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Short Commentary

Better Exposure Definitions and Control Selections are Needed for Chinese Famine Studies

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Famines in human history have been widely used as natural experiments to study how early-life environments may influence adult health outcomes, including overweight/obesity, diabetes and schizophrenia [1,2]. In the past decade, there is a growing popularity in using the Chinese famine of 1959-61 to examine related questions. For example, over 20 independent studies on the Chinese famine and diabetes have been conducted [3,4]. They show the importance of linking early-life environment shock to increased risk of diabetes for their prevention and management, and illustrate the possibility of using the famine as a model to examine the causal effect of prenatal under nutrition on human aging. Their findings have been interpreted as evidence that the prenatal famine exposure drives the T2DM epidemic among Chinese population [5-10]. However, such interpretations can be misleading because most Chinese famine studies have major methodologic problems, including poor famine exposure definitions and inappropriate unexposed control selections [2,3,11].

A recent systematic review and meta-analysis has reported summary effect estimates of fetal and childhood famine exposure on adulthood cardio metabolic conditions including diabetes [12]. This meta-analysis is mainly based on Chinese famine studies. While it provides some valuable information for the impact of early-life famine exposure on adult health, its findings need to be interpreted with caution because it failed to examine the quality of included studies appropriately. First, most Chinese famine studies defined participants born in famine years as exposed subjects but failed to take their birth place into careful consideration [2]. This can lead to misclassifications of exposed and unexposed subjects, and of highly exposed and less exposed subjects, because the severity and timing of the Chinese famine indeed varied substantially across regions. For example, one study used the provincial crude death rate to demonstrate famine severity gradients across provinces [13]. In 1960, the province of Sichuan was considered as a famine severe area because it had 54 deaths per thousand while the province of Heilongjiang had 13 deaths per thousand.

Second, summary effect estimates of both fetal and childhood famine exposure are likely to be inflated without using appropriate unexposed controls [12]. Previous studies have shown in detail that there is an important age difference between famine exposed individuals and unexposed controls in Chinese studies, which can explain most effects commonly attributed to the famine [2-4,14,15]. Chinese studies usually estimated the effect of fetal famine exposure by comparing individuals born during the famine (famine births) to individuals born after the famine (post-famine births) [2,4]. The age difference between famine births and post-famine births is generally about 3-4 years [2,4], and the difference can be as large as 10 years in some studies [16,17]. Using younger unexposed controls will always generate apparent 'famine effects' in older exposed groups because the incidence of most chronic conditions increases nonlinearly with age [2-4]. The same methodologic problem exists for effect estimates of childhood famine exposure by comparing pre-famine births to post-famine births, in which case the age differences even larger.

Above major methodologic problems can be resolved in future Chinese famine studies by learning from studies of other famine settings. Many studies of the Ukraine famine of 1932-33 and the Dutch famine of 1944-45 have set good examples of using ecological data to define famine exposure [1,18]. For example, Dutch studies defined the timing of the famine based on records of the government's daily food rations [19-27]; and Ukraine studies used estimates of population loss to measure the severity in different regions [18,28]. This can also be achieved by integrating historical and demographic records to Chinese famine studies. Besides, Ukraine and Dutch famine studies found no difference in multiple cardiometabolic conditions in adulthood when comparing individuals born before and after famines, including overweight/obesity [24-26], diabetes [22,23,28], and other related health outcomes [19-21,27]. These studies, therefore, combined individuals born before and after famines to form unexposed controls with a comparable mean age as fetal exposed individuals [19-28]. This also implies that childhood famine exposure may not

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increase the risk of related conditions [29]. The Ukraine and Dutch famines were much shorter than the Chinese famine [1], so the mean age and health outcomes were more comparable between individuals born before and after famines in Ukraine and Dutch studies. It will be interesting to explore how the selection of unexposed controls may influence study results across different famine settings.

We have also noticed a growing interest in using meta-analysis to summarize effect estimates of famine effect on health outcomes [30-33]. Their findings can be misleading without a careful examination of above problems. Therefore, we recommend to use meta-analysis to identify differences in the type of methods used across studies and magnitudes of biases caused by existing methodological problems [29,34].

Competing Interests

The authors declare no competing interests.

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