

Exposure to cold and respiratory tract infections

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SUMMARY

There is a constant increase in hospitalizations and mortality during winter months; cardiovascular diseases as well as respiratory infections are responsible for a large proportion of this added morbidity and mortality. Exposure to cold has often been associated with increased incidence and severity of respiratory tract infections. The data available suggest that exposure to cold, either through exposure to low environmental temperatures or during induced hypothermia, increases the risk of developing upper and lower respiratory tract infections and dying from them; in addition, the longer the duration of exposure the higher the risk of infection. Although not all studies agree, most of the available evidence from lab-

oratory and clinical studies suggests that inhaled cold air, cooling of the body surface and cold stress induced by lowering the core body temperature cause pathophysiological responses such as vasoconstriction in the respiratory tract mucosa and suppression of immune responses, which are responsible for increased susceptibility to infections. The general public and public health authorities should therefore keep this in mind and take appropriate measures to prevent increases in morbidity and mortality during winter due to respiratory infections.

KEY WORDS: exposure to cold; hypothermia; respiratory infections; pneumonia; common cold; influenza

RESPIRATORY INFECTIONS are among the most common acute diseases worldwide, leading to considerable morbidity, complications and days lost from work and school. It has long been observed that the incidence of these infections increases in temperate climates during the colder months of the year. Common cold, pharyngitis, laryngitis, croup, otitis of viral etiology, sinusitis, acute bronchitis, viral exacerbations of chronic bronchitis, bronchiolitis and community-acquired pneumonia all occur with peak incidence during winter. Although possible explanations for this seasonal variation, such as increased crowding of people and other hosts of microorganisms that promote transmission and changes in relative humidity that affect the viability of different microorganisms, have been suggested, the role of exposure to cold per se in the incidence and severity of respiratory tract infections is not well understood. The widespread common belief that there is a relationship between exposure to cold and development of respiratory infections has stimulated research into clinical and laboratory evidence in support of this assumption and in the pathophysiological pathways that lead to the development of infections.

LITERATURE SEARCH AND STUDY SELECTION

We searched the PubMed database for studies on the relationship between exposure to cold, either through

exposure to low environmental temperatures or owing to hypothermia induced for surgical or laboratory reasons, and the development of respiratory infections. The key words we used in our literature search were 'exposure to cold, or cold temperatures, or hypothermia' combined with 'respiratory infections, or pneumonia, or common cold'. The abstracts of the articles initially identified were reviewed to select the relevant studies for a more detailed review. The complete texts of original articles considered relevant to our study were read. Our review was limited to studies written in English and that referred to humans.

ASSOCIATION BETWEEN LOW TEMPERATURES AND INCREASED MORTALITY

Low temperatures are associated with increased morbidity, especially in the vulnerable population groups—children and the elderly—and with excess winter mortality due to cardiovascular and respiratory disease. A large-scale epidemiological study in the elderly in the United Kingdom showed a substantial increase (around 30%) in mortality during winter for this age group, with female sex and pre-existing respiratory illness being determinants of vulnerability. However, low socioeconomic status, an indicator of failure to heat homes, did not affect mortality. This finding is explained by the suggestion that the excess winter mortality was

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Article submitted 23 February 2007. Final version accepted 1 May 2007.

caused by brief outdoor exposure to cold rather than by low indoor temperatures.¹

In another study that used 4-year data on the number of deaths/day and weather conditions in two European cities, cold was found to be highly predictive of mortality.² For each degree of extreme cold, mortality increased by 4.2% in London and by 1.8% in Sofia. The main effects occurred after an interval of 3 days and lasted for at least 3 weeks. Mercer reports that in Europe the excess winter mortality reaches a quarter of a million each year and that cardiovascular diseases are responsible for as much as 70% of these deaths in some countries, whereas about half of the remainder is attributed to respiratory disease.³

EFFECT OF LOW ENVIRONMENTAL TEMPERATURES ON THE INCIDENCE OF RESPIRATORY TRACT INFECTIONS

Hajat et al. investigated the association between low temperatures and consultations for infections of the upper and lower respiratory tract infections among the elderly in the UK.⁴ A strong increase in the relative frequency of general physician consultations for lower respiratory tract infections was observed, particularly once temperatures dropped below 5°C, in most locations studied, with the biggest increase in the Norwich area, where a 19% increase (95% confidence interval [CI] 13.6–24.7) was associated with every 1°C drop in mean temperatures below 5°C observed 1–20 days before the day of consultation. Slightly weaker relationships were observed in the case of upper respiratory tract infections.

