



Short Commentary

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

Chihua Li^{1,2*}, Hongkai Lian² and Ningwei Yin²

¹Department of Epidemiology, Mailman School of Public Health, Columbia University, New York, USA

²Zhengzhou Central Hospital Affiliated to Zhengzhou University, Henan, China

Keywords: Age difference; Control selection; Exposure definition; Study quality

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

***Corresponding author:** Chihua Li, Department of Epidemiology, Mailman School of Public Health, Columbia University, 722 W 168th St, New York, NY 10032, USA, E-mail: cl3106@cumc.columbia.edu

Citation: Li C, Lian H, Yin N (2020) Better Exposure Definitions and Control Selections are Needed for Chinese Famine Studies. J Gerontol Geriatr Med 6: 074.

Received: September 26, 2020; **Accepted:** October 12, 2020; **Published:** October 19, 2020

Copyright: © 2020 Li C, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

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

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.

References

- Lumey LH, Stein AD, Susser E (2011) Prenatal famine and adult health. *Annu Rev Public Health* 32: 237-262.
- Li C, Lumey LH (2017) Exposure to the Chinese famine of 1959-61 in early life and long-term health conditions: A systematic review and meta-analysis. *Int J Epidemiol* 46: 1157-1170.
- Li C, Lian H, Lumey LH (2019) Prenatal famine exposure and type 2 diabetes epidemics in China: a systematic review and meta-analysis. *Lancet* 394: 30.
- Li C, Tobi EW, Heijmans BT, Lumey LH (2019) The effect of the Chinese Famine on type 2 diabetes mellitus epidemics. *Nat Rev Endocrinol* 15: 313-314.
- Alberti KG, Zimmet PZ (2014) Diabetes: A look to the future. *Lancet Diabetes Endocrinol* 2: 1-2.
- Zimmet PZ, Magliano DJ, Herman WH, Shaw JE (2014) Diabetes: a 21st century challenge. *Lancet Diabetes Endocrinol* 2: 56-64.
- Ma RCW, Lin X, Jia W (2014) Causes of type 2 diabetes in China. *Lancet Diabetes Endocrinol* 2: 980-991.
- Zimmet PZ (2017) Diabetes and its drivers: The largest epidemic in human history? *Clin Diabetes Endocrinol* 3: 1.
- Ma RCW, Tsoi KY, Tam WH, Wong CKC (2017) Developmental origins of type 2 diabetes: A perspective from China. *Eur J Clin Nutr* 71: 870.
- Zimmet P, Shi Z, El-Osta A, Ji L (2018) Epidemic T2DM, early development and epigenetics: implications of the Chinese Famine. *Nat Rev Endocrinol* 14: 738-746.
- Li C, Lumey LH (2017) Studies into severe famine in early life and diabetes in adulthood: The need to control for differences in participant age and location. *Diabetologia* 60: 1359-1360.
- Hidayat K, Du X, Shi BM, Qin LQ (2020) Foetal and childhood exposure to famine and the risks of cardiometabolic conditions in adulthood: A systematic review and meta-analysis of observational studies. *Obes Rev* 21: 12981.
- Lin JY, Yang DT (2000) Food availability, entitlements and the Chinese famine of 1959-61. *The Economic Journal* 110: 136-158.
- Zou Z, Li C, Patton GC (2020) Early-life exposure to the Chinese Famine and subsequent T2DM. *Nat Rev Endocrinol* 16: 124-125.
- Li C, Tobi EW, Heijmans B, Lumey LH (2019) Reply to 'Early-life exposure to the Chinese Famine and subsequent T2DM'. *Nat Rev Endocrinol* 16: 125-126.
- Wang J, Li Y, Han X, Liu B, Hu H, et al. (2016) Exposure to the Chinese Famine in Childhood Increases Type 2 Diabetes Risk in Adults. *J Nutr* 146: 2289-2295.
