

The Rise of ST-Elevation Myocardial Infarction in Women of Northeast China

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Abstract

The women of China's Liaoning province display some morbidities in ways that defy medical explanation. Women have higher rates of hypertension, hypercholesterolemia, and metabolic syndrome than men, an anomaly for all three conditions. Most of these patients also suffer from Type 2 Diabetes Mellitus (T2DM) while there was a negative association between being female and T2DM for the rest of China. Each of these conditions can exist independently, but the increase in both their rates and congruence is a recent phenomenon. Stranger still is that Liaoning women are now presenting in hospital emergency departments with ST-Elevation Myocardial Infarction (STEMI), while diabetics predominantly suffer more benign Non-STEMI (NSTEMI) events. Confounding factors in any attempt to study this phenomenon include trace metals like manganese that have been shown to reduce systolic blood pressure in Asian men and raise it in Asian women. Some of the phenomenon may also be associated with the gene for Apolipoprotein 5, but its recent nature suggests other factors besides lipid profiles. Trace metals in the air, water, and diet of Liaoning province, or any urban environment, could play a role.

Keywords

ST-segment elevation myocardial infarction, hypertension, hypercholesterolemia, metabolic syndrome, apolipoprotein A5, hyperuricemia, left ventricular hypertrophy, trace elements, women, genotype, environment, diet, Liaoning, Northeast China

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Introduction

The women of China's Liaoning province display some morbidities in ways that defy medical explanation. Women in Liaoning have higher rates of hypertension than men, an anomaly. The same holds for rates of hypercholesterolemia (37.3% for women and 34.1% for men; Zhang et al., 2009). The rates are not only higher than for men in the province, but higher than all of China's other provinces (Zhang et al., 2018). Metabolic syndrome (MetS) again followed the same gender disparity (56.4% vs. 29.2%, $p < .001$), usually with Type 2 diabetes mellitus (T2DM) (Yu, Guo, Yang, et al., 2015). There was a negative association between being female and T2DM for the rest of China (Zhou, Liu, et al., 2018). Stranger still is that Liaoning women are now presenting in hospital emergency departments with ST-Elevation Myocardial Infarction (STEMI), while diabetics predominantly suffer Non-STEMI (NSTEMI) events. Admission rates for STEMI in the province rose from 3.5 per 100,000 people to 15.4 between 2001 and 2011, 10 years (Li et al., 2015). Confounding factors in any

attempt to study this phenomenon include trace metals like manganese that have been shown to reduce systolic blood pressure in Asian men and raise it in Asian women (Zhou et al., 2016). All these details were contained in separate papers and no published study at the time of this writing has been found that connects these disparate facts; no hypotheses exist. This review is an attempt to remedy that absence.

Hypertension, hypercholesterolemia, and T2DM can all exist independently. Patients can have HCh or T2DM and still be normotensive. They can have HTN without HCh or other dyslipidemias. The increase in both their rates and congruence is a recent phenomenon. The change in these disorders would likely have surfaced before now if the cause was purely genetic, but whatever

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Figure 1. China and its administrative areas.

agent is at work has some latency and the end result appears to be STEMI events.

Background

Liaoning province, on China's northeast coast, is one of 23 provinces considered first-level administrative areas, self-governing but answerable to the larger state. The province borders the Yellow Sea and North Korea and its population is largely urban, but mostly sedentary during the colder months due to a Siberian weather pattern. Heavy industries have dominated the local economy since the 1930s. The weather also keeps most rural residents indoors where many are prone to eat, smoke, and drink more than usual. Medical treatment and education levels in rural areas lags behind other provinces and Dong et al. (2008) argued the result is a tendency for those residents to be largely unaware of hypertension and its control. Hypertensives usually go without medication, 40.2% because of their lack of awareness and 32.3% due to financial concerns. The authors wrote that 43.9% felt there was no danger to their lives (see Figure 1).

However, hypertension (HTN) has steadily and substantially increased in China's Liaoning province since 1970 (Zhao et al., 2019). Dietary changes in the province did not really begin until the 1990s with a shift

away from the traditional Chinese diet of rice, pork, and vegetables toward more "Western" fare (Yun et al., 2018). The population has also become more urban with time and better educated residents would normally tend to have lower blood pressure. Rural residents now account for about 40% of Liaoning's population, with the rural share dropping by 56% between 2000 and 2019 (CEIC, 2019). The fact that makes this trend more unusual is that women of Liaoning have higher rates of HTN than men.