It is known that acute laryngitis occurs most frequently with midwinter illnesses. Danielidis et al. showed a statistically significant relationship between several meteorological parameters, such as low temperatures and high humidity, and the occurrence of acute laryngitis ($P = 0.01$).⁵ They observed that significant changes in maximum temperatures (occurring during invasions of cold or warm air masses), as compared to the previous day's conditions favored new cases of the disease.

In a study that examined the relation between the incidence of croup hospitalizations and several meteorological factors, Fielder et al. reported that croup admissions increased significantly during days with lower maximum ($P = 0.001$) and minimum ($P = 0.01$) temperatures, while the wind direction and temperature seemed to be the underlying reason of the development of croup.⁶

Isolated areas of Antarctica, where extremely low temperatures dominate, have often been used for the study of the effects of cold on human health. Muchmore et al. reported a remarkably high frequency of virus isolation from and persistence in throat specimens in a group of 20 socially isolated persons (American Antarctic Research Station personnel).⁷ A total

of 105 routine throat swabs were obtained during the 8.5 months of isolation (six specimens for each participant at intervals throughout this period), 48 of which were positive for *Parainfluenza* virus. Most of the subjects examined (15/20) were found to harbor a respiratory virus more than once, whereas the majority (12/20) were asymptomatic. This persistent virus recovery indicated that the viruses were present for prolonged periods of time in an effective form that could be shed and cause disease. These findings were in accordance with the clinical observation that upper respiratory tract infections occurred among station personnel for several months (2–6 months of isolation in the South Pole).

Another study, also conducted on 16 people at two Antarctic stations, examined shedding of the Epstein-Barr virus (EBV) in saliva specimens and cell-mediated immune responses before, during, and after winter isolation.⁸ The presence of EBV DNA in saliva samples increased from 6% before or after winter isolation to 13% during isolation in Antarctica ($P = 0.013$). Of 16 subjects, 8–11 exhibited diminished delayed-type hypersensitivity reaction to any one of the skin tests. During winter isolation, EBV DNA was shed more frequently when cell-mediated immune response was lower than normal ($P < 0.0005$).

LOW TEMPERATURES AND MORTALITY DUE TO RESPIRATORY INFECTIONS

Huynen et al. conducted a study to investigate the impact of prolonged cold periods, i.e., extreme cold periods lasting at least 9 days, and heat waves on mortality.⁹ The authors found an increase in mortality of 5.2% attributed to respiratory disease for each 1°C drop below the optimum temperature (the temperature value corresponding to the lowest mortality) in the preceding month. This observation was most obvious for the winter of 1985–1986, when the excess mortality due to respiratory disease during a prolonged period with low environmental temperature was 117.2%; the author suggested that an influenza epidemic was responsible for this sharp increase. It is interesting that mortality caused by respiratory diseases seemed to continue during the whole month after the cold period and peaked after mortality due to cardiovascular causes, which were the effect of respiratory cross-infection.

The Eurowinter Group studied cause-specific winter mortality in eight European countries and showed that mortality from respiratory disease, which was generally attributed to cross-infection, increased per 1°C fall in temperature below 18°C, and that higher mortality was greater in warmer regions ($P < 0.01$).¹⁰ Also, mortality from respiratory diseases showed a significant association ($P < 0.05$) with several personal cold exposure factors: people who lived in cooler homes, wore fewer clothes, were less active outdoors

and generally took fewer protective measures against cold were more likely to die from respiratory disease.

Goldsmith et al. reported data from cohorts of infants with cold injury in Israel, a large proportion of whom developed infections (27/51 infants in one cohort), generally pneumonia and sepsis, which were the most common causes of death (5 of 6 infants that died had developed an infection).¹¹ They also suggest that as much as 10% of neonatal deaths attributed to influenza, pneumonia or sudden infant death syndrome in the US may be due to unrecognized cold injury.

