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Increased risk of cardiovascular disease in cold temperatures

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1 Cardiovascular disease and temperature

Cardiovascular disease (CVD) is the leading cause of global mortality and morbidity[1]. The intricate relationships between environmental, lifestyle and genetic factors and their respective and collective involvements in the risk development of CVD poses a colossal challenge to decreasing global burdens[2-3]. Despite difficulties in pinpointing underlying causes for exacerbating CVD, multiple studies have clearly illuminated the impact that climate and temperature, especially cold weather[4-5] and the winter season[6-7], impose on the incidence of cardiovascular events. The irrefutable association between low temperatures and increased prevalence of myocardial infarction events[8-9] is common to both in Northern and Southern hemispheres[10], as well as to countries at various stages of economic development[11]. Hence, the investigation on the mechanisms underlying cold-exacerbated CVD mortalities is highly significant, as seasonal changes in temperature and the natural environment impact global public health.

2 Underlying mechanisms of increased cardiovascular disease at cold temperature

The main interests on the pathogenesis of cardiovascular events at low temperatures can be categorized into three interconnected topics: (1) destabilization events, (2) alterations in vascular resistance and myocardial contractile dysfunction[12], and (3) effects on molecular signaling pathways[11,13]. First and foremost, cold temperatures have an overbearing effect on systemic hemodynamics, which puts those with pre-existing atherosclerotic plaques at higher risk of rupture and thrombotic occlusion[14]. In mice, extended exposure to low ambient temperatures significantly reduces fibrous cap thickness whilst simultaneously increases necrotic core size; a dangerous combination which dramatically increases plaque rupture rate[15]. Moreover, multiple studies have demonstrated increased systolic and diastolic blood pressures at cold temperatures[16].

3 Epigenetic thermoregulatory modulators

Chromatin regulation upon temperature changes play active roles in the pathogenesis of CVD such as atherosclerosis and metabolic syndrome[17-18]. Epigenetic effects on inflammation, metabolism, blood coagulation *etc*. have been reported to respond to low ambient temperatures[19]. Critically, epigenetic alterations are bidirectional, which can occur both up and down regulated[19-20]. Hypomethylation of intercellular adhesion molecule 1 (ICAM1) is just one example of an epigenetic change correlated with low ambient temperatures with a direct effect on the levels of inflammation and C-reactive protein[21]; a known important CVD biomarker. Furthermore, we should not ignore the effects of noncoding RNAs on CVD via post-transcriptional mechanisms at cold temperature. For example, an *in vivo* study has demonstrated that cold exposure aggravates pulmonary arterial hypertension through increasing the levels of miR-146a-5p, miR-155-5p and cytokines TNF-α, IL-1β, and IL-6[22]. To have a panoramic view of the role of epigenetic regulation on CVD at low temperatures, a comprehensive exploration of the effects of length of exposure to cold temperature or degree of pre-existing CVD is highly desirable.

4 Conclusion and future prospective

Studies have strongly indicated an increased risk of cardiovascular events at low ambient temperatures[23]. Hence, future research should aim at both preventative and therapeutic strategies. Importantly, a strong causal relationship is present between low ambient temperatures and epigenetic modulations as claimed by many studies designed to measure acute effects with relatively short intervals between cold exposure and alterations of the expression of some critical proteins (such as C-reactive protein)[24]. The acute changes in inflammatory markers indicate the importance for prevention of cardiovascular complications

in winter season, and interventional approaches should aim to targeting the modulations prior to the exacerbation of acute cardiovascular events.

Building upon this, novel research which investigates the role of relevant risk factors and epigenetic modulators may provide translational insights into the potential therapeutic targets for the treatment of CVD associated with cold ambient temperatures.

Conflicts of interests

No conflicts of interests exist.

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