Editorial

The diabetes epidemic in China is a public health emergency: the potential role of prenatal exposure

Paul Z. Zimmet[1,2], Assam El-Osta[1], Zumin Shi[2,3]

[1]Monash University, Melbourne, Australia; [2]South Australian Health and Medical Research Institute, Adelaide, Australia; [3]Adelaide Medical School, University of Adelaide, Adelaide, Australia

Correspondence to: Paul Z. Zimmet, MD, PhD. Department of Medicine, Central Clinical School, Level 6, 99 Commercial Road, Melbourne 3004, Australia. Email: paul.zimmet@monash.edu.

Comment on: Wang L, Gao P, Zhang M, *et al*. Prevalence and ethnic pattern of diabetes and prediabetes in China in 2013. JAMA 2017;317:2515-23.

Received: 24 September 2017; Accepted: 17 October 2017; Published: 19 October 2017.
doi: 10.21037/jphe.2017.10.01
View this article at: http://dx.doi.org/10.21037/jphe.2017.10.01

Diabetes mellitus is one of the largest epidemics the world has ever faced (1). Globally, the number of people with type 2 diabetes mellitus has more than doubled over the past 20 years. The most recent global estimate from the International Diabetes Federation (IDF) is that in 2015 there were 415 million people with diabetes and that by 2040 the number will be 642 million (2). The global health expenditure was estimated at US$673 billion. The IDF estimates of the number of people with diabetes, and therefore the economic costs to society, are imprecise and underestimate the disease burden (3). It is very likely that both are significant underestimates.

In the face of this information, there can be no doubt that the Peoples Republic of China is now the epicentre of this global diabetes epidemic (1). This is underlined by the recent report in the *Journal of the American Medical Association* (*JAMA*) "Prevalence and Ethnic Pattern of Diabetes and Prediabetes in China in 2013" (4). The findings follow those from the 2010 national study of 113.9 million people which showed an estimated diabetes prevalence of 11.6% in adults 18 years and over (5). Along with this, the prevalence of prediabetes was 50.1% meaning that an estimated 113.9 million Chinese adults had diabetes and a further 493.4 million had prediabetes.

If this was not of great concern to Chinese public health authorities, it should be with the report from Wang and co-workers providing the latest data from the larger 2013 national survey of 170,287 adults. They found the estimated overall prevalence of diabetes was 10.9% and that of prediabetes was 35.7% (4). While the prevalence of total diabetes was 10.9%, diagnosed diabetes constituted only 4% while the undiagnosed cases were 6.9%. This means that for every person with established known diabetes, there were almost two cases undiagnosed. It is noteworthy that complications of diabetes may be present a long time before the diagnosis is made (5). It would be an understatement that these new data represent a serious public health burden in China and the results have huge implications relating to the health, social and economic costs of diabetes to the nation.

Whereas these results are slightly lower than those of the 2010 national study (6), the 2013 study sample was larger and included minority Tibetan and Muslim Chinese who had significantly lower prevalence of diabetes than Han participants (4). Tibetan and Muslim Chinese had significantly lower prevalence of diabetes than the majority Han community—14.7% for Han, 4.3% for Tibetan, and 10.6% for Muslim, respectively. This may be partly responsible for the lower overall prevalence. In addition, the authors noted another limitation in that that the rates may be different due to a different method of measuring glycated haemoglobin (HbA1c) (4). Another potential limitation of the study was that the researchers did not distinguish between type 1 and 2 diabetes.

Never-the-less, this means there were an estimated 388.1 million Chinese adults with prediabetes in 2013. The high prevalence and numerical number of persons with prediabetes should give great concern. Prediabetes is a condition in which people have blood sugar levels that are higher than normal but not sufficiently high to diagnose type 2 diabetes (5). People with prediabetes are at higher

risk of developing type 2 diabetes and cardiovascular disease although this is not inevitable. Between 15 and 30 per cent of people with prediabetes are likely to develop type 2 diabetes within five years (7).