A cross-sectional study in 2006 found the prevalence of HTN in the province for adults between the ages of 35 and 85 are 38.6 % for women and 37.0% for men ($p < .001$) (Zhao et al., 2019). Data from the 2009 China Health and Nutrition Survey (CHNS) conducted every 2 years showed that for adults in a narrower cohort >60 the patterns still held, 48.9% in women and 47.0% in men (Xu et al., 2018). The CHNS is part of China's health surveillance strategy and national averages for HTN in China were 27.2% in women and 28.6% in men during a 2006 study. Earlier studies of HTN in Liaoning also showed the rates for women were lower than men, consistent with findings in Europe and elsewhere, so this is a recent phenomenon (Zhao et al., 2019).

The same gender patterns hold in Liaoning for hypercholesterolemia (HCh) based on the 2009 CHNS

where 37.3% of women were diagnosed compared with 34.1% of men (Zhang et al., 2018). The same gender pattern again applies to metabolic syndrome (MetS), where 56.4% of women in the province with HTN were diagnosed compared to 29.2% of men (Yu, Guo, Yang, et al., 2015). The regional stratification of hypertriglyceridemia (HTG) and HCh are greatest in China's northeast, but family history of Type 2 diabetes mellitus (T2DM) played a greater role in the south (Zhou, Liu, et al., 2018). However, mixed dyslipidemias were found in 14.3% of Liaoning's population and isolated hypertriglyceridemia (HTG) was found in 5.6% (Dong et al., 2008). There is also evidence that HCh buffers the vascular effects of HTN at the microvascular level (Yildirim et al., 2016). The high rate of MetS is then itself a mystery.

MetS may also explain why women in Liaoning are appearing in hospital emergency departments with ST-Elevation Myocardial Infarction (STEMI). Diabetics normally present with Non-STEMI (NSTEMI) events and the genes for the eNOS and MRP4 proteins may play a role (Biasucci et al., 2017). However, Yu, Guo, Yang, et al. (2015) found that women in Northeast China with MetS and hyperuricemia have a pronounced risk of left ventricular hypertrophy (LVH; Yu et al., 2016). Multiple regression analysis of data from 11,107 patients showed the odds ratios for LVH in women were 3.427 and 1.987 for men ($p < .001$). However, women in Northeast China with MetS and not hyperuricemia had a lower odds ratio for LVH [OR (95% CI): 2.313 (1.991–2.686)], but it was still higher than in women with hyperuricemia alone [OR (95% CI): 1.917 (1.166–3.151)]. The link between MetS and LVH is important because LVH was found in 55% of STEMI patients through cardiovascular magnetic resonance and meant larger infarct size (Stiermaier et al., 2018).

The problem is the need to prevent MetS, which would prevent MetS from leading to LVH and the rise in STEMI. However, the metabolic trends are fairly recent phenomena in diseases where the etiology for each is still not completely understood. We discuss the genetic aspects and apolipoproteins at length, but the rise in MetS would have occurred long before the Millennium if purely genetic. We have to consider an agent with some latency. We plan on a clinical phase with sufficient controls to meet the n/10 rule for each of the many confounding variables. For the purpose of this paper, though, we use a hypothesis that trace metals from diet and environmental sources are essential to the development of MetS.

Search Strategy

We searched Google Scholar, PubMed, MEDLINE, EBSCO, Science Direct, China National Knowledge Infrastructure (CNKI), Chinese Biomedical Database (CBM), China Science and Technology Journal

database (VIP), and the Wanfang (Chinese Medicine Premier) databases for relevant studies from January 2000 until November 2019. The timeframe was chosen because many health surveillance studies in China are conducted on a 2-year, 5-year or 10-year basis. Ancestry searching, the review of bibliographies contained in selected papers, often produced results that were too narrow for the purpose of this paper or outdated. Hand searching was not feasible, though the indices of selected publications were reviewed. Boolean and wildcard search techniques often produced results of uneven quality or relevance. Many papers were rejected because of political material or questions over peer-review. However, many papers from smaller publications were included because they were deemed rigorous and largely compliant with PRISMA 2009 standards.

