A Preliminary Study On The Relationship Between Humoral Immunity And Mortality Based On Climatic Factors

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Abstract

Background: Climate affects cell-mediated cellular immunity and antibody mediated humoral immunity. As basic units of humoral immunity, antibodies regulate pathogens and prevent infection, which affect human health. However, the influence of atmospheric temperature and temperature differences on antibodies is still unclear. We provide basic evidence on this topic by analyzing the effects of ambient temperature on immune indexes and mortality.

Method: Based on the physical examination data of a general hospital in a large city in China from January 1, 2018 to December 31, 2019, we analyzed the influence of atmospheric temperature and temperature differences from climatic factors on the concentrations of four kinds of antibodies (IgA, IgM, IgG and IgE) through an epidemiological survey. Relationships between the atmospheric temperature and mortality in the hospital and city were also discussed. On this basis, we explored the relationship between each immunoglobulin and the mortality rate in the hospital and city. To further verify the effects of ambient temperature on IgE related to respiratory system immunity, we designed a field experiment with an artificial environment near the human thermal comfort zone.

Results: The changes of IgM and IgE have seasonal characteristics. There was a significantly positive correlation between ambient temperature and IgE concentration related to respiratory immunity in natural and artificial environments (natural environment: P=0.021, R 2 =0.428 in; artificial environment: P=0.009, Spearman=−0.495). The IgM and IgE levels were the inverted "U" type with the temperature difference, while the IgA and IgG levels were the "fishbone" type. The IgM and IgE concentrations were the highest when the temperature difference was equal to zero. The mortality rate of the hospital and city was U-shaped with the season, and the mortalities were strongly negatively correlated with local atmospheric temperature (hospital: P=0.006, Spearman=-0.544**; city P = 0.000, Spearman = 0.743 **). The concentration of IgE related to respiratory system immunity was significantly negatively correlated with the hospital and city mortalities (hospital: P=0.014; city: P=0.048). IgE levels can be used as a biological parameter to predict death.

Conclusions: Low temperature and large increases or decreases in temperature are not conducive to the secretion of antibodies, especially IgE related to respiratory immunity, which can increase the mortality rate to some extent. In the future, based on the findings of our artificial environment study, the span between stressors can be narrowed to determine the temperature range that can cause changes in antibody concentrations. Thus, the duration and lag time of the influence of each temperature on human immune indexes were studied, as well as how the immune indexes changed.

Highlights

1. We analyzed the influence of atmospheric temperature and temperature differences from climatic factors on the concentrations of four kinds of antibodies (IgA, IgM, IgG and IgE) through an epidemiological survey.

2. Relationships between the atmospheric temperature and mortality in the hospital and city were also discussed.

3. This paper explored the relationship between each immunoglobulin and the mortality rate in the hospital and city from the point of view of immunology.

4. Further verify the effects of ambient temperature on IgE related to respiratory system immunity through designing a field experiment with an artificial environment near the human thermal comfort zone.

5. It was found that IgE related to the immunity of respiratory system can represent the hospital patient death.

Introduction

According to the data released by the World Health Organization, there are 3 to 5 million people infected with seasonal influenza every year, causing approximately 290000 to 650000 deaths (Cox, 2020). Influenza is a self-limited disease (Oh et al., 2019), and the immune system is extremely important for preventing influenza. When pathogens (bacteria, viruses, fungi, toxins, etc.) enter the human body, the immune system produces immune responses, including B-cell-mediated humoral immunity and T-cell-mediated cellular immunity(Parish, 1972; Parkin and Cohen, 2001). The former can prevent pathogens from entering deep tissues or the blood(Stewart, 2009). Antibodies are the basic functional units of humoral immunity, and the function and quantity of antibodies are very important for fighting pathogens(Stewart, 2009).

Humans have five basic types of antibodies, including IgG, IgM, IgA, IgE, and IgD, which are also known as immunoglobulins(Stewart, 2009). IgG is the most common antibody in the blood, accounting for 80% of the total antibody content and providing the vast majority of antibody-mediated immunity against pathogens (Puissant-Lubrano et al., 2015). IgM is produced by the immune system after its first exposure to pathogens and has memory functions. IgA accounts for approximately 15% of serum immunoglobulins in healthy people (Macpherson and Slack, 2007). IgA synthesis occurs in the plasma cells of the spleen, lymph node, and mucous membrane, and this type of antibody is present in the serum and secretions. The production of secretory immunoglobulin A (S-IgA) plays a primary effector role in the mucosal immune system and provides the first line of defense against pathogens (Fagarasan and Honjo, 2003; Korzeniewski et al., 2013; Swaminathan et al., 2014). IgE is present in low concentrations and is a specific antibody that binds to receptors on mast cells, eosinophils, and basophils and induces the release of inflammatory mediators such as tricarboxylic acid, leukotriene, histamine, and trypsin (Makabe-Kobayashi et al., 2002; Starkl et al., 2020). The IgE level in the body is associated with respiratory infection (Freeman and Olivier, 2016; Girodet et al., 2005).

The concentration of serum immunoglobulin is highly varied and may be affected by demographics, lifestyle(Wada et al., 2017; Watamura et al., 2010), and metabolic and environmental factors(Carballo et al., 2017). In addition to chemicals(Glover-Kerkvliet, 1995; Kimber and Dearman, 2002), dust mites(McKnight et al., 2017; Soto-Quiros et al., 2012), and pollen(Olivieri et al., 2016; Qiu et al., 2020),other environmental factors increase blood immunoglobulin (IgE), and their secretion is also sensitive to climate(Nwaogu et al., 2020; Silva and Elliot, 2016; Swaminathan et al., 2014). As one of the important climatic factors(Zhang et al., 2020), ambient temperature hinders immunoglobulin secretion by affecting the intake of nutrients(Chandra, 1997; Kang et al., 2009; Zhao et al., 2017). More importantly, temperature affects not only the binding rate of antigens and antibodies(Hanson, 1997; Krepper et al., 2018)but also the number and activity of immune cells in human blood(Cross et al., 1996). Therefore, ambient temperature is an important factor affecting the strength of immunity. The diurnal temperature difference is an appropriate indicator for assessing climate change(Dai et al., 1999). Temperature differences affect humoral immunity at multiple levels, such as the molecular structure of antibodies and the amount of antibody secretion(Krepper et al., 2018; Vermeer and Norde, 2000). Therefore, temperature difference is one of the important factors affecting the strength of immunity.

