Influenza and Acute Myocardial Infarction

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(See the article by Warren-Gash et al, on pages 1710–8.)

Excess winter mortality is widely recognized in countries with temperate climates, although the cause has been debated for >80 years [1]. Some studies have suggested that environmental factors such as temperature and humidity could be responsible for triggering thrombotic and cardiovascular events [2–5]. The association of winter excess cardiovascular and respiratory mortality with the circulation of seasonal influenza has also been postulated [1, 2, 5–9]. Winter surges in mortality correlate with hospital respiratory and cardiovascular admissions, particularly in the elderly [7, 10, 11]. Estimation of influenza-related excess mortality often includes not only influenza but excess cardiovascular and other respiratory-related deaths, as deaths coded as influenza tend to be few and greatly underestimate the impact of influenza, especially in the elderly [2, 6].

Including excess causes of death other than influenza to measure influenza-associated disease burden is justified because influenza testing is not performed in most cases or when performed, rapid antigen tests with suboptimal sensitivity are often used [12]. In addition, persons with influenza can die from pneumonia, exacerbation of chronic respiratory disease, or secondary complications related to other underlying medical conditions [9, 13]. The direct and indirect effects of influenza on cardiovascular and respiratory mortality are difficult to estimate [13]. Although an association between influenza and cardiovascular events has been described as plausible and demonstrated in many studies [1, 2, 5–9, 14], the specificity of this association has been questioned because the relationship of influenza to specific causes of cardiovascular mortality has not been well described.

In this issue of the Journal, Warren-Gash et al [15] shed considerable light on the complex relationship of climate, influenza, and a major source of cardiovascular mortality, acute myocardial infarction (AMI). Warren-Gash et al assessed the relationship between the circulation of influenza viruses in the community and hospital admissions and death due to AMI in the temperate climate of England and Wales, where influenza has a marked winter peak, and the subtropical climate of Hong Kong, where influenza viruses circulate year-round with much less pronounced peaks during winter and summer months. This natural experiment allowed the evaluation of the relationship of influenza to AMI, independent of cold weather effects. ICD-9 and ICD-10–coded data on AMI–related hospitalizations and deaths were obtained from both jurisdictions from January 1999 through December 2008. General practitioner consultation rates for influenza-like illness (ILI) in the United Kingdom and the percentage of respiratory specimens positive for influenza in Hong Kong were used as measures of influenza activity and compared with AMI hospitalizations and death rates by week. Data were modeled using Poisson regression, where level of influenza activity was the primary exposure, controlling for temperature and relative humidity. Sensitivity analyses were performed for the independent variables. Finally, the percentages of AMI deaths and hospitalizations attributable to influenza were calculated. The authors also modeled coded data on colon cancer and fractured neck of the femur with the same independent variables as controls.

There was a strong association between population levels of influenza and AMI hospitalizations and deaths in both temperate and subtropical climates after adjusting for seasonality and environmental factors. In both countries, the strongest association between influenza and AMI was among the oldest age groups. The sensitivity analyses had little effect on the magnitude or direction of the estimates. Conversely, colon cancer and fractured neck of the femur were not associated with influenza activity. In this study, 3.9%–5.6% of AMI deaths in Hong Kong and 3.1%–3.4% AMI of deaths in
England and Wales were attributable to influenza, while the influenza-attributable proportion of hospitalizations in Hong Kong and England and Wales was 0.7%–1.2% and 3.0%–3.3%, respectively. The influenza-attributable proportion was highest for AMI deaths (10%) and hospitalization (8%) during the most active periods of influenza virus circulation, substantiating the association.

This study is an ecologic study and as such could lead us to draw conclusions about relationships on a population level that may not reflect biologic effects at the individual level (the ecological fallacy). Although the authors attempted to quantify weekly influenza virus circulation, viruses other than influenza were not explored. In particular, infection with other respiratory pathogens such as respiratory syncytial virus and human metapneumovirus can also cause clinical syndromes that are similar to influenza, particularly among older persons [16–18]. An additional limitation of this study is the inconsistent lag times observed between countries and among outcomes for ILI visits/influenza virus circulation and hospitalizations and deaths. Lag times could be related to health-seeking behavior, data reporting lags, or the pathophysiology of influenza-associated AMI. Many influenza-associated deaths from secondary bacterial infections [19, 20] or exacerbations of chronic illness (eg, congestive heart failure, AMI, or chronic obstructive pulmonary disease) occur after the initial infection [21, 22]. Despite its limitations, this well-designed and -analyzed study adds to the pool of evidence supporting a relationship between influenza and AMI independent of temperature and humidity and is the first to our knowledge to propose influenza-attributable proportions for acute myocardial hospitalization and death.