From a general point of view, diabetes rates in China have risen dramatically over the past decades (1). The prevalence of diabetes in Shanghai was less than 1% in 1980 (8) and had increased ten-fold in some areas within two decades (1,9). Also in Qingdao, there was a substantial increase in diabetes between 2001–2002 and 2006 (10), 11.3% for both men and women in 2001–2002, to 19.2% for men and 16.1% for women in 2006. Findings from a national 2007–2008 survey showed that at that time, China now had more people with diabetes than has any other nation in the world with approximately 92 million people affected (11). So how do we explain this dramatic rise in diabetes? The impact of these enormous numbers of people with diabetes within four decades could be compared to a major strength earthquake on the Richter scale, in geological terminology!

Clearly, China has gone through rapid changes since 1980 when the low diabetes prevalence was reported in Shanghai (8). This dramatic, epidemic increase in diabetes may have a number of interrelated and interacting causes, many associated with industrialization and globalization with the consequential changes in lifestyle (1,12,13). But there is one other potential factor, the subject of increasing interest in epidemiology and public health, the impact of deleterious effect of the intrauterine environment and the resulting epigenetic changes that may also convey increased risk of type 2 diabetes and other chronic diseases in adult life (1,13-15). These epigenetic changes can be transmitted to future generations (16) and therefore become intergenerational. A recent study has reported that in the Chinese Famine of 1959-1961 compared with the offspring of non-exposed parents, the offspring with exposed parents had a 2-fold increased risk of hyperglycaemia in adulthood (17).

The interest in early development and adult risk of diabetes goes back to a serious famine in the Netherlands, "The Dutch Hunger Winter Famine 1944-1945" (18) at the conclusion of World War 2. The famine occurred during the German occupation and exposed pregnant women to a very poor diet and consequent undernourishment in early pregnancy. Some 30 years later, a study in adult life of children born during the famine and whose mothers were undernourished in early pregnancy, were found to have higher rates of type 2 diabetes, obesity, hypertension (18), and schizophrenia (19).

The ability of the cell to interpret extracellular stimuli such as hyperglycemia is essential to understand the metabolic memory involved (20). Cells stimulated under hyperglycemic conditions show dramatic changes in the histone code as well as genomic methylation. In line with its proposed role in conferring persistent epigenetic changes in experimental models, the clinical evidence has remained largely uncharted because of technological and computational limitations. Let's reconsider The Dutch Hunger Winter Famine once more because of the role of time in decades (21). Individuals peri-conceptually exposed to the famine of 1944–1945 had significantly reduced DNA methylation on the imprinted insulin-like growth factor II (*IGF2*) gene when compared to unexposed siblings. Fundamental evidence for differential methylation was presented showing this association on the IGF2 gene six decades later was not observed for individual's subject to famine late in gestation. This triggered the concept of early development events such as adverse maternal conditions increasing the risk of diabetes and other chronic disorders in adult life.

How might early developmental risk of diabetes in adult life apply to the epidemic in China? At the time of the famous Chinese Famine of 1959–1961 (22), diabetes was uncommon in in China. Yet, 50 years after this famine by 2007, there were some 92 million people with diabetes (11) and by 2013, there were about 120 million Chinese with diabetes (4). It is likely that the famine has played a significant role, albeit not exclusively, in this type 2 diabetes epidemic, as well as other non-communicable diseases such as hypertension (15). The resulting intergenerational epigenetic transmission cycle appears to have operated in China to increase the risk of diabetes in this and future generations.

The epigenetic and intergenerational risk scenario presented here and elsewhere (13) poses huge social and economic problems to China and most nations in Asia and is likely a threat to national development through premature morbidity and mortality from chronic diseases (1,23). Research and actions which address prevention of diabetes cannot be confined to lifestyle measures alone such as used in the famous and landmark DaQing study (24) and prevention programs in Western nations (25) where the additional use of pharmaceutical agents such as metformin have been used.

Because national estimates of the diabetes burden have important implications for future public health planning,

it is essential that they provide reliable data to understand and address the drivers of the epidemic (3). In particular, those relating to developmental origins of type 2 diabetes and its comorbidities should be included (13,14). This would provide a more comprehensive and far-sighted approach for prevention strategies to address this rising public health "tsunami." This should include intervention strategies instituted in potential and already pregnant mothers to prevent malnutrition and paradoxically over nutrition, alcohol, smoking and other potential risk factors acting in utero.