Methods

“Because of pressure for timely and informed decisions in public health and medicine and the explosion of information in the scientific literature, research results must be synthesized to answer urgent questions” (Stroup et al., 2000, p. 2008). The authors represent the Meta-analysis of Observational Studies in Epidemiology (MOOSE) Group at the U.S. Centers for Disease Control and Prevention (CDC). “However, in many situations randomized controlled designs are not feasible, and only data from observational studies are available” (p. 2008). Constraints include time, controls, or exposure to harmful agents that would make a randomized clinical trial (RCT) unethical. Stroup and the MOOSE group also argue that systematic reviews and traditional literature reviews are themselves observational studies. Rothman et al. (1998) wrote “Studies in which validity is less secure have sometimes been referred to as ‘hypothesis-generating’ studies to distinguish them from so-called ‘analytic studies,’ in which validity may be better” (p. 78). However, the team prefers the term “hypothesis-screening” since investigators create the hypotheses and any kind of data can test them before moving to more rigorous and costlier designs.

We were aware of these limitations from the beginning and took measures to increase rigor since clinical methods are currently impractical. We adapted the CDC/MOOSE guidelines to this paper because the group shared its findings with the Cochrane Collaboration and the guidelines promote greater rigor than the 2009 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist. However, the PRISMA Group's efforts serve a vital role in research and our choice was situational.

We searched for papers related to the problem in five main fields; cardiometabolic disorders; cardiovascular disease; left ventricular hypertrophy; ST-Elevation Myocardial Infarction; and the effects of trace metals, either from dietary or environmental sources. We did not

set out with those five fields in mind. The review began by noting HTN followed an unusual pattern in Liaoning that correlated with a rise in STEMI and expanded from there. It was later noted that many of the factors involved go beyond dichotomies of Han or minority, urban or rural, and may be issues elsewhere in Asia and beyond.

Some of the 120 papers we gathered were meta-analyses, but the vast majority addressed either cohort or case-control studies. A few were about randomized clinical trials. It may sound strange, but the amount of relevant literature was rather small. A vast literature base exists on STEMI, HTN, and T2DM, just not in the context of Northeast China or North Asia and our survey of the apolipoproteins showed particular genotypes are pertinent. There are also a number of confounding factors besides the typical. Adjusting for all of them obliterated any gender differences in some papers and emphasized them in others, but that suggests a need for better methodologies. There was no need for data coding, multiple raters, blinding, or rater reliability for this paper. We did, though, review each other's list of candidates for this study before deciding on their inclusion.

Literature Review

A person can be normotensive while diagnosed with HTG, HCh, or both. Hypertension does not always correlate with lipid profiles. A similar relationship can be seen with HTN and diabetes. The Hong Kong Cardiovascular Risk Factor Prevalence Study found 42% of diabetics were normotensive while 56% with HTN had normal glucose tolerance (Cheung & Li, 2012). It was noted earlier that HTN in Liaoning did not begin a steady rise until about 1970, but any way to negate the progression toward MetS and LVH will save lives, so we searched for clues in the literature.

Cardiometabolic Factors and Cardiovascular Disease

At least one-third of people in Western Europe have both HTN and HCh and the renin-angiotensin-aldosterone system and oxidative stress have been proposed as a link to atherosclerosis (Ivanovic & Tadic, 2015). Endothelial dysfunction and increased production of endothelin-1 are also suspected. However, most of the research related to Liaoning and Northeast Asia is focused on the liver and apolipoprotein A5 (APOA5). APOA5 has an essential role in lipid metabolism and in the 20 years since its discovery has been linked to MetS, but the mechanism remains unclear (Su et al., 2018). The protein regulates triglycerides by lowering production of very-low density lipoproteins (VLDL) and increasing production of lipoprotein lipase (LPL) (Sibuea et al., 2015). Three single-nucleotide polymorphisms (SNPs) of the gene for APOA5 (rs662799,

rs3135506, rs2075291) are instead associated with higher plasma triglycerides (Hubacek, 2016).