However, due to limits induced by the Experimental Exposure Safety Committee, studies on the influence of environmental temperature and temperature differences on serum immunoglobulin concentrations have mainly focused on animal experiments(Chen et al., 2002; Dang et al., 2015; Hu et al., 2016; Li et al., 2020). The only human experiments performed were occurred in the Antarctic space(Magnadottir et al., 1999; Shearer et al., 2001; Yadav et al., 2012), which contains many additional factors that cannot be excluded (isolation, cold, fear of the unknown, etc.), and showed that suppressed immune system functions further affects immunoglobulin secretion(Shephard and Shek, 1998). In addition, there are interactions between the abovementioned factors(Shephard and Shek, 1998). Therefore, it is necessary to study how environmental temperature and temperature differences affect the immune index and how the immune index affects human health.

Thus, we used an epidemiological survey to clarify the influence of outdoor ambient temperature and temperature differences on different immunoglobulin levels in the blood. The relationship between immunoglobulin concentration and mortality was further examined to verify whether the immunoglobulin level affects human health.

Epidemiological Survey

2.1 Materials and methods

2.1.1 Data collection

The risk of death and effect of temperature in the temperate monsoon climate and subtropical monsoon climate are increased(Chen et al., 2018; Liu et al., 2019). Therefore, the physical examination data of a general hospital in a large city in the temperate monsoon climate zone were analyzed. The city population is 7 to 8 million, and the hospital, including its emergency department, receives 1.6~ 1.9 million outpatient visits per annum, and the Physical Examination Center receives 40,000 to 60,000 visits per annum. Taking into account that the human immune system is fully mature after puberty (10~19 years old) (Swaminathan et al., 2014), healthy physical examinations of individuals who were 20 years old were selected as the research objects.

The blood indexes, including IgA, IgM, IgG, and IgE, of each sample in the hospital Physical Examination Center from January 1, 2018 to December 31, 2019 were statistically analyzed. Immunoglobulin levels were determined by rate immune scatter turbidimetry.

We sent a written informed notice to each physical examination individual and obtained their consent before obtaining the samples. The samples were excluded when the subject declined to participate at any step throughout the process.

2.1.2 Statistical analysis

To facilitate the comparative analysis between indicators, in the following analysis, each index is dimensionless. In this method, the measured value of each index is compared with the lower limit of the normal range value of the index (i.e., the measured value/lower limit value).

To facilitate the comparative analysis between the indicators, each indicator is treated by dimensionless theory in the following analysis. In this method, the ratio of the measured value of each indicator is compared to the lower limit of the normal range of the indicator, namely, the measured value/lower value.

The contribution level of atmospheric temperature, temperature difference, age, and gender to each immunoglobulin was analyzed by the neural network module of SPSS 20, for which the processing method is as follows: 1) the temperature difference is defined as the difference between the atmospheric temperatures of two consecutive days, (i.e., the difference between the average atmospheric temperature of the day and that of the previous day); 2) temperature, temperature difference, and age were defined as continuous variables and gender as a categorical variable; 3) the immune indexes were divided into three grades including 0, 1, and 2, where 0, 1, and 2 represent lower than the normal range, within the normal range, and higher than the normal value, respectively; and 4) 70% of the samples were used for training, and the grouping variables were generated by calculating the variables. Then, 70% of the samples were used for training, and the grouping variables were generated by calculating the variables.

To study whether the influence of different atmospheric temperatures and temperature differences on immunoglobulins were statistically significant, the data were analyzed by independent sample tests (Kruskal-Wallis) with SPSS 20. Data processing was as follows: 1) the temperature corresponding to the effective samples was divided into 1 to 12 grades according to the epidemiological survey; 2) the temperature difference value was divided into different grades based on the difference in the daily average temperature on two adjacent days, (i.e., if there were n different temperature differences, the temperature difference grade was n); and 3) the air temperature, temperature difference, and the four kinds of immunoglobulins were tested as independent samples.

2.2 Results

2.2.1 Basic data

A total of 1147 valid samples were obtained, of which 68.4% were male. The age range of the participants ranged from 20 to 83 years (mean ± SD: 47 ± 11 years).

2.2.2 Immune index statistics

The results of the statistical analysis of immunoglobulins from the effective samples are shown in Table 1.

Table 1
Statistical analysis of immune indexes

Parameter	Max	Min	Median	Mean ± SD
IgA(g/L)	7.50	0.40	2.32	2.43 ± 0.93
IgG(g/L)	21.00	1.08	11.90	12.05 ± 2.32
IgM(g/L)	2.97	0.23	0.87	0.96 ± 0.46
IgE(IU/mL)	886	17.3	40.80	79.3 ± 95.12
Atmospheric temperature (°C)	30.0	-6.0	14.5	14.0 ± 9.5

As shown in Table 1, the level of IgG was the highest among the four kinds of serum immunoglobulins, followed by IgA, IgM, and IgE. The median and mean values of all immune indexes were within the normal limits. Due to the the living habits and personal physical conditions, the standard deviation of each index was large, especially that of IgE related to upper respiratory tract infection, and the standard deviation exceeded the average value.

The maximum, minimum, and daily average temperature were 30°C, -6°C, and 14.0°C, respectively. Compared with the limit temperature (11°C) that the respiratory system can bear, the average temperature was 3°C higher, while the minimum atmospheric temperature was much lower than the limit, with a difference of 17°C. When humans stay outside in an atmospheric environment below 11°C (Carder et al., 2005) this is extremely harmful to human health, especially to patients with respiratory diseases.

2.2.3 Contribution of various factors to immunity

The contribution levels of atmospheric temperature, temperature difference, age, and gender to each immunoglobulin concentration are shown in Fig. 1.

Figure 1 shows that the factors affecting the level of immunoglobulins in the blood are not unique. In terms of temperature, temperature difference, age, and gender in this study, different factors have different effects on the levels of immunoglobulins. The contribution of atmospheric temperature and temperature differences on IgA, IgM, and IgE was significantly increased, and temperature difference had the greatest effect. More than 50% of the IgA and IgE concentration was caused by the temperature difference, especially the latter. The contribution level of each factor to the IgA concentration was consistent with that of IgM, and the order from high to low was temperature difference, atmospheric temperature, age, and gender. The difference is that the effect of gender on IgA was very small (only 0.006), while that of IgM was 0.115, with a difference of 0.109. The importance of the factors affecting IgE concentration were as follows: temperature difference, atmospheric temperature, gender, and age. The contribution of gender and age were almost the same, with only a 0.002 difference. For IgG, temperature had the least effect, while gender had the greatest effect, followed by temperature difference, but the difference between the two factors was small, with a value of 0.04. In general, there are differences in the influence of air temperature, temperature difference, gender, and age on immune indexes, but the first two factors contributed more to immunoglobulin concentrations than the latter factors.

2.2.4 Effects of atmospheric temperature and temperature differences on immune indexes of the respiratory system

As described in Sect. 3.2.3, IgA, IgM, and IgE were most affected by atmospheric temperature and temperature differences, while temperature differences and gender had the similar influences on IgG. To further determine whether the influence of atmospheric temperature and temperature differences on immunoglobulin concentrations was significant, a single factor analysis was conducted. The results are shown in Table 2.