DIRECT EFFECT OF LOW TEMPERATURES ON THE RESPIRATORY TRACT

Whether the development of respiratory infections is influenced by the exposure of body surfaces to cold (such as exposure of the feet to cold water or surfaces) is controversial. Some studies support that acute cooling of the body surface is responsible for the onset of respiratory infections. In a case-control study, Johnson et al. showed that acute chilling of the feet caused the onset of common cold symptoms in the 4–5 days following the chill procedure in 26/90 case subjects, compared to 8/90 control subjects ($P = 0.001$).¹²

THERAPEUTIC HYPOTHERMIA AND INFECTIOUS COMPLICATIONS

Induced hypothermia is used to protect the brain, spinal cord and sometimes other organs from post-ischemic and post-traumatic injury. It has been implicated in the development of postoperative pneumonia, among other infections.¹³ Schwab et al. in a study examining the safety and feasibility of moderate hypothermia induced with cooling blankets and ice bags, and its potential to reduce intracranial hypertension in acute stroke patients, found that pneumonia was one of the most frequent complications (48% of patients, a proportion markedly higher compared to those reported from intensive care unit patients), and that its prevalence increased with longer duration of hypothermia.¹⁴ Yanagawa et al. reported that 11 of 13 patients who recovered from out-of-hospital cardiopulmonary arrest and underwent mild hypothermia developed pneumonia, as compared to 5/15 normothermic patients ($P = 0.02$), whereas 4/11 pneumonia patients in the hypothermia group died as compared to 2/5 pneumonia cases in the normothermic group.¹⁵ A meta-analysis of randomized controlled trials that analyzed the effect of hypothermia versus normothermia on mortality and outcome in patients with traumatic brain injury indicated that patients treated with normothermia were less likely to develop pneumonia (odds ratio [OR] for pneumonia in the normothermic group 0.42, 95% CI 0.25–0.70, $P = 0.001$).¹⁶

DATA SUPPORTING THE ABSENCE OF A RELATIONSHIP BETWEEN EXPOSURE TO COLD AND RESPIRATORY INFECTIONS

On the other hand, there are studies that have not found any etiological associations between induced hypothermia and higher risk of pneumonia.^{17–19} In some of these studies it is suggested that infectious complications were avoided because antibiotics were administered to the patients as a preventive measure, or because of a shorter duration of and milder hypothermia, or because of the small study size.

Laboratory studies often fail to prove any relationship between exposure to cold and subsequent immunosuppression and increase of the potential of developing an infection. Castellani et al. showed that after cold-air exposure, there was an increase in leukocyte and granulocyte counts and in plasma IL-6 concentrations, while natural killer (NK) cell activity was not impaired, and that these alterations were influenced by exercise and possibly attributed to stress hormone release;²⁰ they thus concluded that moderate acute cold exposure had no detrimental effect on the innate component of the immune system. Similarly, Delahanty et al. found small and non-significant increase in NK cell activity—NK cells are among the major defensive mechanisms against viral infections—after intermittent immersion of the hands of 31 males in cold (3°C) water for 6 minutes, as compared with significantly increased NK cell activity after exposure to another laboratory stressor, a mental arithmetic task.²¹

Christie reported a reduction in the number of colds developed in volunteers exposed to low temperatures before virus inoculation,²² while Douglas et al. failed to prove any effect of exposure to cold on susceptibility to infection in a similar design study.²³

A review of randomized clinical trials that examined the effects of heated water vapor in the treatment of the common cold also argues the positive association between inspiration of cold air and increased risk of infection and the hypothesis that increase of nasal mucosal temperature helps inhibit rhinoviral replication.²⁴ There was no difference regarding the decrease of symptoms between the treatment and control groups, and there was no evidence of decreased viral shedding in patients treated with warm vapor inhalation.