Xia et al. (2015) used case-control methods to find that all SNPs on the gene for APOA5 were associated with increased risk of HTG and coronary artery disease (CAD) in Asians. A similar association in Caucasians was found in only a handful of genotypes. Another study explored the role of APOA5 rs662799 in Korean databases (Kim et al., 2018). The minor C allele variant found in about half the population had the same effect as in Chinese studies, lower HDL and higher TG levels. However, Evans et al. (2005) reported increased TG and lower HDL were greater in patients who also had at least one $\epsilon 4$ allele in the APOE gene. SNPs in the $\epsilon 2$ allele of the APOE gene were also found in most patients with Type III hyperlipidemia (HLP), though only 10% with these polymorphisms went on to develop the condition. The majority of that 10% which developed HLP, which was 53%, also had at least one polymorphism of APOA5. The findings suggest that more than one genetic or metabolic factor is responsible.

The kidneys need to be considered as well as the liver when it comes to heart health and a rise in hyperuricemia (HUA) in China has been noted since 2005 (Yu et al., 2016). Adjustment for confounding factors showed HUA in Northeast China associated with abdominal obesity, general obesity, HTG, HTN, HCh, and low HDL-C in both genders. Significantly, hyperuricemia was related to diabetes and high LDL-C in women only. Ma et al. (2019) used multiplex polymerase chain reaction to genotype 47 SNPs already associated with obesity and MetS and discovered some were also associated with uric acid levels. The team adjusted for body mass index and central obesity and found the MSRA polymorphism rs545854 was an independent factor for the risk of HUA (OR=2.81, 95% CI=1.18–6.70, $p=.0196$). This brings us back to MetS, mentioned at the beginning of the section, as hyperuricemia is a risk factor for all of the syndrome's components.

The question, though, is which comes first. HUA and obesity together are associated with a significant risk of HTN (Tian et al., 2019). Ma et al. (2019) assessed 8,331 participants in four groups in Liaoning province: normal body mass without HUA; obese (BMI > 25) without HUA; normal body mass with hyperuricemia; and obese with HUA. The obese-HUA group had a significantly elevated risk of HTN (OR 2.98 [95% CI: 2.48–3.57]) while the risk for those with HUA alone was barely altered (OR 1.14 [95% CI: 0.92–1.42]). Tian et al. (2019) found that the risk of HUA and obesity combined was greater than the risk presented by either factor alone. Obesity also gradually increased in China between 1992 and 2017 while the importance of a family history for T2DM, a component of MetS, declined (Zhou, Liu, et al., 2018). Researchers anticipated finding a small number of genes with large effects and argued the reality

is instead a large number with small effects, which leaves substantial room for external influence.

Metabolic Disorders and Left Ventricular Hypertrophy

The association between HUA and MetS is a strong predictor of left ventricular hypertrophy (LVH) in the women of Northeast China (Yu, Guo, Yang, Zheng, et al., 2015). The left ventricular mass index for height 2.7 (LVMH2.7) was significantly higher in women of a hyperuricemia/MetS patient group than for those in a normouricemia/non-MetS control (52.43 ± 16.60 g/m^{2.7} vs. 40.04 ± 10.72 g/m^{2.7}, $p < .001$). Multiple regression analysis put the odds ratios for LVH at (OR: 3.427 for women [$p < .001$], OR: 1.987 for men [$p < .001$]). It was also found that either HUA or MetS alone will increase the odds of LVH, but the risk is greatest with both in combination. This finding in Northeast China matters because LVH was found in 55% of patients with ST-Elevation Myocardial Infarction (STEMI) and meant larger infarct size (Stiermaier et al., 2018).

