about the completeness of the data we presented.

Zou et al. re-analysed the five studies included in a Review by Zimmet et al.[3] together with their own study that combined pre-famine and post-famine controls from the 2011 China Health and Retirement Longitudinal Study[4]. They claim a statistically significant overall effect on the risk of type 2 diabetes mellitus (T2DM) from an odds ratio of 1.25 (95% CI 1.15–1.37) for all studies combined using age-balanced controls and a random-effects model. Using the data as provided by Zou et al. in their supplementary table 1 (REF.[1]), we undertook the same analysis, including their added study, and still find a non-significant overall effect on the risk of T2DM with an odds ratio of 1.05 (95% CI 0.87–1.26). A summary of our calculations is attached (Supplementary Fig. 1).

For their re-analysis of studies in severely affected famine areas, Zou et al., in our view, should have been more careful in their choice of studies. The findings from the included Suihua cohort show an increase in T2DM in famine births compared with post-famine births[5], but demographic and population census data suggest that the study area was in one of the provinces least affected by the famine[6,7]. This calls for a re-examination of their findings on severe famine exposure effects.

We do not dispute that Zou et al. could be correct in believing that the famine had a marked effect on current and future T2DM epidemics in China. This conclusion, however, cannot be drawn from current studies. For example, the Ukraine and Dutch famines had a statistically significant effect on later T2DM[8,9], and the same could be true in China. Ideally this would be demonstrated

in studies in which first, the timing and severity of the famine at the time of birth can be documented in well-defined study populations; and second, the populations can be followed over the life course for disease onset and mortality. The better that future studies are able to meet these goals, the better we will be able to determine the long-term impact of the Chinese Famine.

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