A number of additional ecologic studies have examined the correlation between the timing of influenza virus circulation or ILI and respiratory and cardiovascular mortality [1, 2, 5, 6, 8, 9]; and there are several specifically related to cardiovascular mortality [7, 14]. Despite differences in design and inherent limitations, all of these studies report a moderate to strong correlation between cardiovascular and respiratory mortality and timing of ILI or influenza virus circulation. In Madjid’s study of ILI and autopsy-confirmed coronary heart diseases, influenza epidemics were associated with a 30% increase in autopsy-confirmed AMI [14].

Individual-level observational studies have also corroborated the relationship between AMI and acute respiratory tract infection but have not been specific to influenza. In a small, early case–control study, Spodick [23] found that cases with myocardial infarction were twice as likely to have had a diagnosis of acute respiratory tract infection within 14 days before onset. Among 1922 cases with AMI and 7649 matched controls, Meier et al [22] found significantly more cases diagnosed with an acute respiratory tract infection 10 days prior to myocardial infarction than controls, adjusting for smoking and body mass index. The risk of AMI was 3 times higher in the first 5 days after diagnosis of acute respiratory infection and declined linearly and incrementally to reach baseline levels 30 days after diagnosis. In a large case series study [24], rates of AMI and stroke were substantially higher after the diagnosis of acute respiratory infection. The incidence ratio for AMI was 4.95 in the first 1–3 days after diagnosis and declined linearly to 1.4 after 29–91 days.

A few studies have examined individual-level biologic markers of acute respiratory infection and risk of AMI, but the results have not been consistent. Mattila observed that patients with AMI were more likely than controls to have had a recent ILI, but antibodies to influenza were not consistently positive [25]. Pesonen et al [26] found that cases with an acute coronary event were more likely than age-matched controls to have ILI and markers of acute infection, including elevated C-reactive protein. Guan et al [27] found that cases with AMI were more likely than controls to have positive immunoglobulin G antibodies to influenza A and B after adjustment for confounding factors, but timing of the influenza was unclear.

What pathophysiologic mechanisms might be responsible for the association between cardiovascular mortality and acute respiratory tract infection? Inflammation plays a decisive role in the pathophysiology of acute thrombotic events such as AMI [28, 29]. Vascular events may be related to short-term alterations of endothelial function and vascular relaxation, and these states could cause changes in the composition of atherosclerotic plaques. Acute respiratory infection with concomitant leukocytosis and cytokine response may precipitate atheroma instability and subsequent plaque rupture, causing vascular events in persons who have had fairly stable states of atherosclerosis [22, 24, 28, 29]. Myocardial dysfunction with abnormal electrocardiogram was noted in a study of healthy young adults with influenza and without known cardiovascular disease; more than half of subjects had abnormal electrocardiogram findings within 3 days of influenza onset, and frequency of findings declined to 23% at 28 days [30].

Is there enough evidence to support the association between influenza and AMI? There is consistent ecologic evidence that overall cardiovascular mortality is related to influenza virus circulation and ILI activity, and there is consistent ecologic and individual-level evidence that occurrence of AMI can be temporally related to acute respiratory infection including ILI. These associations have been reproducible in studies with different designs and are biologically plausible. Furthermore, the incidence of AMI declines linearly in relation to the onset of the respiratory infection (dose–response). However, ecologic evidence is not sufficient to answer this question, and most individual-level studies did not use laboratory-confirmed
influenza as the outcome. Thus, there may not be enough evidence yet, but the data are compelling so far. What are needed are individual-level prospective studies of AMI that include laboratory markers of acute influenza infection.

Nevertheless, the study by Warren-Gash et al [15] has important policy implications. Cardiovascular disease is the leading cause of death in the United States: 935,000 myocardial infarctions and 425,000 AMI-related deaths occur every year [31]. Interventions targeted against influenza could avert some proportion of influenza-related AMI. Vaccination is the most important tool available for reducing the risk of influenza illness [32], and increasing vaccination coverage in persons at risk for myocardial infarction might reduce the occurrence of, and death from, AMI [15, 33–36]. Several retrospective studies have evaluated whether influenza vaccination reduces the risk for acute cardiovascular events, but the results have not been consistent among studies [37–41]. Because influenza vaccine effectiveness is suboptimal, especially in older people, the opportunity to prevent influenza-related complications in this population will benefit from the development of more immunogenic and effective vaccines. Antiviral medications can also be used for the prevention and/or treatment of influenza, and limited data suggest that they also likely may reduce the risk for severe illness or death related to influenza [42–45], but the effectiveness in preventing AMI among elderly infected with influenza is unknown. Observational studies among persons with laboratory-confirmed influenza are needed to further understand the influenza-attributable risk for cardiovascular events, the pathophysiology of influenza-related cardiovascular events, and the degree to which influenza vaccine or antiviral agents can avert influenza-related cardiovascular complications.

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**References**