Pre-existing LVH also meant lower myocardial salvage index (47.8 vs. 54.4; $p < .01$), larger extent of microvascular obstruction (0.4 vs. 0% LV; $p < .01$) and lower LV ejection fraction (47.9% vs. 53.2%; $p < 0.01$) compared to STEMI patients without LVH (Stiermaier et al., 2018). Cardiovascular magnetic resonance imaging was performed on 795 patients within 10 days of their event. Major Adverse Cardiovascular Events (MACE) at 12 months were numerically higher for LVH patients but not to the point of statistical significance. Similar results were found after examining 30-day survivors of STEMI in patients with LVH (Park et al., 2015). Another difference is that patients had also received percutaneous coronary intervention (PCI) by that time. All-cause mortality (OR: 5.110; 95% CI, 1.454–17.9, $p < .001$) was independently associated with LVH severity. Similar findings were reported from a Danish hospital except the proportion of STEMI patients with LVH was about 33%, not the 55% in Northeast China, which suggests LVH varies by ethnicity (Nepper-Christensen et al., 2017).

Biomarkers creatine kinase-MB (CK-MB) and troponin I were shown to be poor predictors of infarct size in patients with LVH after STEMI (Daaboul et al., 2016). Left ventricular mass was found to be an independent predictor and accounted for about half the variance from predictions based upon biomarkers alone. LVH also increases LV wall tension and subjects sub-endocardium to ischemia, which leads to larger necrotic areas after STEMI (Cetin et al., 2018). These factors may lead to adverse remodeling after an event, but metformin may be able to reverse LVH by reducing inflammation and insulin resistance (Mordi et al., 2018). A randomized clinical trial showed 12 months of metformin reduced

the LV mass index compared to a placebo in diabetics. Diabetic patients treated with other drugs than metformin fared worse. However, many diabetics in Northeast China are already using metformin and efforts are underway to find alternatives for use where metformin as a monotherapy is inadequate (Du et al., 2017).

Another item for future research not yet addressed in any study of acute myocardial infarction (AMI) in Liaoning is that HCh prevents ischemic post-conditioning, though the mechanism is unknown (Wu et al., 2015). The most common dyslipidemia in Liaoning is isolated HCh, found in 34.1% of men and 37.3% of women with diabetes (Superko et al., 2017). The average level of all blood lipids for HTN patients in Liaoning was higher in women than men (Liu et al., 2007). However, the study did not differentiate whether patients were taking metformin.

ST-Elevation Myocardial Infarction (STEMI)

It was noted earlier that diabetics predominantly suffer more benign NSTEMI events, while women in Liaoning increasingly present with STEMI. The goal is to perform PCI within 120 minutes of a STEMI diagnosis to reduce infarct size or provide thrombolytics beyond that window (Vogel et al., 2019). However, STEMI is difficult to diagnose from ECG alone (Sullivan et al., 2016). There are a number of mimics and troponin assays usually used to diagnose NSTEMI are not helpful in this case. Another factor affecting patient prognosis is that only half of men with STEMI arrived within two hours of the onset of symptoms in all of China, and only one-third of women (Zhang et al., 2016). There are few studies of prehospital delay in China and most were conducted in the Beijing area, which means delays could be longer.

The gender difference will likely remain, though, due to different symptom profiles for women and psychological factors. Women in general present far less frequently with chest pain or discomfort than men (averages of 42.0% for women and 30.7% in men) and that gap is more pronounced in younger patients (Canto et al., 2012). The results are from a study of the U.S. National Registry of Myocardial Infarction and involved 1,143,513 cases, but no comparable data could be found for China. Patients without chest pain tend to present later and are treated less aggressively, almost doubling the short-term mortality compared with those presenting with more typical symptoms (Canto et al., 2012). The difference in presentation within China also ran counter to the Swedish MONICA study and Worcester Heart Attack Study (Zhang et al., 2016). The gender difference and prehospital delay may also contribute to the high proportion of out-of-hospital deaths.

However, in-hospital deaths for women in Liaoning with STEMI events are greater than in men (Zhang et al., 2013). Care and patient data for 1,429 consecutive patients in Liaoning hospitals were analyzed from

24-hours after symptom onset with patients divided into two groups depending on whether they received PCI. The PCI group showed mortality for men was 4.2% and 11.2% for women ($p < .001$). The non-PCI group ($n=675$) saw 13.0% of men die within 24-hours compared to 22.9% of women ($p < .001$). Multivariate linear regression suggests that being female in Liaoning is an independent risk factor for early death after STEMI (OR: 1.691, $p = .007$).

