From surveillance to causation: advancing aetiological insights with cohort evidence

Fiona Bragg[1,2], MBChB; Zhengming Chen[1], MBBS

1. Clinical Trial Service Unit & Epidemiological Studies Unit (CTSU), Nuffield Department of Population Health, University of Oxford, UK
2. Health Data Research UK Oxford, University of Oxford, Oxford, UK

Address for correspondence:

Prof Zhengming Chen
CTSU, Nuffield Department of Population Health
BDI Building, Old Road Campus
University of Oxford
Oxford OX3 7LF, UK
Email: zhengming.chen@ndph.ox.ac.uk

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Abbreviations

CHD	Coronary heart disease
CVD	Cardiovascular disease
CVD EVENTS	Cardiac-cerebral Vascular Disease EVENT Surveillance
ICH	Intra-cerebral haemorrhage
IS	Ischaemic stroke

Despite improvements in prevention and treatment, cardiovascular diseases (CVD) remain a major public health challenge. [1] In China, CVD causes >4.5 million annual deaths[2] and the epidemic continues to evolve. [3] Nationwide surveillance constitutes an important component of the multifaceted approach required to address this challenge. In this issue of JACC, Zheng et al reported findings from a newly established nationwide CVD surveillance study, yielding new evidence about the burden of CVD in China. [5]

The study analysed healthcare and death registry data from China's Cardiac-cerebral Vascular Disease EVENT Surveillance (CVD EVENTS) project, covering 238 million people (~17% of the total population) from 400 sites across China's 31 provinces. It showed an overall CVD incidence rate of 620 per 100,000 population in 2023. Consistent with existing knowledge of CVD epidemiology in China, but in contrast with most populations globally, [1] stroke incidence rates were about four times as high as rates of coronary heart disease (CHD) (491 vs. 129 per 100,000). Moreover, the high rates and disparities in CVD burden, for example, by age, sex, region and level of socioeconomic development, are broadly comparable with previous studies in China. [2,3]

Apart from its unique size and nationwide coverage, an important strength of CVD EVENTS is the focus on CVD incidence and differentiation between first and recurrent events. This granularity contributes new insights into the evolving natural history of CVD in China, showing the relatively high proportion of recurrent events (17%). This provides new data to inform prioritisation and resource distribution to both maximise primary prevention and address inadequate secondary prevention of CVD. [4,5]

Understanding the burden of CVD through surveillance can highlight public health priorities and inform health policy and programme planning, implementation and evaluation. However, this is also dependent on appropriate understanding of disease aetiology, including causal risk factors, typically derived from population-based cohort studies. Several such studies have been established in China during recent decades, including the China Kadoorie Biobank (CKB), [6] the Shanghai Men's and Women's Health Studies[7,8] and more recently as part of the Million Cohort Initiative. [2]

Findings from these studies provide aetiological insights into lifestyle factors underlying the higher age-standardised CVD incidence rates among men than women reported by Zheng. In China, national surveillance data showed persistently higher prevalence of tobacco smoking and alcohol drinking in men (both ~60%) than in women (~2% and ~20%, respectively). [9,10] As well as confirming these disparities, [11,12] cohort studies have provided vital evidence of the causal importance of these lifestyle factors for CVD. For example, using Asian-specific genetic variants strongly affecting alcohol metabolism, CKB has demonstrated for the first time that alcohol intake uniformly increases stroke risk, with those drinking moderately (i.e. one to two drinks a day) having 12% higher risk and with alcohol intake accounting for about 8% of ischaemic stroke (IS) and 16% of intracerebral haemorrhage (ICH) among men in China. [12] These findings help to plausibly explain the marked sex-difference in haemorrhagic stroke incidence observed in Zheng's report. Likewise, rates of cigarette smoking have increased substantially among recent generations of Chinese men, first in urban and then rural areas, in contrast with a decreasing trend among women during the same period. [11] Furthermore, progressively younger age at starting and exclusive use of manufactured cigarettes (as opposed to traditional forms of tobacco) have led to rising CVD (and many other diseases) risks per smoker. [11] As a consequence, not only has smoking contributed to existing higher CVD rates among men in China, but future smoking-attributable disease burden and associated sex-differences are projected to increase, particularly in rural areas. Appropriate understanding of sex-specific associations with CVD of lifestyle and other factors (eg, medical history) has also facilitated development of risk prediction models, enabling enhanced individual-level primary prevention. [13] Nationwide surveillance programmes such as CVD EVENTS will be essential for monitoring the evolution of the tobacco epidemic and rising sex-disparity in CVD burden (and life expectancy) over time, as well as the effectiveness of prevention efforts.