Table 2 Significance analysis of atmospheric temperature and temperature differences on immunoglobulins

Parameters	Temperature (°C)	Temperature difference (°C)
IgA(g/L)	0.068	0.150
IgM(g/L)	0.011	0.007
IgG(g/L)	0.007	0.003
IgE(IU/mL)	0.000	0.000

As shown in Table 2, the atmospheric temperature and temperature difference had statistically significant effects on the concentrations of IgM, IgG, and IgE in human blood, but there was no significant difference on IgA concentration in each month. Temperature change caused obvious variations in IgM, IgG, and IgE concentrations in the next 2 days.

2.2.5 Effects of the month on immune indexes

Based on the findings in Sect. 3.2.4, we analyzed the seasonality of each immunoglobulin. The results are shown in Fig. 2.

As shown in Fig. 2, the atmospheric temperature increased first and then decreased by month, and reached a maximum in August. IgM and IgE concentrations showed an inverted "V" shape with the month, and their relationship exhibited a Gaussian distribution. IgA and IgG had no seasonal characteristics. As shown in Fig. 2 (a), the concentration change of IgE with climate was more obvious than that of IgM. However, in general, the trend in the concentration changes of IgM and IgE was basically consistent with the atmospheric temperature, especially from May to November. The difference was that the highest concentrations of IgM and IgE occurred in September, while the temperature was highest in August, which indicated that the effect of temperature on blood immunoglobulin has a lag.

It can be seen in Fig. 2 (b) that there was no significant change in IgA concentration by month. However, the concentration gradually increased with time from July to September, and the peak value occurred in September. The trend was consistent with that of IgM and IgE. From June to August, when the temperature gradually increased or even reached a maximum, the IgG concentration gradually decreased, but the highest value still occurred in September. The concentrations of IgA and IgG dropped sharply in October and returned to the previous levels in November and December. This change may be related to the temperature drop after National Day in October. When the human body adapts to a cold environment, the effect of temperature on IgA and IgG concentrations was no longer obvious.

Figure 2 (a) and (b) shows that the concentrations of the four immunoglobulins were also lower in January, November, and December, coinciding with lower temperatures. In addition, IgA, IgM and IgE concentrations were increased in February and April. The reason for these effects is that the climate is coldest in January and heating is stopped in April.

In summary, climate has different effects on the levels of different immunoglobulins in human blood, and the influence has a temporal lag. Maintaining a high ambient temperature is conducive to increasing the concentration of immunoglobulin in human blood, which can improve human immunity to some extent.

2.2.6 Effect of temperature difference on immune indexes

Temperature difference is an important and independent factor affecting human immunity(Cheng et al., 2014). We analyzed the relationship between the four immunoglobulins and temperature differences to explore the effect of temperature differences on IgM and IgE concentrations. The results are shown in Fig. 3.

It can be seen in Fig. 3 that IgM and IgE concentrations exhibit the inverted "U" relationship with temperature differences, while IgA and IgG concentrations show a "fish bone" relationship.

The concentrations of IgM and IgE peaked when $\Delta t = 0°C$, while the maximum concentrations of IgA and IgG were at $\Delta t = 1.5°C$ and $\Delta t = 2°C$, respectively.

We found that the temperature difference ranges corresponding to the four immunoglobulins were slightly different at higher concentrations, as shown in Fig. 3 (a), (b), (c), and (d). The range of temperature differences corresponding higher concentrations of IgE was the largest (7°C), which was

[-3.5, 3.5°C]. Due to the concentrations of IgA, IgM, and IgG being very sensitive to the daily mean temperature difference during two consecutive days, the temperature difference range corresponding to the increased concentration was narrower, which was [-3, 2.5°C], [-3.5, 3°C], and [-2, 2.5°C], respectively.

Comprehensive analysis showed that an increase or decrease in environmental temperature reduced immunoglobulin concentrations in human serum and subsequently reduced human immunity. Long term exposure to a stable environment or cold and hot stimulation within a small temperature range is conducive to increasing human immunoglobulin concentrations, which can improve human immunity.

2.2.7 Effect of climate on mortality in the hospital and the entire city

Climate change impacts changes in mortality due to high or low temperatures (Arbuthnott et al., 2020; Ma et al., 2020; Vicedo-Cabrera et al., 2018). The respiratory tract is more susceptible to infection due to the invasion of cold air when people are in an environment that is less than 11°C, which results in frequent respiratory diseases. This phenomenon is more prominent during the cold period(Carder et al., 2005; Ma et al., 2011; Xie et al., 2013). We analyzed the changes in mortality in the hospital and the entire city over time during the investigation period to explore the relationship between air temperature and mortality. In view of the influence of atmospheric temperature on the respiratory tract, we defined the period when the atmospheric temperature was less than 11°C as the low temperature zone and focused on this period. The results are shown in Fig. 4.

As shown in Fig. 4, the relative mortality rate of the hospital and the whole city exhibits a "U" distribution with climate. From April to October, the air temperature was higher, the relative mortality rate of the hospital and the entire city was lower, and the trend was relatively mild. The relative mortality rate increased significantly and changed sharply in the low temperature period, especially in the coldest month (January), and the relative mortality rate of the hospitals and the whole city peaked. This result shows the effect of low temperature on mortality and is consistent with other research results(Braga et al., 2002; Guo et al., 2016; Guo et al., 2012; Ye et al., 2012). The analysis of the correlation between the atmospheric temperature and the relative mortality rate of the hospital and the entire city showed that atmospheric temperature was strongly correlated with the death toll at the hospital and the entire city (P_H = 0.006, Spearman=-0.544**, P_E = 0.000, Spearman=-0.743**).

Thus, maintaining a higher atmospheric temperature can improve the antibody level in human serum and reduce human mortality within a certain temperature range. An increase or decrease in temperature is not conducive to the secretion of antibodies.

2.2.8 Correlation analysis of immune indexes and mortality

Humoral immunity, as an important part of the immune system, can make the immune system hyperactive (upregulation) or immunosuppressed (downregulation), and then cause human diseases(Swaminathan et al., 2014). We analyzed the correlation between the concentration of immunoglobulin and the number of deaths in hospitals and the entire city at the monthly level to explore the relationship between human immune indexes and relative mortality. The results are shown in Fig. 5.

As shown in Fig. 5, there was no correlation between the death tolls of the two investigation sites with IgA, IgM, or IgG, while IgE related to respiratory system immunity was significantly negatively correlated (hospital: $P = 0.014$; City: $P = 0.048$). This result indicates that the concentrations of IgA, IgM, and IgG affect human health, but these levels are not directly related to deaths in response to climatic conditions. The IgE level related to the immunity of the respiratory system can be used as a biological parameter to predict death.

3.3 Brief summary

Based on the above analysis, the influence of atmospheric temperature on immune indexes is summarized in Table 3.