- Wang N, Cheng J, Han B, Li Q, Chen Y, et al. (2017) Exposure to severe famine in the prenatal or postnatal period and the development of diabetes in adulthood: An observational study. *Diabetologia* 60: 262-269.
- Lumey LH, Vaiserman A (2013) *Early life nutrition, adult health and development: Lessons from changing diets, famines and experimental studies*. Nova Science publishers, New York, USA.
- Carroll D, Ginty AT, Painter RC, Roseboom TJ, was Phillips ACW (2012) Systolic blood pressure reactions to acute stress are associated with future hypertension status in the Dutch Famine Birth Cohort Study. *Int J Psychophysiol* 85: 270-273.
- de Rooij SR, Painter RC, Holleman F, Bossuyt PM, Roseboom TJ (2007) The metabolic syndrome in adults prenatally exposed to the Dutch famine. *Am J Clin Nutr* 86: 1219-1224.
- Lumey LH, Martini LH, Myerson M, Stein AD, Prineas RJ (2009) No relation between coronary artery disease or electrocardiographic markers of disease in middle age and prenatal exposure to the Dutch famine of 1944-5. *Heart* 98: 1653-1659.
- Lumey LH, Stein AD, Kahn HS (2009) Food restriction during gestation and impaired fasting glucose or glucose tolerance and type 2 diabetes mellitus in adulthood: Evidence from the Dutch Hunger Winter Families Study. *J Dev Orig Health Dis*: 164.
- Ravelli AC, van der Meulen JH, Michels RP, Osmond C, Barker DJ, et al. (1998) Glucose tolerance in adults after prenatal exposure to famine. *Lancet* 351: 173-177.
- Ravelli A, van der Meulen JH, Osmond C, Barker D, Bleker O (1999) Obesity at the age of 50 y in men and women exposed to famine prenatally. *Am J Clin Nutr* 70: 811-816.
- Ravelli G, Stein Z, Susser M (1976) Obesity in young men after famine exposure in utero and early infancy. *N Engl J Med* 295: 349-353.
- Stein A, Kahn HS, Rundle A, Zybert PA (2007) Anthropometric measures in middle age after exposure to famine during gestation: Evidence from the Dutch famine. *Am J Clin Nutr* 85: 869-876.
- Stein AD, Zybert PA, van der Pal-de Bruin K, Lumey LH (2006) Exposure to famine during gestation, size at birth, and blood pressure at age 59 y: evidence from the Dutch Famine. *Eur J Epidemiol* 21: 759-765.
- Lumey LH, Khalangot MD, Vaiserman AM (2015) Association between type 2 diabetes and prenatal exposure to the Ukraine famine of 1932-33: A retrospective cohort study. *Lancet Diabetes Endocrinol* 3: 787-794.
- Li C, Tobi EW, Heijmans BT, Lumey LH (2019) Reply to 'Chinese famine and the diabetes mellitus epidemic'. *Nat Rev Endocrinol* 16: 123-124.
- Liu H, Chen X, Shi T, Qu G, Zhao T, et al (2020) Association of famine exposure with the risk of type 2 diabetes: A meta-analysis. *Clin Nutr* 39: 1717-1723.
- Liu L, Wang W, Sun J, Pang Z (2016) Association of famine exposure during early life with the risk of type 2 diabetes in adulthood: A meta-analysis. *Eur J Nutr* 57: 741-749.
- Xin X, Yao J, Yang F, Zhang D (2018) Famine exposure during early life and risk of hypertension in adulthood: A meta-analysis. *Crit Rev Food Sci Nutr* 58: 2306-2313.
- Zhou J, Zhang L, Xuan P, Fan Y, Yang L, et al. (2018) The relationship between famine exposure during early life and body mass index in adulthood: A systematic review and meta-analysis. *PLoS One* 13: 0192212.
- Greenland S (1994) Can meta-analysis be salvaged? *Am J Epidemiol* 140: 783-787.