Cardiometabolic Effects of Trace Metals

The causes of hypertension are still undetermined, but its role in the cascade of dyslipidemias leading to LVH and STEMI events is undisputed. Dong et al. (2008) argued that both genetic and environmental factors combine. Trace metals need to be considered in any study of Liaoning because prevailing wind patterns in China run from West to East, with the lowest rates of MetS in the West and South and highest rates in six Northeastern provinces, including Liaoning. Some heavy metals are essential to life, like iron, copper, manganese, and zinc. However, too much can be bad, and these can also be replaced by heavier metals with a similar valence configuration. Cadmium, as one example, can replace iron and copper within cell structures and create oxidative stress (Akther et al., 2019). Several metals that are common pollutants (including arsenic, lead, cadmium, and copper) are associated with an increased risk of cardiovascular disease (CVD) and coronary heart disease (Chowdury et al., 2018). Metals can impair the ability of antioxidant enzymes to scavenge reactive oxygen species (ROS), which are basically cellular waste products. Metals can also subvert function of the renin-angiotensin-aldosterone system so that control of vasoconstriction and dilation itself creates oxidation and damage to endothelium (Akther et al., 2019). The role of iron in the renin-angiotensin-aldosterone system has been linked to both diabetic kidney disease and CVD (Chowdury et al., 2018).

The focus on trace metals is usually at the cellular level, but a Korean team found that manganese (Mn) can reduce blood pressure in a cross-sectional study of 640 normotensive adults equally divided by gender that found the correlation from the participant's normal dietary intake (Lee et al., 2015). However, the benefit was limited to men. A more detailed study showed an association between higher Mn intake and a reduced risk of MetS in Chinese men (Zhou et al., 2016). The mean daily intake of Mn was 6.07 mg for men and 5.13 mg in women, compared with 4.2 mg and 4.1 in the Korean study, with rice being the main source of Mn in the Chinese diet. Manganese was also inversely associated with abdominal obesity and HTG in Chinese men while positively associated with low HDL-C in both men and women. Research suggested the increased risk of MetS in Chinese women may be due to the effect of Mn on HDL-C (Zhou et al., 2016). More metals were

implicated in MetS by a study that compared residents of Shenzhen and surrounding Guangdong province (Lei et al., 2011). The prevalence of MetS in Shenzhen was 7.76%, significantly higher than for Guangdong. T-test analysis of blood samples also showed clear differences in potassium, sodium, iron, manganese, and retinol between MetS and non-MetS participants.

The trend toward a more Western diet, as in Shenzhen, alters the mix of heavy metals further. China has conducted nationwide total diet studies every 5 years since 1990 with cereals and vegetables shown as the main source of exposure for many metals (Wei et al., 2019). Meat, beverages and water are the next most important exposure source. The start of the 5-year surveys in 1990 corresponds with a rise in urban living standards from industrialization. However, the China Health and Nutrition Survey (CHNS) is conducted every 2 years and showed wide fluctuations in the Diet Quality Index (DQI) from 2004 to 2011 (Huang et al., 2017). Income and urbanicity were positively associated with DQI scores, which suggests a shift in diet toward a higher metal load. Middle-aged and older Chinese were less likely to adapt their diets.

Rapid changes in Chinese dietary patterns make it difficult to assess how much of an effect on heart health is due to trace metals or bad food choices. China's change from a traditional diet has been more rapid than in developed nations, especially in urban areas (Yun et al., 2018). Europe and North America transitioned over 200 years toward more animal fat and less fiber. Some researchers blame the changing Chinese diet for higher MetS rates (Fong et al., 2019). CHNS data showed the proportion of Chinese who ate red meat, fish, and poultry grew from 65.7% in 1991 to 86.1% in 2011 (Wang et al., 2015). One study found associations between modern and traditional diets on BMI and waist circumference, but no significant links between diet and HTN (Xu et al., 2016). The same team changed their opinion 2 years later and argued the link between diet and HTN was now clear (Xu et al., 2018). The authors found the traditional Chinese diet (rice, pork, and vegetables) was inversely associated with known HTN. The team also discovered the intake of dietary lead (Pb) was strongly associated with HTN, especially in women.