Table 3 Regression analysis of atmospheric temperature and immune indexes

Parameters	**Statistical parameters**	
	• Correlation coefficient R^2	**Significance level P**
IgA	0.021	0.652
IgM	0.055	0.464
IgG	0.032	0.579
IgE	0.428	0.021

As shown in Table 3, the atmospheric temperature was positively correlated with IgE ($P = 0.021$, $R^2 = 0.428$) but not with other immune indexes. Maintaining a higher ambient temperature increased the IgE concentration related to respiratory system immunity and reduced the mortality rate.

Effect Of Temperature Regulation On Ige In An Artificial Environment

We designed an artificial environment experiment to verify the effect of environmental temperature changes on IgE concentrations. The experimental design and data analysis are described below.

4.1 Materials and methods

4.1.1 Experimental design

Three temperature conditions were selected: partial cooling (18°C), comfortable (24°C) and partial heat (30°C). Other environmental parameters such as wind speed, relative humidity, and pressure were constant during the experiment. The experimental procedure is shown in Fig. 6.

There was interaction between exercise and cold exposure on the immune system. Except for saliva collection in the last 5 minutes, the subjects at quietly for the first 30 minutes of the experiment to avoid the effects of exercise and temperature on IgE being obscured or exaggerated. Saliva was placed into disposable cotton swab test tubes by spitting and immediately placed at -80°C for analysis.

4.1.2 Measurement of IgE concentration

The concentration of IgE in saliva samples was measured by ELISA using the SimpleStep kits, USA. The experimental procedure and data analysis were carried out in strict accordance with the product instructions.

4.13 Subject recruitment

IgE concentrations in the body are affected by obesity, smoking, and oral diseases, Therefore, we recruited healthy subjects whose body mass index (BMI) was within the normal range, who did not smoke or drink alcohol, and who had no allergic symptoms such as gingivitis and stomatitis. Informed consent was provided by the subjects in advance. Ethical Committee of Qingdao University of Technology approved the present study (QUT.L.01). The subjects' daily routines were reasonably constrained 2 days before and during the experiment to avoid influences of the routines on the experimental results. The constraints mainly included: 1) avoiding drastic changes in eating habits and maintaining a balanced intake of nutrients every day; 2) trying to get enough sleep; 3) avoiding big mood swings; and 4) avoiding drugs or supplements that affect immune function, such as vitamins.

A total of 10 subjects (6 males and 4 females) were recruited for the experiment. The age range of the subjects was 22–25 years old, and the BMI range was 18.9–22.8.

4.2 Results

The effect of ambient temperature on IgE concentrations in the artificial environment is shown in Fig. 7.

It can be seen in Fig. 7 that changes in IgE concentrations with ambient temperature in the artificial environment were consistent with those of the natural environment, and at higher ambient temperatures, the IgE levels were higher. Environmental temperature had a significant effect on IgE concentration in the natural environment, as determined by the Kruskal-Wallis test ($P = 0.04$), and IgE strongly correlated with ambient temperature ($P = 0.009$, Spearman = − 0.495). This conclusion is consistent with the results of the correlation analysis between temperature and IgE concentration in the natural environment.

4.3 Brief summary

Maintaining a high ambient temperature is conducive to increasing IgE concentrations and improving immunity in natural and artificial environments.

Environmental temperature was strongly correlated with IgE in natural and artificial environments based on the above analysis. Within a certain temperature range, higher ambient temperature can make the body's humoral immune system more active and more conducive to the neutralization of pathogens, thus making the body less susceptible to infection and disease.

Discussion

The influence of climate on human immune indexes and death is significant. In this study, we analyzed the influence of the climactic factors temperature and temperature difference on the concentrations of IgA, IgM, IgG, and IgE in blood, and further explored the correlation between immune indexes and relative mortality. The results showed that 1) the environmental temperature has a significant effect on IgM, IgG, and IgE levels. Maintaining a higher ambient temperature is conducive to improving the level of immune indexes in the blood. 2) The concentrations of IgM and IgE varied seasonally and showed an inverted-U pattern with the month. 3) The concentration of each immunoglobulin decreased with an increase or decrease in temperature. However, there were differences in the sensitivity of immune indexes to temperature differences, among which IgE was the least sensitive and was maintained at a high concentration over a wide temperature range. 4) The average IgE level significantly correlated with the seasonal mortality of the population.

5.1 Effect of low temperature on immune indexes and mechanism

In this study, low temperature was not conducive to the secretion of antibodies in blood, which was consistent with the research results of(Francis et al., 2002; Gleeson et al., 2000). The conclusion given by Yadav et al. was contrary to that of the present paper(Yadav et al., 2012), and although the Antarctic environment is a typical low temperature environment, it is complicated with many other pressure factors, which increases the serum IgA level and explained the abovementioned phenomenon(Shephard and Shek, 1998). In contrast, our research focused on the natural environment in which people are relaxed. We also found that at higher temperatures, higher concentrations of immunoglobulin were present in saliva, which was consistent with the conclusion of Francis et al. and Gleeson et al. (Francis et al., 2002; Gleeson et al., 2000). In addition, low temperature significantly reduced the concentration of IgE in the nasal fluid of healthy people and patients with rhinitis(Ko et al., 2017), which supported our conclusion to some extent. The main reasons for the above phenomena are as follows: after inhaling cold air, the fluidity of cell membrane and the secretion of antibodies decreased (Johnstone et al., 1990). In the human nasal cavity, nasal blood vessels contract under low temperature, cilia movement slows, antigen-antibody binding rates decrease, and the ability of the body to resist viral invasion is reduced while antibody secretion is decreased (Heier et al., 1992; Levison et al., 1968). We also found that the environmental temperature has the same effect on IgE concentrations in blood and saliva, mainly because saliva is produced by blood flowing out of the salivary gland to supply blood vessels, and changes in serum levels are reflected in saliva(Farhad-Mollashahi et al., 2020).

The mechanism of cold stress reactions involves almost all organs and tissues (Shephard and Shek, 1998). The thermoregulatory system plays a significant role in maintaining the core temperature of the human body in low temperature environments(Messmer et al., 2014; Paricio-Montesinos et al., 2020; Tan et al., 2016). These results showed that cold sensitive neurons were excited and heat sensitive neurons were inhibited, which led to increased cardiac output and the loss of plasma volume, thus inhibiting immune functions and further reducing the secretion of immune indexes. Low environmental temperatures inhibited cellular- and antibody- mediated immunity, and the former could further affect the latter. For cellular-mediated immunity, low temperatures not only affect the number of immune cells but also hinders immune cell functions. Cold exposure decreased the levels of white blood cells, IFN-γ, IL-2, and IL-4, and increased the inhibitory lymphokines IL-10, IL 2 and IL 4, which mainly mediate humoral immunity(Hu et al., 2016). Additionally, IL 4 is an indispensable factor for IgE production by the immune system(Wu and Scheerens, 2014).