POSSIBLE EXPLANATORY MECHANISMS OF THE OBSERVED DIFFERENCES

Under normal circumstances, the human body adjusts physiologically to exposure to cold by increased shivering thermogenesis and increased peripheral vasoconstriction to maintain the core body temperature. On the other hand, there is some evidence that the immune system also responds to cold stress. Polderman supports the immunocompromizing effects of thera-

peutic hypothermia.¹³ He argues that the drop in the core body temperature causes leukocytopenia, suppression of chemotactic migration of leukocytes, suppression of phagocytosis, reduction of the release of cytokines, insulin resistance and hyperglycemia, factors that increase susceptibility to infections.

The effect of cooling of the nasal airway on the susceptibility to respiratory tract infections was analyzed by Eccles.²⁵ In this review, it is proved that exposure of the upper airways to cold air compromises local defense and therefore increases the incidence of upper respiratory tract infections. The author suggests that the inspiration of cold air causes a decrease in the temperature of the respiratory epithelium. The latter is responsible for the decrease of mucociliary clearance and the local immune responses of the airway, i.e., it compromises phagocytic activity leading to increased susceptibility to infection. It is stressed that the epidemics of respiratory tract infections after a short period of cold weather may be explained by the conversion of asymptomatic clinical infections into symptomatic infections. In another review, Eccles points out that the reflex vasoconstriction in the nose and upper airway epithelium caused by the cooling of the body surface, which has been found to be more prolonged in people who are prone to upper respiratory infections (those who experience many episodes in colds each year), is responsible for the onset of common cold symptoms because of the reduction in blood flow and supply of leukocytes it induces.²⁶

There have been a number of recent advances in knowledge of the interplay between the respiratory and cardiovascular systems in response to air pollution, e.g., bone marrow release of leukocytes. The cold-related cardiovascular morbidity and mortality are associated with ischemic heart disease and may result from thrombosis due to hemoconcentration in the cold or from immediate reflex effects of cold.²⁷ A rise in ischemic heart disease episodes followed by pneumonia represents a possible link between respiratory and cardiovascular responses to cold.²⁸

EVALUATION OF THE AVAILABLE LITERATURE

In the Table, we summarize the different lines of evidence supporting an association between exposure to cold and respiratory tract infections. The data available suggest that exposure of the body surface or the upper airways to cold temperatures may contribute to the development of upper or lower respiratory tract infections. The inhalation of cold air or cooling of a part of the body surface is associated with an increased risk of respiratory infections. However, it is evident that only a proportion of the people who are exposed to cold will develop an infection, and this finding suggests that there are other underlying factors that may reduce resistance to infections. An interesting point from the literature search is that there

Table Lines of evidence regarding the association between exposure to cold and the incidence and severity of respiratory tract infections

Clinical evidence

- Periods of low environmental temperatures lead to an increase in the incidence of respiratory tract infections
- Periods of low environmental temperatures lead to an increase in mortality primarily due to cardiovascular diseases, and to a lesser extent due to respiratory tract infections
- Therapeutic hypothermia leads to an increase in infectious complications from the respiratory tract

Experimental evidence

- Acute chilling of the feet can cause the onset of common cold symptoms within 4–5 days

Pathophysiological mechanisms

- Cooling of the nasal airways compromises local defense
- Cooling of the body surface causes reflex vasoconstriction in the upper airway epithelium, leading to reduction in the supply of leukocytes
- Therapeutic hypothermia has immunocompromising effects, such as leukocytopenia and reduction in cytokine release

is more evidence regarding the effect of cold temperatures on systemic immune function compared to the effect on local immune defenses of the respiratory tract. It should be emphasized that one of the most difficult aspects to address in human studies of this topic is the control of possible confounders. Animal studies have also shown that low environmental temperatures affect the severity of experimentally produced infections.²⁹

It is also evident that the duration of exposure to cold is associated with greater susceptibility to infection. The effect of extreme cold environmental temperatures might be more severe if the period of extreme cold is longer. In case of induced hypothermia, the risk of respiratory tract infections appears to increase when patients are cooled for 48 h or more. Finally, it is suggested that the effect of exposure to cold on the incidence and severity of respiratory tract infections is delayed, e.g., the greatest increase in the incidence of infections or mortality from them was observed 2–3 days after the drop in temperature, whereas epidemics that occur immediately following a period of very cold weather are believed to be due to the conversion of many asymptomatic subclinical infections into symptomatic clinical infections.