In a country as large and diverse as China, regional variation in disease burden is inevitable. As expected, Zheng found higher CVD incidence rates in China's northern regions, likely reflecting effects of lifestyle, environmental and genetic factors. For example, a recent report from CKB using *MHTFR* genotype as a proxy for homocysteine exposure demonstrated eight-fold (5%-41%) differences in TT genotype frequency (associated with higher homocysteine levels) across 10 study

sites and that individuals with the TT genotype had 13% (95% CI: 9-17%) higher stroke risk (IS: 1.11 [1.07-1.15]; ICH: 1.24 [1.17-1.32]), but not CHD risk, compared with the CC genotype. [14] In China, population mean blood folate levels were much lower than in typical Western populations due to lack of mandatory folic acid fortification (which reduces homocysteine levels). [15] Together with CKB findings, this may explain, at least in part, the high stroke burden and geographical variation in stroke incidence. In contrast, previous studies of *MTHFR* genotype and randomised trials of homocysteine-lowering interventions in populations with adequate folate levels as a consequence of fortification failed to demonstrate any apparent effects on stroke. [16] These highlight the potential value for stroke prevention in China of folic acid, including through policies for mandatory food fortification, and of further randomised trials of folate supplementation. Moreover, they illustrate the need for aetiological evidence from diverse populations with different exposures, disease rates and genetic architecture.

Higher average blood pressure during winter months is widely reported, [17] reflecting clinically relevant correlation with ambient temperature. [17,18] Previous CKB findings indicated that each 10˚C lower ambient temperature was associated with ~6/2 mmHg higher systolic/diastolic blood pressure. [18] In combination with the known causal relationship of blood pressure with CVD, stronger for stroke than for CHD, [19,20] and excess CVD rates in winter associated with low ambient temperature, [21] this supports Zheng and colleagues' suggestion that blood pressure contributes to observed seasonal variation in CVD incidence, including higher rates during winter months. Moreover, it likely also contributes to higher CVD rates in China's northern regions, with more extreme cold winters. In a population in which hypertension and other CVD risk factors are frequently inadequately detected and managed, [22,23] such seasonal effects should be considered, with intensification of blood pressure monitoring and treatment during winter months. [24,25] There was also good evidence from CKB that among participants living in northern regions, proper central heating markedly attenuated the winter increase in blood pressure, [18] highlighting a further potential strategy, informed by combined insights from surveillance and cohort studies, for reducing CVD burden in these populations.

Surveillance is a vital tool in disease control efforts. However, to maximise potential additional gains for population health, CVD EVENT should also aim to expand by integrating other data types and sources, including CVD risk factor, environmental monitoring (eg, air pollution, ambient temperature) and personal wearables (eg, physical activity) data. Moreover, as described, surveillance data are of greatest value when integrated with aetiological evidence from cohort studies. Together, these can provide a comprehensive understanding of the burden, geographical distribution, time trends and determinants of CVD. As well as facilitating the development of new initiatives to prevent and manage CVD, surveillance will play an important role in informing the future targeting, implementation, monitoring and evaluation of these initiatives that are vital for the success of efforts to tackle the continuing threat of CVD to the health of China’s population.

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