Moreover, cold stress-mediated inhibition of the immune system is also characterized by increases in some hormone levels. Sympathetic nerve activity is strengthened by cold exposure, which makes the sympathetic adrenal medullary system highly activated and enhances the synthesis, release and turnover of adrenaline and norepinephrine(Sapolsky et al., 2000). After cold stress acts on the human body, the hypothalamus-pituitary-adrenal cortex is activated, which causes the hypothalamus to release corticotropin releasing hormone into the pituitary via the portal vein, activating the adrenocorticotropic hormone receptor and stimulating the secretion of adrenocorticotropic hormone. Adrenocorticotropic hormone (ACTH) acts on the adrenal cortex through the blood circulation, promotes cholesterol uptake, converts cholesterol to cortisol and corticosterone, and stimulates the synthesis of adrenal glucocorticoid (GC). Lymphatic dysfunction caused by environmental stress is a key factor in immunosuppression (Kelley, 1980). Epinephrine and norepinephrine bind to the receptors on the surface of lymphocytes, activate intracellular adenylate cyclase, promote the transformation of adenosine triphosphate into cyclic adenosine monophosphate, and increase intracellular cyclic adenosine monophosphate levels. Cyclic adenosine monophosphate can inhibit antibody secretion. When glucocorticoid specifically binds to receptors on the cell membrane, antibody secretion decreases.

5.2 Effect of low temperature on mortality and mechanism

As the interface of many factors that are sensitive to climate changes, the immune system affects human health(Swaminathan et al., 2014). At least 80% of diseases are caused by the immune system. The relationship between atmospheric temperature and the mortality of many diseases (cardiovascular, stroke (Polcaro-Pichet et al., 2019), cerebrovascular, myocardial infarction and respiratory diseases) exhibits "U", "V" and inverted "J" distributions, and the specific relationships are affected by geographical location (Arbuthnott et al., 2016; Luo et al., 2013; Ye et al., 2012). The attribution score of temperature to respiratory tract infection-related diseases was 23.14%(Chen et al., 2018). When the ambient temperature is lower than 11°C, the effect of temperature on mortality associated with the respiratory system is severe. The mortality of respiratory diseases increases by 4.8% when the temperature drops by 1°C (Carder et al., 2005). Winter and cold weather significantly increased hospital mortality, especially for elderly individuals and children with respiratory tract infections(Achebak et al., 2019; Deng et al., 2019;

Gomez-Acebo et al., 2013). We have reached a consistent conclusion based on the above pathology and found that the mortality rate is significantly related to atmospheric temperature.

The concentrations of IgM, IgA, and IgE in blood can predict the occurrence of some diseases (Polmar et al., 1972). From the perspective of immunology, the cause of more deaths associated with respiratory diseases in winter is the reduction in antibody secretion and weakened opsonization of pathogens after inhaling cold air, which combines the relationship between environmental temperature, immune index and mortality in our study, results in viral concentrations that are more robust than the immune response, and leads to disease or even death. The antigen-antibody binding rate slows in low temperatures, which decreases the body's ability to neutralize existing pathogens. In this state, pathogens can enter deep tissues and the blood, proliferate rapidly in cells, and even destroy cells. The mortality rate increased significantly within 4 weeks after the end of the cold season (Gasparrini et al., 2015), and this effect could be explained by the lag effect of ambient temperature on antibody concentrations.

However, there are still some limitations in our research that should not be ignored. First, we analyzed the effect of temperature on immune indexes in the natural environment, and other factors such as pollution and allergens, however, are also important, especially in the context of IgE. Therefore, the above limitation will be excluded or studied in future research. Second, due to the limitations of the data sources, the relationships between immune indexes and relative mortality were derived from different populations. In the future, the relationship between immune indexes and health indexes from the same person can be monitored over time by other methods or platforms. Finally, the epidemiological survey in this study was limited to one city. In the future, we can expand the scope of the epidemiological survey and analyze data from different cities in the same climate zone.

Limitations and further research

This study has some limitations. In this study, we only analyzed outdoor environmental temperature and future researches considering other factors such as environmental physical parameters (relative humidity, solar radiation, and air velocity) and population (race, different climate zone people).

In addition, it is necessary to expand the sample size and continue to study the effects of chronic and acute cold and heat exposure on oral mucosal immunity. An experiment considering these factors is ongoing. In the future, we will continue to answer the following questions: 2) dynamic characteristics of S-IgE in saliva with exposure time in different conditions with a wider range of thermal stimulation; 2) the effects of heat exchange, heart rate, blood pressure, and other parameters on respiratory mucosal immunity.

Declarations

Ethics approval and consent to participate

The study involved the human Ethics. Ethical Committee of Qingdao University of Technology approved the present study (QUT.L.01).

Consent for publication

Consent.

Availability of data and materials

Not Applicable

Conflict of interest

The authors have no conflict of interest to declare.

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Authors' contributions

Xiaoxia Zhang: Writing - original draft, Methodology, Investigation, Validation, Data curation. **Songtao Hu**: Conceptualization, Formal analysis, Supervision, Writing - review &editing. **Yongming Ji**: Methodology, Formal analysis, **Gang Wang**: Methodology, Software. **Guodan Liu**: Funding acquisition Writing - review &editing, Visualization. **Hui Li**: Data curation, Methodology.

