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On the footsteps of Hippocrates, Sanctorius and Harvey to better understand the influence of cold on the occurrence of COVID-19 in European countries in 2020

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ABSTRACT

COVID-19 pandemic has been characterized by a pattern of consecutive declines and regrowth in European countries in 2020. After being partially regressed during the summer, the reappearance of the infection during fall 2020 in many temperate countries strongly suggests that temperature and cold may play a role in influencing the infectivity and virulence of SARS-CoV-2. While promoting medicine as an art, Hippocrates interpreted with logical reasoning the occurrence of diseases such as epidemics, as a consequence of environmental factors, in particular climatic variations. During the Renaissance, Sanctorius was one of the first to perform quantitative measurements, and Harvey discovered the circulation of blood by performing experimental procedures in animals. We think that a reasoning mixing various observations, measurements and experiments is fundamental to understand how cold increases infectivity and virulence of SARS-CoV-2.

By this review, we provide evidence linking cold, angiotensin-II, vasoconstriction, hypoxia and aerobic glycolysis (the Warburg effect) to explain how cold affects the epidemiology of COVID-19. Also, a low humidity increases virus transmissibility, while a warm atmosphere, a moderate airway humidity, and the production of vasodilator angiotensin 1-7 by ACE2 are less favorable to the virus entry and/or its development. The meteorological and environmental parameters impacting COVID-19 pandemic should be reintegrated into a whole perspective by taking into account the different factors influencing transmissibility, infectivity and virulence of SARS-CoV-2. To understand the modern enigma represented by COVID-19, an interdisciplinary approach is surely essential.

Contents

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1. Introduction

In the 5th century BC, Hippocrates noticed that climate, seasons, water, air, orientation of cities, and sun have an influence on the occurrence of epidemics. He established a logical relationship between the body, the diseases, and the variations occurring in the natural environment. Thus, the four moods, which he had sometimes seen flow from the body, were linked to the four qualities of the seasons, namely heat, cold, drought and humidity [1]. However, without measuring instruments and calculating methods, Hippocrates could not verify the validity of his assumptions and intuitions. Later in the Renaissance, Santorio Santorio (1561–1636), also named Sanctorius, developed the first thermoscope, an ancestor of the thermometer. He discovered that the body temperature is not variable from one individual to another (as we thought since Hippocrates), but it is physiologically fixed around 37 °C [2]. Sanctorius also invented instruments to measure humidity and wind force and was a pioneer of the new quantitative medicine that originated at this time. William Harvey (1578–1657) discovered the circulation of blood, through a methodic experimental procedure in animals, and progressing step by step with checking and deduction.

We believe that the approach of these pioneers - mixing logical reasoning with observations of natural phenomena and clinical symptoms, measurements, and experiments - is still relevant to understand how cold influences the infectivity and virulence of COVID-19 disease.

2. COVID-19 epidemic is affected by seasonal variations in temperate regions

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) first spread in the Hubei province of China and subsequently in Western Europe, in countries all experiencing cold temperatures during winter 2020. During this period, it became clear that severity of the disease increased with age and co-morbidities, in particular systemic arterial hypertension, obesity and diabetes type 2 [3]. The influence of cold, suspected on the basis of empirical observations, was reinforced by data accessed by the Worldometers organization [4], which showed that in the first months of 2020 most cases occurred in countries with cold winter. For example, on 30th April 2020, approximately 80% of COVID-19 cases have occurred in Europe and North America, while other continents (with hot seasons, tropical climate or monsoon) accounted for 4–5% or less [4]. The influence of temperature on virulence was also suspected on mortality, since among regions of a given country there were variations which could not be explained by density population, nor availability or quality of health system resources, nor by the total number of people screened. For example, in Spain, on April 30th, 2020, the total number of COVID-19 cases were 143, 637, and 918/100,000 inhabitants in Andalusia, Catalonia and Madrid Autonomous Community, respectively. Also, recorded number of deaths were 14, 65, and 123/100,000 inhabitants, respectively [5]. These different rates of incidence and mortality between cold and warmer regions of a same country (Madrid with colder climate versus Andalusia with warmer climate), were also reported between northern and southern areas of France and Italy. Although the influence of age, socio-economic status, social distancing practices, and government legislature should be also taken into consideration, there was a suspicion at that time that cold temperature could increase the incidence rate of infection, and likely also the death rate. This reasoning was supported by a mathematical analysis, which calculated that there was a positive association between COVID-19 cases and 14-day-lagged temperature [6]. Similarly, weather data from various countries and cities, concluding that there was lower temperatures (particularly between 5 and 11 °C) promote COVID-19 incidence, in contrast to higher temperatures [7].