Additional studies are needed to clarify the relationship between exposure to cold and respiratory tract infections. The focus should probably be on clinical research studies using analytical methodology to provide support for or to refute the association between exposure to cold and respiratory tract infections. Appropriately designed and powered population (community) based randomized controlled trials and case control studies may shed more light on this issue. If the association between exposure to cold and increased incidence and/or severity of respiratory tract infections is found to be adequately supported, relevant guidelines regarding preventive measures should be generated, published and applied as public health practices.

CONCLUSION

The relationship between exposure to cold and respiratory tract infections is based on a complex interaction, and many efforts have been made throughout the last centuries to clarify the mechanisms behind this association. The data available suggest that exposure to cold environment increases the risk of respiratory tract infections and their severity. It is therefore important that, during periods of low environmental temperatures, individuals and public health authorities take measures to prevent the adverse effects of cold air, especially among vulnerable populations. Although not proven as interventional measures, excess morbidity and mortality could be substantially reduced by personal protective measures against indoor and outdoor cold stress, such as appropriate heating of houses, appropriate clothing and outdoor physical activity.

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R É S U M É

On note une augmentation régulière des hospitalisations et de la mortalité au cours des mois d'hiver ; cet accroissement de morbidité et de mortalité est dû dans une large mesure aux maladies cardio-vasculaires ainsi qu'aux infections respiratoires. Les données disponibles suggèrent que l'exposition au froid, que ce soit une exposition à une température basse dans l'environnement ou au cours d'une hypothermie induite, augmente le risque de développement d'infections du tractus respiratoire supérieur et inférieur et les décès qui en résultent. En outre, plus longue est la durée de l'exposition au froid et plus élevé est le risque d'infection. Bien que toutes les études ne soient pas d'accord, la majorité des preuves disponibles provenant d'études cliniques ou de laboratoire

suggèrent que l'inhalation d'air froid, le refroidissement de la surface corporelle et un stress par le froid provoqué par l'abaissement de la température centrale du corps provoquent des réponses physiopathologiques telles qu'une vasoconstriction de la muqueuse du tractus respiratoire et une suppression des réponses immunitaires qui sont responsables de l'accroissement de la sensibilité aux infections. Dès lors, les gens tout autant que les autorités de santé publique devraient prendre cette information en considération et prendre les mesures nécessaires pour prévenir une certaine proportion de l'augmentation de morbidité et de mortalité associée aux infections respiratoires pendant les jours de froid.

R E S U M E N

Durante los meses de invierno se observa regularmente un aumento de las hospitalizaciones y de la mortalidad. Una gran proporción de esta morbilidad y mortalidad adicional se debe a enfermedades cardiovasculares y a infecciones respiratorias. Se ha designado con frecuencia la exposición al frío como un factor asociado con la mayor incidencia y gravedad de las infecciones de las vías respiratorias. Los datos existentes indican que la exposición al frío, por exposición a bajas temperaturas medioambientales o durante estados de hipotermia inducida, aumenta el riesgo de contraer infecciones de las vías respiratorias superiores e inferiores y de morir por esta causa ; además, entre más prolongada sea la exposición al frío, mayor es el riesgo de infección. Si bien

no todos los estudios son unánimes, la mayoría de los datos aportados por estudios de laboratorio y estudios clínicos proponen que el aire frío inhalado, la disminución de la temperatura de la superficie corporal y el estrés por frío provocado por la disminución de la temperatura central provocan una respuesta fisiopatológica, que incluye vasoconstricción de la mucosa de las vías respiratorias y supresión de las respuestas inmunitarias, con lo cual se aumenta la susceptibilidad a las infecciones. Por esta razón, los individuos en general y las autoridades sanitarias deberían tener en cuenta esta información y tomar las medidas necesarias, a fin de prevenir en parte el aumento de morbilidad y mortalidad por infecciones respiratorias durante los períodos fríos.