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Figures

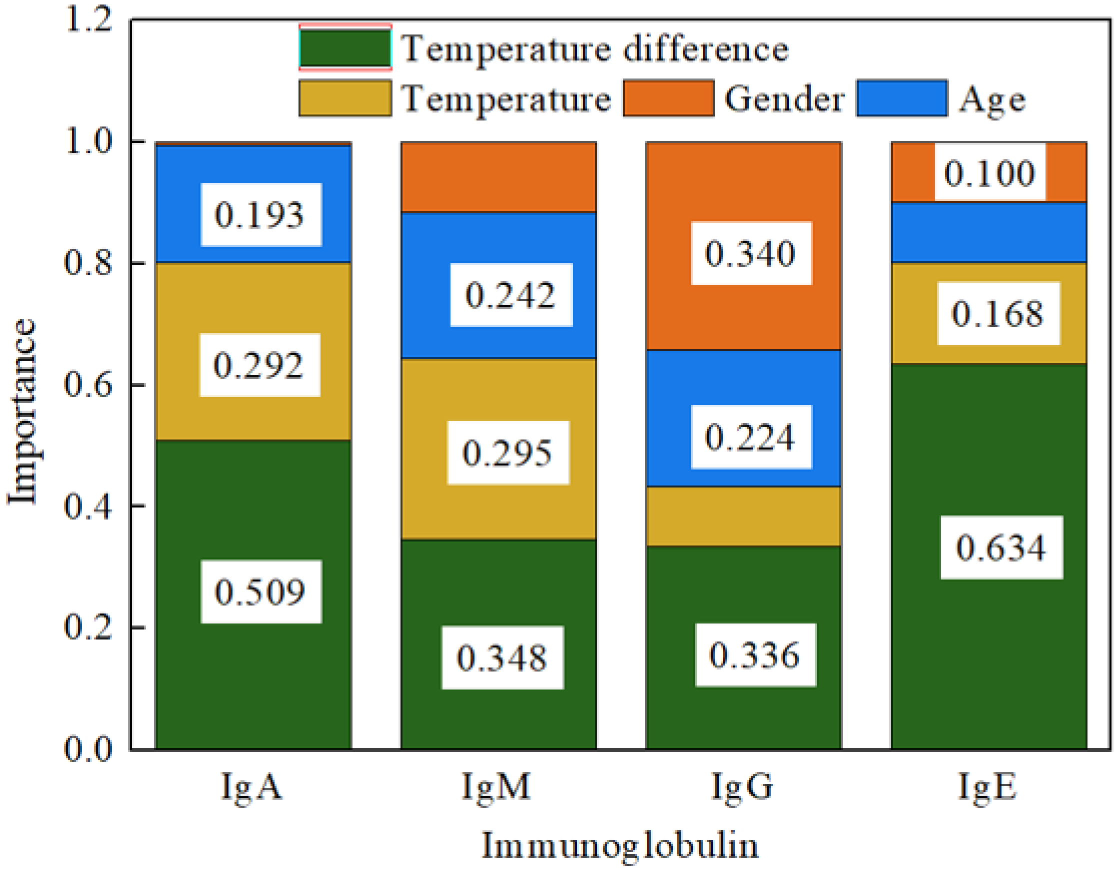
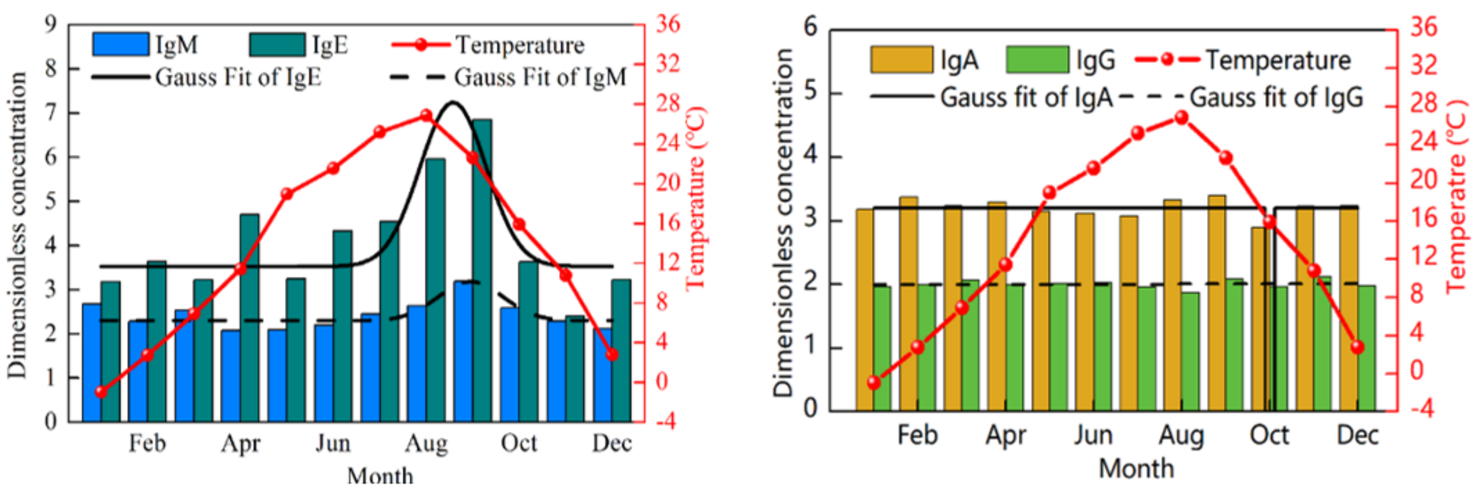


Figure 1

Contribution level of atmospheric temperature/temperature difference/gender/age to the concentration of immunoglobulins



