

# Unveiling the causes of heart disease in China

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Despite more than 80% of the global burden of cardiovascular diseases now occurring in low- and middle-income countries,<sup>1</sup> most of what we know about the causes of these diseases comes from studies of populations in North America and Western Europe. Many of the resulting clinical and public health policies in these high-income regions are being applied in lower-income regions, but perhaps sometimes inappropriately, since many lower-income countries have physical, social and economic environments that are substantially different from those in richer parts of the world. Helping to close this gulf in cardiovascular knowledge is the INTERHEART case-control study. Spread across one-quarter of the world's countries, including 30 or so lower- and middle-income countries, the study is a unique resource for assessing causes of coronary heart disease in different contexts.<sup>2-5</sup> For this reason, and because of its sheer size (12 000 cases of acute myocardial infarction (AMI) and 15 000 controls), INTERHEART has rightly become a landmark study.

New INTERHEART findings for China are unveiled in this edition of the journal (*see page 1857*).<sup>6</sup> The 12 000 INTERHEART cases included 3000 in China, and the results for this subgroup are compared with those for the other 51 countries taken together. While all nine main INTERHEART cardiovascular risk factors were associated with MI in the China subgroup, there was significant heterogeneity in the strength of the association for some of these factors between China and the rest. The results suggest that the effects of diabetes and of psychosocial stress may be unusually strong in China, that the effects of abdominal obesity may be unusually weak, and that there are substantially different distributions of major risk factors between the north and the south of the country.

Other studies have also shown great differences in risk factors (and in cause-specific mortality rates) between the north and the south,<sup>7,8</sup> as well as between the affluent coastal belt and poor inland areas, and even between quite nearby areas that have distinct cultural traditions.<sup>7</sup> Indeed, China is epidemiologically more diverse than some continents, and should not be considered an epidemiologically monolithic entity. Furthermore, many of the differences in mortality patterns between areas cannot be accounted for by differences in known risk factors,<sup>7</sup> which suggests that important causes of disease, including of heart disease and stroke, might yet await discovery in China.

INTERHEART is less concerned with new risk factors, though, than with established ones, and among those that it assessed are three anthropometric measures: body mass index (BMI), waist circumference and waist to hip ratio. In 2005, the study reported that the overall association of MI risk with waist to hip ratio was twice as strong as that with waist circumference, and an even more extraordinary four times as strong as that with BMI.<sup>3</sup> Furthermore, although the association with BMI was quite strongly positive in several ethnic groups, there was no evidence of an important association at all in two ethnic groups: Arabs and South Asians. These were not oversliced subgroup analyses: each analysis involved over 1000 cases, and the resulting confidence intervals were narrow. If correct, these are radical findings.

However, a couple of vexing problems may lurk in the detail. First, the overall association with BMI reported in INTERHEART was much weaker than has been reported for large-scale prospective studies. For example, a collaboration sharing data from 57 prospective cohort studies (the Prospective Studies Collaboration) recently reported<sup>9</sup> that each 5 kg/m<sup>2</sup> higher BMI was associated with about 40% higher coronary heart disease mortality (hazard ratio = 1.39, 95% CI 1.34 to 1.44), whereas in INTERHEART the same difference in BMI was associated with just 12% higher

MI risk (odds ratio = 1.12, 95% CI 1.08 to 1.16).<sup>3</sup> That is, the INTERHEART result was weaker by two-thirds. MI is the main type of event by which coronary heart disease kills, so it is odd that the results of these two big studies should be so discrepant. There is no obvious explanation.

Second, in INTERHEART there was major heterogeneity between ethnic groups not only with respect to BMI, but also with respect to waist circumference and waist to hip ratio, and in ways that are more startling than the text of the 2005 paper reveals.<sup>3</sup> For, whereas BMI had no discernible association with MI risk in Arabs or South Asians, waist to hip ratio had an especially strong association in each, a finding taken in the paper to mean that central adiposity is more important than general adiposity for these ethnic groups in particular. But, in the same ethnic groups, waist circumference was *also* not associated to any notable extent with MI risk. The waist to hip ratio finding for Arabs and South Asians must therefore reflect, almost entirely, strong inverse associations with hip circumference. This implication is so unexpected that it is hard to know what to make of it biologically, epidemiologically, or for clinical or public health. Indeed, little has been made of these curious details, and appropriately so, as they probably should not be relied upon until confirmed by evidence from large-scale, local, prospective cohort studies. Some such studies are underway in China<sup>10</sup> and elsewhere,<sup>11-13</sup> but others may well be needed.

Prospective cohort studies have potentially important advantages over case-control studies. For example, they are not susceptible to the biases that occur in case-control studies when the controls are not adequately representative of the population that was at risk of becoming cases (selection biases), and they are less susceptible to the effects of disease on risk factor levels (reverse causality). But, case-control studies also have some important advantages. Most notably, they are usually quicker and more cost efficient than prospective cohort studies, since for a given outlay of resources they can much more rapidly accumulate large numbers of cases. Furthermore, case-control studies often allow disease status to be ascertained with greater rigour than is possible in prospective cohort studies. In a world that needs to both husband resources and to do epidemiological studies with large numbers of rigorously ascertained cases (so that causes of ill health can be assessed reliably), there is an important place for

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big case-control studies of disease, disability and death in many different parts of the world. But, such studies must avoid the main potential pitfalls of case-control studies, by strenuously taking steps to avoid selection bias, and by avoiding questions for which reverse causality may be intractable.

Where does this leave China? To inform clinical, public health and research decisions, China continues to need nationwide monitoring of cause-specific mortality rates, health care utilisation and risk factor levels.<sup>9</sup> It also needs big epidemiological studies—including both case-control and prospective cohort studies—of common causes of death and disability in the population (such as stroke, heart disease, diabetes, cancer and chronic lung disease). Of particular concern are the effects of tobacco on future health in China since, for example, about two-thirds of Chinese men start smoking cigarettes in early adult life. Although smoking is already known to be a major cause of heart disease (as well as of many other conditions) in China,<sup>14 15</sup> the hazards from tobacco are expected to increase substantially during the next few decades as a delayed effect of the recent rise in cigarette use.<sup>16</sup> Further increases in obesity in China as a result of changes in dietary patterns and physical activity may exacerbate these and other hazards.<sup>17</sup>

Similar problems now afflict many other developing populations around the world. Working out the reasons for the distinctive patterns of disease in China may benefit not only its people but also, indirectly, people in other developing populations. The INTERHEART paper in this issue of the journal is a step along that path.

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