These interventions should supplement healthy nutrition and adequate physical activity for not only individuals but also society as important components to be included in future strategies for type 2 diabetes prevention (1). Unless drastic steps are taken through national prevention programs in China to curb the escalating trends, the social, economic, and health care challenges will be insurmountable.

The Dutch Winter Famine (18) associated with increased risk of diabetes and the China Famine (17) with this national diabetes epidemic many decades later (4) hold an important and urgent public health warning for nations with or at risk of future famines. The warning is an emergency call to their public health authorities as well as international relief organizations. It is not currently "on the international radar" for them and may well affect the lives of millions of people in developing countries in the years to come. The famine now occurring in countries in the Horn of Africa provides an excellent example. It is timely that the United Nations (UN), the World Health Organization, and the UN Development Program and other NGOs who handle food relief during and after a famine take note of this pattern and the future health risks of the nature of their food handouts.

"Diabetes begets diabetes", that is the children of mothers with diabetes are at greater risk of obesity and diabetes (13). So it is that famines may increase risk of diabetes in adult life and future epidemics will be seen in those developing countries if and when they begin to prosper. The lessons learned from the Chinese famine send a clear message to international agencies that their emergency food relief needs to be tailored to the long-term benefits and not handicapped by perpetuating the risk of diabetes and other chronic diseases in adult life. The next major diabetes epidemics may occur in countries on the African continent, for example in the Horn of Africa, if we do not pay attention to the lessons of history which suggest the responsible and appropriate manner of handling the nutritional and social issues in terms of relief aid and food supplies.

Finally, the challenge for China is to tackle a health problem that affects a very large sector of their adult population. The resources required are formidable. Just from the aspect of individuals, there are potentially devastating and costly complications of diabetes such as diabetic eye disease leading to blindness, kidney disease leading to renal failure and dialysis, and heart disease and stroke. There are also associated comorbidities such as sleep apnea, fatty liver leading to cirrhosis, and depression. Professor Juliana Chan, arguably one of the most important leaders in diabetes care and research in China, has pointed out the health care systems in many developing areas are not designed to manage and support a person's multiple health needs for 30 to 40 years or more (12). The costs of diabetes are largely those that address the prevention of, and management of diabetes complications (1).

China has a notable history being one of the world's four ancient civilizations, and its written history dates back over 3,000 years. More recent history now provides an important public health message for tackling the future burden of diabetes, its complications and associated chronic diseases. The imperative is to be addressing not only lifestyle measures for prevention of diabetes but also maternal and child health focusing on healthy early development of the fetus in utero to reduce the risk of diabetes in adult life to future generations.

Never-the-less China, with and despite its booming economy, faces a huge public health problem and challenge from the diabetes epidemic which could bankrupt its health system. The big question now is how China can reverse the trend, and how it will develop the capacity to deal with a health problem of such "cyclonic" magnitude.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned and reviewed by the Section Editor Tao Mao (Department of Health Education, Jiangsu Provincial Center for Disease Control and Prevention, Nanjing, China).