（a） IgM and IgE （b） IgA and IgG

Figure 2

Changes in immunoglobulin concentration by month

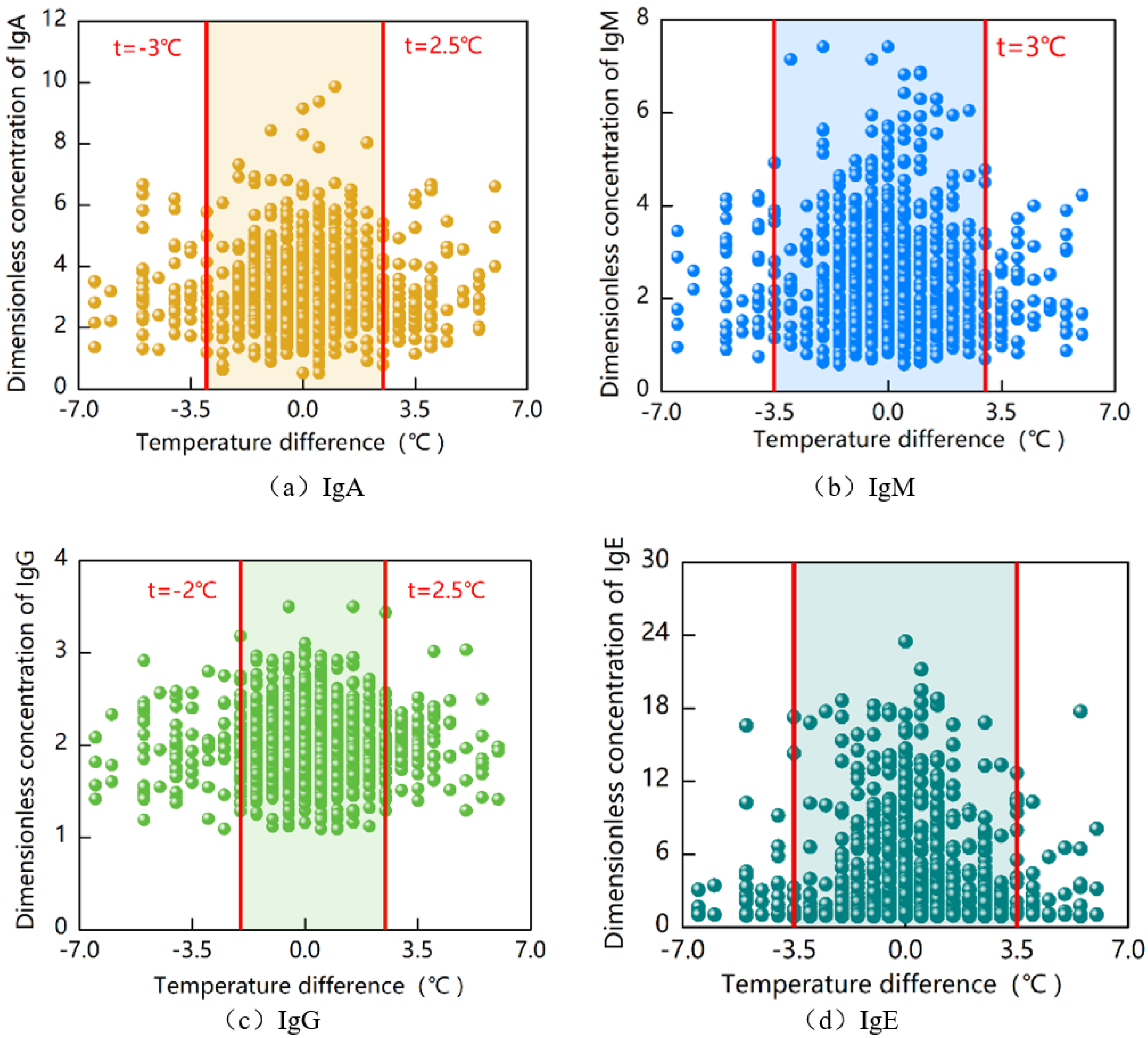


Figure 3

Changes in immunoglobulins with temperature difference

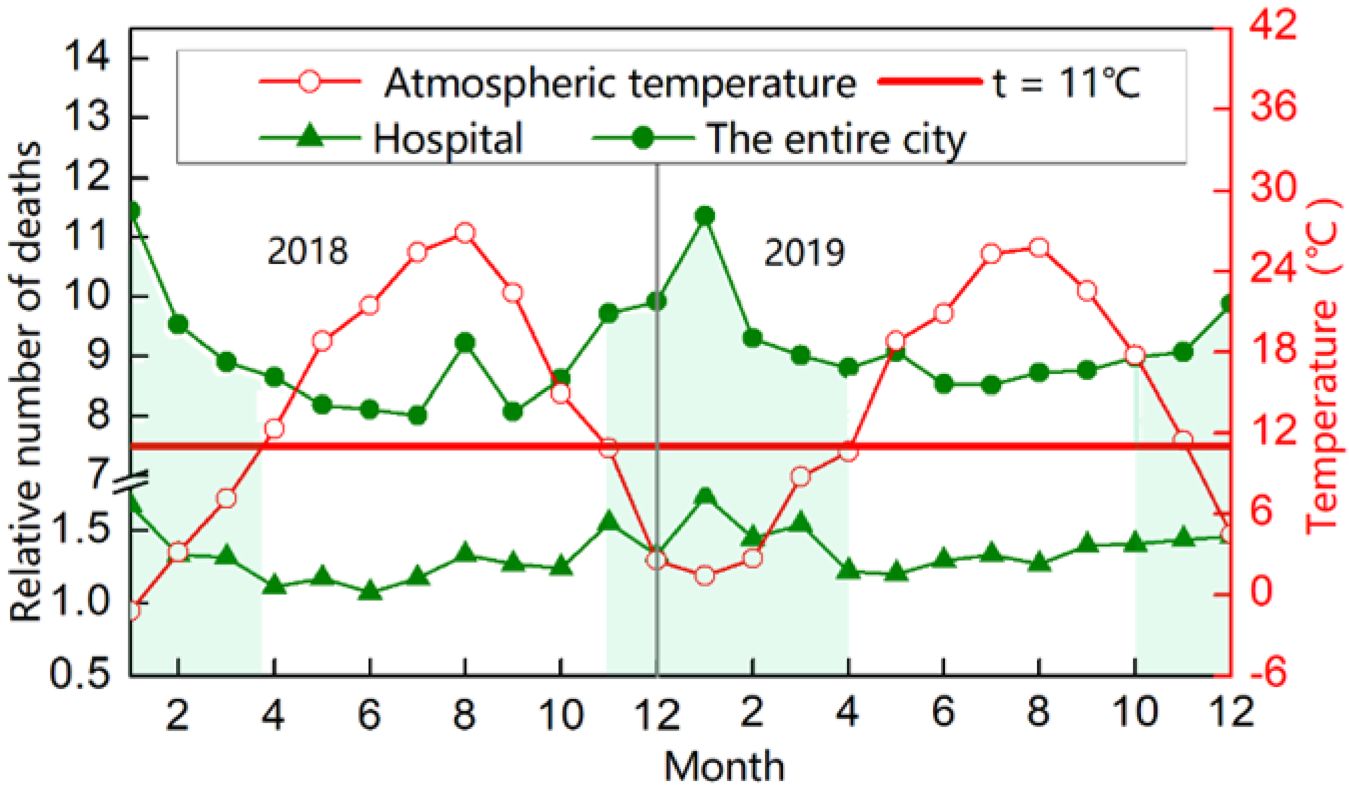


Figure 4

Variations in atmospheric temperature and death toll with time

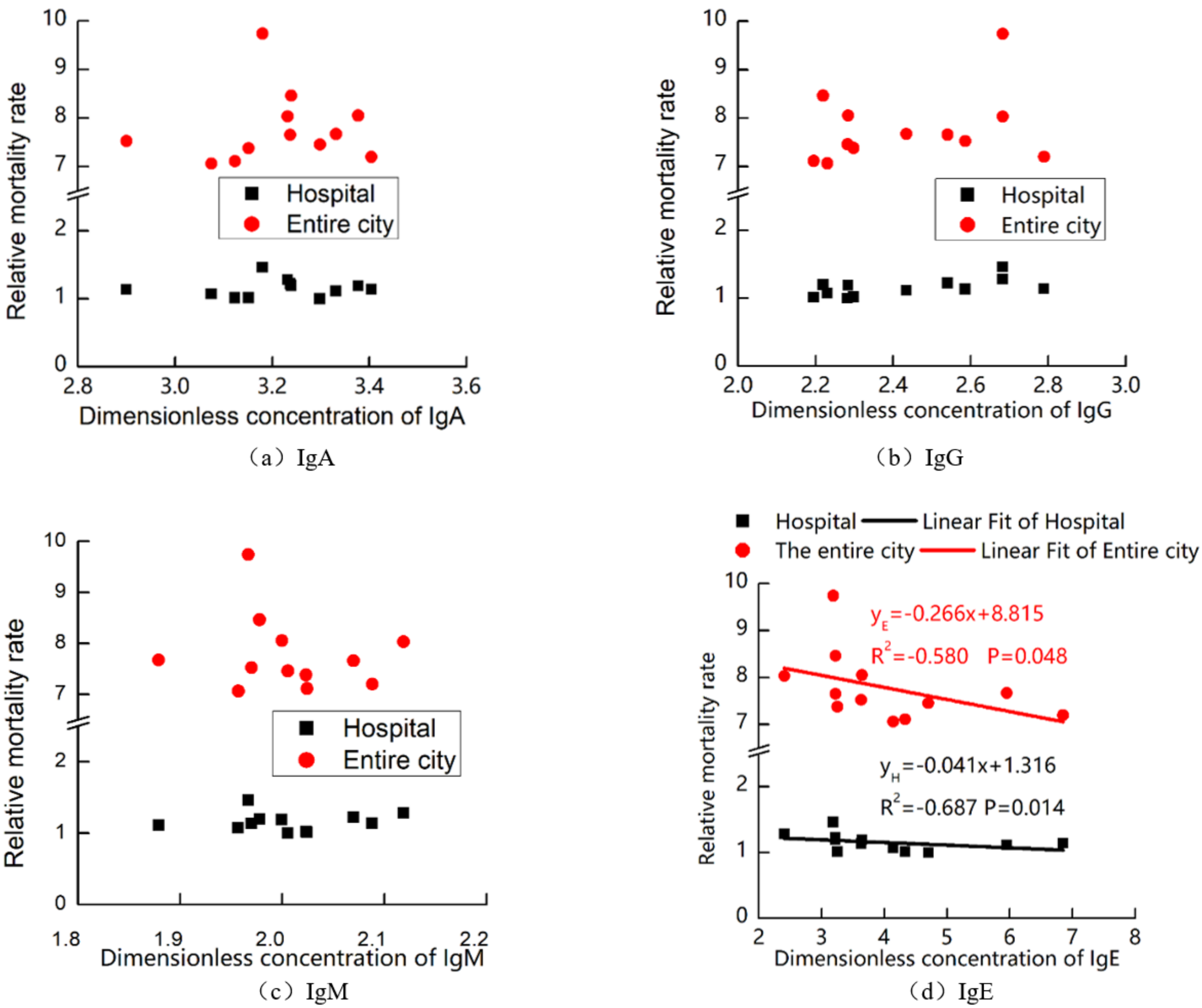


