Chinese Famine and the diabetes mellitus epidemic

Paul Zimmet, Zumin Shi, Assam El-Osta and Linong Ji

We thank Li et al. (The effect of the Chinese Famine on type 2 diabetes mellitus epidemics. *Nat. Rev. Endocrinol.* **15**, 313–314 (2019))[1] for their interest in our paper and agree that some studies on the association between the Chinese Famine and chronic disease have limitations. Most have not addressed the age difference between different exposure groups due to the 3-year-long famine. Our Review[2] excluded literature published in Chinese; these studies were conducted in regions severely affected by famine (such as Chongqing and Anhui) and did not include less severely affected regions as controls. In addition, some of these studies did not report odds ratios with adjustments for potentially confounding factors[1]. However, we respectfully disagree with the meta-analysis and the age-balanced control approach they conducted for reasons discussed here.

The use of an age-balanced control might underestimate the risk of fetal exposure to famine. An assumption made by this approach is that childhood exposure to famine has no effect on subsequent metabolic health. This approach suggests that the difference in type 2 diabetes mellitus (T2DM) prevalence in different cohorts is purely the result of ageing. A robust way to address the age issue is to use the difference in difference method to compare the effect of famine in areas with different famine severity. However, neither method addresses the question of whether fetal famine exposure increased the risk of early-onset (at 18–45 years of age) T2DM. A study published in 2019 found that early-life exposure to famine exacerbated the association between hyperglycaemia and cardiovascular disease[3], which suggests that famine exposure might increase the risk of early-onset T2DM.

The long-term effects of early-life malnutrition related to famine might be largely underestimated, even when the post-famine cohort (that is, 1962–1964) was used as the control, as the burden of undernutrition among children was very high before the 1970s[4]. In addition, conducting meta-analyses of the Chinese famine studies is difficult, as most of the existing studies used different methods to define the cohort. Furthermore, the method used to diagnose diabetes mellitus differed, with some studies not measuring HbA_{1c} (REF.[5]), and diabetes mellitus prevalence increased rapidly over the past decade[6].

In the re-analysis of the studies included in our paper, Li et al. did not discuss the considerable interaction between famine severity and fetal exposure relating to the risk of hyperglycaemia in the 2002 China National Nutrition Survey (CNNS)[5]. Both the DFTJ cohort and SPECT studies did not consider famine severity[7,8]. Indeed, in the SPECT study[8], the age-balanced control included participants with a 21-year age range, while the fetal exposure group had a 3-year range. Thus, it is challenging to use a meta-analysis to synthesize the odds ratio as described in the article and presented in supplementary table 3 (REF.[1]). Furthermore, the existing studies were conducted between 2002 and 2015 (REF.[1]), and the ages of the participants in the fetal exposure group were substantially different in these studies. In some studies, the fetal exposure group might not have reached the T2DM onset age.

A study published in 2019 suggested that early-life exposure to the Chinese Famine increased *IGF2* gene methylation in adulthood[9], which is consistent with findings from the Dutch famine[10] and supports the link between early-life famine exposure and chronic disease risk. The Chinese Famine intergenerational effect[11] might also be due to dramatic changes in diet and lifestyle factors in China, which are substantially different from those in the controlled animal studies.

Current evidence supports a link between early-life exposure to Chinese famine and T2DM. Future studies can integrate regional data and test the interaction between famine severity and the famine exposure group. The age-period-cohort method[12] can also be used, which can separate the effect of famine from age.

There is a reply to this letter by Li, C. et al. *Nat. Rev. Endocrinol.* https://doi.org/10.1038/s41574-019-0301-8 (2019).

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1. Li, C. et al. The effect of the Chinese Famine on type 2 diabetes mellitus epidemics. *Nat. Rev. Endocrinol.* **15**, 313–314 (2019).
2. Zimmet, P. et al. Epidemic T2DM, early development and epigenetics: implications of the Chinese Famine. *Nat. Rev. Endocrinol.* **14**, 738–746 (2018).
3. Zhang, Y. et al. Exposure to Chinese famine in early life modifies the association between hyperglycaemia and cardiovascular disease. *Nutr. Metab. Cardiovasc. Dis.* **29**, 1230–1236 (2019).
4. Zong, X.-N. et al. Child nutrition to new stage in China: evidence from a series of national surveys, 1985–2015. *BMC Public Health* **19**, 402 (2019).
5. Li, Y. et al. Exposure to the Chinese famine in early life and the risk of hyperglycemia and type 2 diabetes in adulthood. *Diabetes* **59**, 2400–2406 (2010).
6. Xu, Y. et al. Prevalence and control of diabetes in Chinese adults. *JAMA* **310**, 948–959 (2013).
7. Wang, J. et al. Exposure to the Chinese Famine in childhood increases type 2 diabetes risk in adults. *J. Nutr.* **146**, 2289–2295 (2016).
8. Wang, N. et al. Is exposure to famine in childhood and economic development in adulthood associated with diabetes? *J. Clin. Endocrinol. Metab.* **100**, 4514–4523 (2015).
9. Shen, L. et al. Early-life exposure to severe famine is associated with higher methylation level in the IGF2 gene and higher total cholesterol in late adulthood: the Genomic Research of the Chinese Famine (GRECF) study. *Clin. Epigenetics* **11**, 88 (2019).
10. Heijmans, B. T. et al. Persistent epigenetic differences associated with prenatal exposure to famine in humans. *Proc. Natl Acad. Sci. USA* **105**, 17046–17049 (2008).
11. Li, J. et al. Prenatal exposure to famine and the development of hyperglycemia and type 2 diabetes in adulthood across consecutive generations: a population-based cohort study of families in Suihua, China. *Am. J. Clin. Nutr.* **105**, 221–227 (2017).
12. Xie, S. H. & Lagergren, J. A possible link between famine exposure in early life and future risk of gastrointestinal cancers: Implications from age-period-cohort analysis. *Int. J. Cancer* **140**, 636–645 (2017).

Competing interests
The authors declare no competing interests.

Reply to 'Chinese famine and the diabetes mellitus epidemic'

Chihua Li, Elmar W. Tobi, Bastiaan T. Heijmans and L. H. Lumey

We thank Zimmet et al. (Chinese famine and the diabetes mellitus epidemic. *Nat. Rev. Endocrinol.* https://doi.org/10.1038/s41574-019-0300-9 (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 main concerns.

Zimmet et al. are concerned that age-balanced controls could underestimate the risk of fetal famine exposure. This potential