Conflicts of Interest: All authors have completed the ICMJE

uniform disclosure form (available at http://dx.doi.org/10.21037/jphe.2017.10.01). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Zimmet PZ, Magliano DJ, Herman WH, et al. Diabetes: a 21st century challenge. Lancet Diabetes Endocrinol 2014;2:56-64.
2. Ogurtsova K, da Rocha Fernandes JD, Huang Y, et al. IDF diabetes atlas: global estimates for the prevalence of diabetes for 2015 and 2040. Diabetes Res Clin Pract 2017;128:40-50.
3. Zimmet P, Alberti KG, Magliano DJ, et al. Diabetes mellitus statistics on prevalence and mortality: facts and fallacies. Nat Rev Endocrinol 2016;12:616-22.
4. Wang L, Gao P, Zhang M, et al. Prevalence and ethnic pattern of diabetes and prediabetes in China in 2013. JAMA 2017;317:2515-23.
5. Xu Y, Wang L, He J, et al. Prevalence and control of diabetes in Chinese adults. JAMA 2013;310:948-59.
6. World Health Organization. Dept. of Noncommunicable Disease Surveillance. Definition, diagnosis and classification of diabetes mellitus and its complications: report of a WHO consultation. Part 1, Diagnosis and classification of diabetes mellitus. Geneva: World Health Organization,1999.
7. Center for Disease Control and Prevention. Atlanta: a snapshot of diabetes in the United States, 2014. Available online: http:www.cdc.gov/diabetes/pdfs/library/socialmedia/diabetes-infographic.pdf
8. Shanghai Diabetes Research Cooperative Group. Diabetes mellitus survey in Shanghai. Chin Med J (Engl) 1980;93:663-72.
9. Li R, Lu W, Jiang QW, et al. Increasing prevalence of type 2 diabetes in Chinese adults in Shanghai. Diabetes Care 2012;35:1028-30.
10. Ning F, Pang ZC, Dong YH, et al. Risk factors associated with the dramatic increase in the prevalence of diabetes in the adult Chinese population in Qingdao, China. Diabet Med 2009;26:855-63.
11. Yang W, Lu J, Weng J, et al. Prevalence of diabetes among men and women in China. N Engl J Med 2010;362:1090-101.
12. Chan JC. Diabetes and noncommunicable disease: prevent the preventables. JAMA 2013;310:916-7.
13. Ma RCW, Tsoi KY, Tam WH, et al. Developmental origins of type 2 diabetes: a perspective from China. Eur J Clin Nutr 2017;71:870-80.
14. Gluckman PD, Hanson MA, Cooper C, et al. Effect of in utero and early-life conditions on adult health and disease. N Engl J Med 2008;359:61-73.
15. Shi Z, Nicholls SJ, Taylor AW, et al. Early life exposure to Chinese famine modifies the association between hypertension and cardiovascular disease. J Hypertens 2017. [Epub ahead of print].
16. Li Y, Jaddoe VW, Qi L, et al. Exposure to the Chinese famine in early life and risk of metabolic syndrome in adulthood. Diabetes Care 2011;34:1014-8.
17. Li J, Liu S, Li S, 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 2017;105:221-7.
18. Ravelli AC, Van der Meulen JH, Michels RP, et al. Glucose tolerance in adults after prenatal exposure to famine. Lancet 1998;351:173-7.
19. Lumey LH, Stein AD, Kahn HS, et al. Cohort profile: the Dutch Hunger Winter families study. Int J Epidemiol 2007;36:1196-204.
20. El-Osta A, Brasacchio D, Yao D, et al. Transient high glucose causes persistent epigenetic changes and altered gene expression during subsequent normoglycemia. J Exp Med 2008,205:2409-17.
21. Heijmans BT, Tobi EW, Stein AD, et al. Persistent epigenetic differences associated with prenatal exposure to famine in humans. Proc Natl Acad Sci USA 2008;105:17046-9.
22. Li Y, He Y, Qi L, et al. Exposure to the Chinese famine in early life and the risk of hyperglycemia and type 2 diabetes in adulthood. Diabetes 2010;59:2400-6.
23. Nanditha A, Ma RC, Ramachandran A, et al. Diabetes in Asia and the Pacific: implications for the global epidemic.

Diabetes Care 2016;39:472-85.
24. Pan XR, Li GW, Hu YH, et al. Effects of diet and exercise in preventing NIDDM in people with impaired glucose tolerance. The Da Qing IGT and Diabetes Study. Diabetes Care 1997;20:537-44.
25. Knowler WC, Barrett-Connor E, Fowler SE, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med 2002;346:393-403.

doi: 10.21037/jphe.2017.10.01
Cite this article as: Zimmet PZ, El-Osta A, Shi Z. The diabetes epidemic in China is a public health emergency: the potential role of prenatal exposure. J Public Health Emerg 2017;1:80.