With the recurrence of COVID-19 pandemic in October 2020, in temperate regions of Europe like France, Germany and Italy, the possibility that the epidemic was influenced by the cold was suspected even further, like for many other respiratory viral infections [8]. For example, in France (Table 1) the daily estimated number of infections and deaths decreased from March to May 2020, were minimal from June to August, and clearly re-increased in October.

3. How cold promotes entry of the virus in the respiratory tract?

Like Hippocrates, let's start from the common observation that the cold favors seasonal infections, a process that everyone has experienced by saying "I caught a cold, a sore throat", while grandmothers recommend covering warmly to avoid "a fatal pneumonia". Thus, how can we explain these empiric observations made from the night of times? How can a sudden cold exposure induce a rapid viral infection and sometimes a lethal pneumonia?

Cold is a well-known anesthetic. For example, it is used in ocular surgery, and cold spray decreases the perception when the surface temperature drops to 10 °C [9]. Also, cold has protective effects on cells by down regulating their metabolism [10]. For example, the first cardiac operations were performed in ice water baths [11]. Then, topical cooling for myocardial protection has been replaced by cold blood or cold crystalloid cardioplegia: moderate hypothermia (below 28 °C) induces cardiac arrest [12], while profound hypothermia (temperature around 17.5 °C) is sometimes used for total circulatory arrest and brain protection [13]. Of note, accidental hypothermia impairs vital functions until it vanishes (e.g. < 20–25 °C), but a deeply hypothermic person, which may appear dead, can be sometimes resuscitated if rewarmed correctly [14]. Preservation of organs (kidney, liver, heart, and lung) with cold solutions is possible for few hours before transplantation.

These examples show that cold inhibits the metabolism of organs and tissues, paralyzing cells' functioning. Thus, sudden cooling of head and face, nose and sinuses, throat and chest could slow

Table 1
Number of recorded active cases and daily death at the indicated days in France in 2020. (https://www.worldometers.info/coronavirus/).

	Mar 30th	Apr 30th	May 30th	Jun 30th	Jul 30th	Aug 30th	Sep 30th	Oct 30th	Nov 30th	Dec 30th
Active Cases	29,542	46,925	11,585	9072	14,846	70,543	196,689	575,369	350,464	246,371
Daily death	418	289	57	30	–	29*	63	545	509	377

* = referred to 31st August.

down or arrest the functioning of cells, particularly those located in the mucosa and submucosa of the upper respiratory tract. Although the exact mechanism is not completely understood, we could speculate that it is possible that cilia move slower, or mucus production form goblet cells is decreased. Thus, barriers against microbes ensured by mucocillary cells and pro-inflammatory immune cells (constituted by macrophages, neutrophils, innate and memory lymphocytes) could be altered. Therefore, germs and in particular viruses, may enter and/or develop in the airway upper tract. Accordingly, experimental studies showed that that horses breathing cold air (−5 °C) have lower immunologic response, in comparison with horses breathing warm air (25 °C) [15]. The immune response is also reduced in ferrets exposed to 4 °C, this animal sharing similarities with humans regarding their protection from cold by fat tissue [16]. Besides affecting the effectiveness of the immune response, cold could have a direct effect on SARS-CoV-2 viral fitness. Indeed, studies indicate that the virus is more stable at low-temperature and low-humidity conditions, whereas warmer temperature and higher humidity reduce its half-life [17–19]. Overall, these studies suggest that climatic factors may significantly influence the virus spread, although additional demographic factors may play a role in affecting the transmission of the virus, sometimes even overcoming the effects of climate.