Figure 5

Relationship between the relative mortality rate and the concentrations of immunoglobulins in hospitals and the entire city

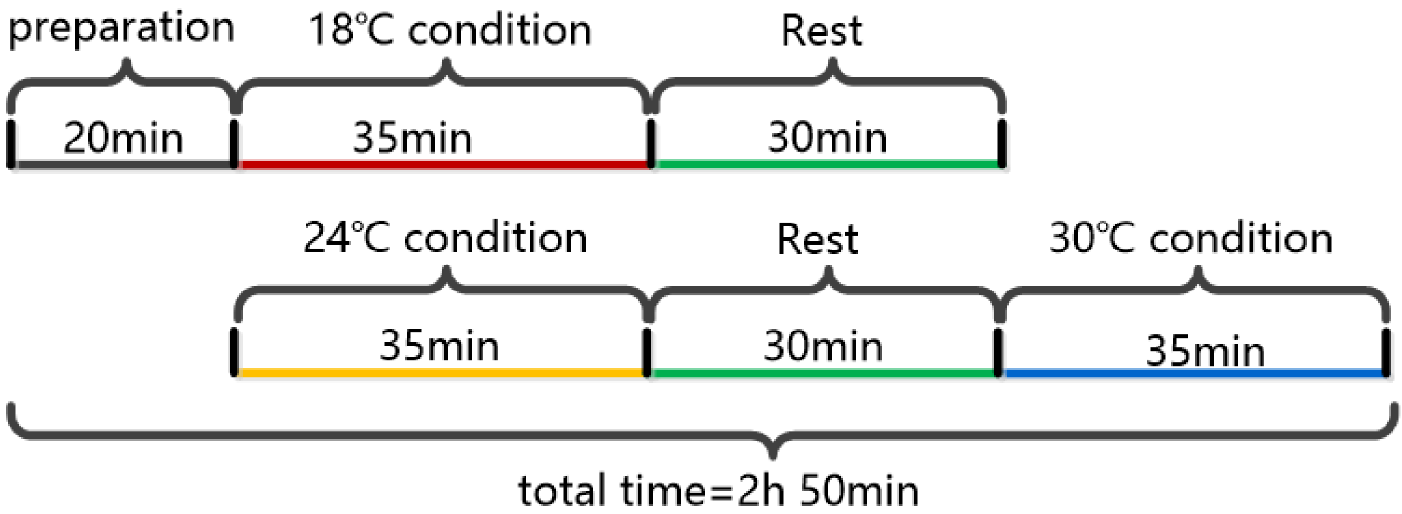


Figure 6

Experimental process

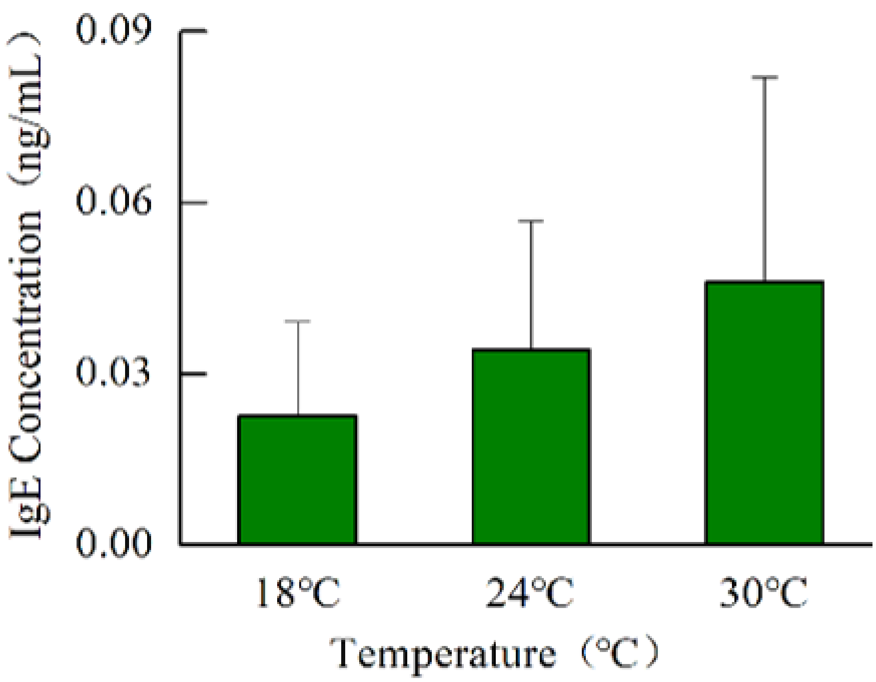


Figure 7

Changes in IgE concentrations with temperature in the artificial environment