The other source of trace metal exposure is outside of personal choice, the environment. Liaoning's Hun River contains zinc and copper and feeds the Dahuofang Reservoir, a major source of drinking water for Northeast China (Zhang et al., 2017). A case-control study examined urinalysis of 502 HTN patients and another 502 who were normotensive in China (Wu et al., 2018). Adjusted results suggested environmental Zn and Cu were positively associated with HTN. However, serum zinc levels in another study were also found to be significantly lower in patients with HTN than in controls (Li et al., 2019). Manganese, Cu, and Zn in their +2 forms enable metalloproteins in the cell to fold (Totter

et al., 2008). The Mn bond is stable, but less so for Cu and Zn. However, no mechanisms are known to explain these associations between trace metals and HTN.

Air is another way trace metals can enter the body and the Henan Rural Cohort Study found an association between particulate matter and T2DM (Liu et al., 2019). The study assessed 39,259 residents for their 3-year average exposure to particulate matter with an aerodynamic diameter $\leq 1.0\mu\text{m}$ and $\leq 2.5\mu\text{m}$ (PM1 and PM2.5) through a spatiotemporal model. Increases of $1\mu\text{g}/\text{m}^3$ in PM1 were associated with a 4.0% rise in the odds for T2DM, and PM2.5 at the same concentration produced a 6.8% increase. A randomized study of 24,845 participants selected from across China found a $10\text{-}\mu\text{g}/\text{m}^3$ increase in PM1 and PM2.5 was associated with a 5% increase in odds for HTN (OR:1.05; 95% CI 1.01–1.10) (Yang et al., 2019). Another approach using data from the Henan Rural Cohort Study found each $1\text{-}\mu\text{g}/\text{m}^3$ increment of PM2.5 was associated with increased TC and LDL-C, and decreased TG and HDL-C (Mao et al., 2019). The 33 Communities Chinese Health Study produced similar associations between particulates and blood lipids (Yang et al., 2018). The difference is that the 33 Communities data showed increased TC, TG, and LDL-C while HDL-C was lowered. The strongest associations in these studies were in women, the overweight or obese, and older residents. The results of the three studies suggest that the composition of the particulates may need further research.

Discussion

Rigor was considered a greater issue than bias in the papers we included for this review, which were observational rather than experimental. We included papers published in both large “Western” journals where relevant and smaller parochial journals since the effects on the women of Liaoning can be seen by some as a regional issue. We did not consider the inclusion of Chinese authors or publications an impediment. Tian et al. (2017) used the Assessing the Methodological Quality of Systematic Reviews (AMSTAR) and PRISMA methodologies to assess 100 journals each from the US and China. Scores for journals in both nations using both protocols were comparable, and in many categories China’s authors took the lead for rigor. Tian et al. did, though, suggest that the quality of papers could be improved in both countries.

Statistical methods were appropriate and defended. Epidemiological methods were largely followed, with the greatest weakness being adjustment for confounding variables (Greenland et al., 2016). Some data sets were small, but adequate. Those papers were often the only ones found addressing a specific issue. The converse was large often nationwide databases that diluted the effects of regional variance. We found instances of teams using the same data to reach different conclusions

and included all. We strove to include dissenting views whenever they could be found.

Conclusion

The sudden rise in HTN in China, and Liaoning especially, was not discovered until the 1970s. The rise in obesity was not discovered until the 1990s, and HUA in 2005. The agents at work have some latency and some of China’s health surveillance reporting is too far apart to assess secular trends. Another issue is that the disorders that go into MetS are “multifactorial” and their etiologies are still not fully understood. Evidence we gathered suggests there may be two separate mechanisms at work in the Liaoning population and Northeast China, the renin-angiotensin system and SNPs in apolipoproteins. We considered the effects of diet and airborne particulates and found PM2.5 had the same effects as polymorphisms in APOA5, raised TC, TG, LDL-C, and reduced HDL-C. The parallels suggest a role for trace metals. Future research needs to focus on the role of trace metals in both these mechanisms and developments in one will provide insights into the other. The women of Liaoning provide an opportunity to save lives and learn lessons that can be applied across ethnicities. If HTN and MetS can be prevented through a common pathway, MetS might not lead to STEMI and more deaths.

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