Reply to 'Chinese famine and the diabetes mellitus epidemic'

Li, C.H.; Tobi, E.W.; Heijmans, B.T.; Lumey, L.H.

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).

Paul Zimmet[1], Zumin Shi[2], Assam El-Osta[1,3] and Linong Ji[4]*
[1]Department of Diabetes, Central Clinical School, Monash University, Melbourne, Victoria, Australia.
[2]Human Nutrition Department, School of Health Sciences, QU Health, Qatar University, Doha, Qatar.
[3]Hong Kong Institute of Diabetes and Obesity, Prince of Wales Hospital, The Chinese University of Hong Kong, Hong Kong, China.
[4]Peking University Diabetes Center, Department of Endocrinology and Metabolism, Peking University People's Hospital, Beijing, China.
**e-mail: paul.zimmet@monash.edu*

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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

underestimation might be a problem and therefore needs further examination in famine settings. In studies of the Ukraine Holodomor famine of 1932–1933 and of the Dutch Hunger Winter famine of 1944–1945, we demonstrated that there was no difference in type 2 diabetes mellitus (T2DM) when we compared individuals born before the famine (and hence exposed during childhood) with individuals born after the famine[3,4]. We therefore combined these groups to form an age-balanced control group. We further addressed the age issue with difference in difference analytic methods, comparing the effect of famine in different severity areas. Findings in our Dutch famine study were also confirmed using same-sex siblings without famine exposure as controls[1]. These approaches protect from possible biases arising from the rapidly increasing prevalence of T2DM in these settings and in the Chinese population in the past few years.

Our problem with a recent study[5] mentioned by Zimmet et al. in support of a possible interaction between famine exposure and the risk of hyperglycaemia and cardiovascular disease is that the study failed to use age-balanced controls. This omission probably inflated the estimated risk of hyperglycaemia following exposure to famine and thereby inflated estimates of any further interactions with hyperglycaemia.

Zimmet et al. question whether meta-analysis is an appropriate tool to help synthesize findings from a multitude of Chinese famine studies and T2DM risk. We used meta-analysis in the first place to identify differences in the type of controls used across studies. This approach shows that most studies failed to use age-balanced controls and reported false-positive findings. Subsequently, we described consistent patterns across all studies, regardless of famine exposure definition or of T2DM assessment methods. When age-balanced controls are used, the studies to date fail to show an association between prenatal famine exposure and later life T2DM. Adjustment for covariates — as is conducted in some studies — does not change this pattern. If the Chinese Famine had a long-term impact on T2DM, the failure to demonstrate this in most Chinese Famine studies is most likely due to classification errors in the timing or severity of famine exposure and perhaps also to the limited range of exposure in the studied populations.

In their response, Zimmet et al. state they excluded studies published in Chinese because "these studies were conducted in regions severely affected by famine […] and did not include less severely affected regions as controls". We see no justification for this omission, as studies published in Chinese accounted for half of all published famine studies and covered several regions with appropriate famine controls[2]. Indeed, most of these studies had similar designs to those published in English. Ignoring these Chinese studies will give an incomplete, and possibly biased, picture of the findings on this topic. Zimmet et al. also seem to uncritically accept what is claimed about the severity of famine in selected study populations. As an example, the Suihua Beilin area of Heilongjiang province was classified as 'a severe famine area' by the study's authors[6]; however, based on demographic and population census data at either the prefecture or the provincial level, the Heilongjiang province was one of the provinces least affected by the famine compared with others[7]. The famine severity classification of the study was entirely based on the reported loss of grain production in the area and not on any other data. This information was not further discussed by the study authors.

The final point made by Zimmet et al. is that, in a recent study published in 2019 (REF.[8]), early-life exposure to the Chinese Famine increased *IGF2* gene methylation in adulthood, 'agreeing with findings from the Dutch famine' as reported by us[9]. We see no agreement with Dutch findings, however, as only one CpG in the cited study shows an association in the desired direction and all others show effects in the opposite direction.

*Chihua Li[1,2], Elmar W. Tobi[3,4], Bastiaan T. Heijmans[3] and L. H. Lumey[1,3]**
[1]Department of Epidemiology, Mailman School of Public Health, Columbia University, New York, NY, USA.
[2]Zhengzhou Central Hospital Affiliated to Zhengzhou University, Henan, China.
[3]Molecular Epidemiology, Department of Biomedical Data Sciences, Leiden University Medical Center, Leiden, Netherlands.
[4]Division of Human Nutrition, Wageningen University and Research, Wageningen, Netherlands.
**e-mail: lumey@columbia.edu*

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Competing interests
The authors declare no competing interests.

Early-life exposure to the Chinese Famine and subsequent T2DM

Zhiyong Zou, Changwei Li and George C. Patton

Over the past 10 years, 17 studies have reported that antenatal exposure to the Chinese Famine across the first 3 years of life increased the subsequent risk of type 2 diabetes mellitus (T2DM) and/or hyperglycaemia. A 2018 review also concluded that the famine has contributed to China's current T2DM epidemic[1]. However, in a Comment published in *Nature Reviews Endocrinology* (Li, C. et al. The effect of the Chinese Famine on type 2 diabetes mellitus epidemics. *Nat. Rev. Endocrinol.* **18**, 313–314 (2019))[2], which included discussion of a 2017 meta-analysis of published Chinese famine studies using age-matched controls[3], Chihua Li and colleagues found that famine was not associated with an increased risk of T2DM.

We agree with Li and colleagues that both the age of assessment and severity of exposure contribute to the differences in findings. In the 2002 China National Nutrition and Health Survey (CNNHS), the mean ages for participants in the non-exposed, fetal-exposed, early-childhood-exposed, mid-childhood-exposed and late-childhood-exposed cohorts were 39, 42, 45, 47 and 49 years, respectively[4]. Similarly, in the Survey on Prevalence in East China of Metabolic Diseases and Risk Factors (SPECT-China), the mean ages for the non-exposed, fetal-exposed, childhood-exposed and adolescence-exposed or adult-exposed cohorts were 40–51, 52–55, 56–65 and 66–93 years, respectively[5].