- Advances In Industrial Biotechnology | ISSN: 2639-5665
- Advances In Microbiology Research | ISSN: 2689-694X
- Archives Of Surgery And Surgical Education | ISSN: 2689-3126
- Archives Of Urology
- Archives Of Zoological Studies | ISSN: 2640-7779
- Current Trends Medical And Biological Engineering
- International Journal Of Case Reports And Therapeutic Studies | ISSN: 2689-310X
- Journal Of Addiction & Addictive Disorders | ISSN: 2578-7276
- Journal Of Agronomy & Agricultural Science | ISSN: 2689-8292
- Journal Of AIDS Clinical Research & STDs | ISSN: 2572-7370
- Journal Of Alcoholism Drug Abuse & Substance Dependence | ISSN: 2572-9594
- Journal Of Allergy Disorders & Therapy | ISSN: 2470-749X
- Journal Of Alternative Complementary & Integrative Medicine | ISSN: 2470-7562
- Journal Of Alzheimers & Neurodegenerative Diseases | ISSN: 2572-9608
- Journal Of Anesthesia & Clinical Care | ISSN: 2378-8879
- Journal Of Angiology & Vascular Surgery | ISSN: 2572-7397
- Journal Of Animal Research & Veterinary Science | ISSN: 2639-3751
- Journal Of Aquaculture & Fisheries | ISSN: 2576-5523
- Journal Of Atmospheric & Earth Sciences | ISSN: 2689-8780
- Journal Of Biotech Research & Biochemistry
- Journal Of Brain & Neuroscience Research
- Journal Of Cancer Biology & Treatment | ISSN: 2470-7546
- Journal Of Cardiology Study & Research | ISSN: 2640-768X
- Journal Of Cell Biology & Cell Metabolism | ISSN: 2381-1943
- Journal Of Clinical Dermatology & Therapy | ISSN: 2378-8771
- Journal Of Clinical Immunology & Immunotherapy | ISSN: 2378-8844
- Journal Of Clinical Studies & Medical Case Reports | ISSN: 2378-8801
- Journal Of Community Medicine & Public Health Care | ISSN: 2381-1978
- Journal Of Cytology & Tissue Biology | ISSN: 2378-9107
- Journal Of Dairy Research & Technology | ISSN: 2688-9315
- Journal Of Dentistry Oral Health & Cosmesis | ISSN: 2473-6783
- Journal Of Diabetes & Metabolic Disorders | ISSN: 2381-201X
- Journal Of Emergency Medicine Trauma & Surgical Care | ISSN: 2378-8798
- Journal Of Environmental Science Current Research | ISSN: 2643-5020
- Journal Of Food Science & Nutrition | ISSN: 2470-1076
- Journal Of Forensic Legal & Investigative Sciences | ISSN: 2473-733X
- Journal Of Gastroenterology & Hepatology Research | ISSN: 2574-2566
- Journal Of Genetics & Genomic Sciences | ISSN: 2574-2485
- Journal Of Gerontology & Geriatric Medicine | ISSN: 2381-8662
- Journal Of Hematology Blood Transfusion & Disorders | ISSN: 2572-2999
- Journal Of Hospice & Palliative Medical Care
- Journal Of Human Endocrinology | ISSN: 2572-9640
- Journal Of Infectious & Non Infectious Diseases | ISSN: 2381-8654
- Journal Of Internal Medicine & Primary Healthcare | ISSN: 2574-2493
- Journal Of Light & Laser Current Trends
- Journal Of Medicine Study & Research | ISSN: 2639-5657
- Journal Of Modern Chemical Sciences
- Journal Of Nanotechnology Nanomedicine & Nanobiotechnology | ISSN: 2381-2044
- Journal Of Neonatology & Clinical Pediatrics | ISSN: 2378-878X
- Journal Of Nephrology & Renal Therapy | ISSN: 2473-7313
- Journal Of Non Invasive Vascular Investigation | ISSN: 2572-7400
- Journal Of Nuclear Medicine Radiology & Radiation Therapy | ISSN: 2572-7419
- Journal Of Obesity & Weight Loss | ISSN: 2473-7372
- Journal Of Ophthalmology & Clinical Research | ISSN: 2378-8887
- Journal Of Orthopedic Research & Physiotherapy | ISSN: 2381-2052
- Journal Of Otolaryngology Head & Neck Surgery | ISSN: 2573-010X
- Journal Of Pathology Clinical & Medical Research
- Journal Of Pharmacology Pharmaceutics & Pharmacovigilance | ISSN: 2639-5649
- Journal Of Physical Medicine Rehabilitation & Disabilities | ISSN: 2381-8670
- Journal Of Plant Science Current Research | ISSN: 2639-3743
- Journal Of Practical & Professional Nursing | ISSN: 2639-5681
- Journal Of Protein Research & Bioinformatics
- Journal Of Psychiatry Depression & Anxiety | ISSN: 2573-0150
- Journal Of Pulmonary Medicine & Respiratory Research | ISSN: 2573-0177
- Journal Of Reproductive Medicine Gynaecology & Obstetrics | ISSN: 2574-2574
- Journal Of Stem Cells Research Development & Therapy | ISSN: 2381-2060
- Journal Of Surgery Current Trends & Innovations | ISSN: 2578-7284
- Journal Of Toxicology Current Research | ISSN: 2639-3735
- Journal Of Translational Science And Research
- Journal Of Vaccines Research & Vaccination | ISSN: 2573-0193
- Journal Of Virology & Antivirals
- Sports Medicine And Injury Care Journal | ISSN: 2689-8829
- Trends In Anatomy & Physiology | ISSN: 2640-7752

Submit Your Manuscript: <https://www.heraldopenaccess.us/submit-manuscript>