Thus, as for many other respiratory viruses, cold exposure could favor the entry and development of SARS-CoV-2 by increasing its survival and by altering the defense barriers in the pharynx, larynx, and/or sinuses. In the vast majority of cases, viruses would be destroyed by the pro-inflammatory cytotoxic response, first mentioned by Cornelius Celsus two thousand years ago as the classical triad of inflammation “dolor, calor, and rubor” [20]. Then, an anti-inflammatory response takes place, allowing healing. However, in some cases (as it seems to be for SARS-CoV-2), the virus can reach the lung, where it replicates and may cause more or less extensive pneumonia. We suppose that this sequence could be likely favored by a strong breath of cold air, which could carry high amounts of virus in lung alveoli (as a consequence of both increased viral fitness and reduced defenses of the upper respiratory tract). By gravity, the inoculum deposits preferentially in the lower parts of the lungs, more frequently in peripheral and subpleural areas, as showed by computed tomographic (CT) scans revealing signs of lung pneumonia at early time, on day 2 or 3, even in asymptomatic patients [21,22]. Knowing that cardioplegia with temperature below 28 °C induces cardiac arrest [12], it is possible that the breathing of cold air and/or chest exposure to low temperature downregulates the metabolism of alveolar pneumocytes and macrophages, thus favoring the replication of SARS-CoV-2 in lung further.

4. How cold can promote extensive pneumonia?

It is a well-known observation that cold exposure induces a white skin, in particular of extremities of the limbs and of the face, a phenomenon due to acute vasoconstriction of the vessels of dermis and hypodermis. A prolonged exposure can result in frostbite and gangrenes because intense vasoconstriction limits the blood supply, induces hypoxia in skin and tissues, and finally leads to anoxic irreversible cells damages. Hypoxia activates aerobic glycolysis and results in lactate production, muscular pain and decrease sensibility of the skin, all signs clinically observed in patients with ischemic limbs due to arterial thrombosis [23]. Acute or chronic exposure to cold temperature also elicits vasoconstriction of pulmonary arteries, as shown in humans [24–26], in various mammals [27–29], and also in broilers showing signs of pulmonary hypertension (PAH), such as larger diameter of the main pulmonary artery and thicker pulmonary artery wall [30].

Arterial vasoconstriction is related to the production of angiotensin II (Ang II), the major vasoconstrictor of the renin-angiotensin-aldosterone system (RAAS) which is produced by the angiotensin converting enzyme (ACE). This carboxypeptidase is expressed by the endothelial cells of vessels, including lung arteries [31]. In normal physiologic condition, the vasoconstrictor effect of Ang II is counterbalanced by angiotensin 1-7 (Ang1-7), a vasodilator which decreases the systemic and pulmonary arterial pressure [32]. Ang1-7 is formed by angiotensin converting enzyme 2 (ACE2), which both degrades Ang II and leads to formation of Ang 1–7 [33,34]. When exposed to ambient temperature, broiler chickens have a higher Ang 1–7 content and a lower Ang II concentration in lung tissue than their counterparts exposed to cold temperature [30]. Remarkably, ACE2 is also the membrane receptor of SARS-CoV-2 in host cells [35], and it is particularly expressed in endothelial cells of lung vessels [36,37]. It is now well established that high blood pressure is associated with COVID-19 severity [3] and related mortality. Of note, patients with arterial hypertension appear especially exposed to supplementary Ang II-induced vasoconstriction in response to cold exposure. This is particularly true in cases of low baseline ACE2 and Ang 1–7 levels [37,38]. This “phenotype” likely favors decompensation of comorbidities, such as preexisting PAH, cardiac insufficiency or chronic renal failure [3]. It is noteworthy that cold vasoconstriction can be reinforced by a sympathetic adrenergic stress response [39], which is exacerbated by hypertension. This adrenergic response can be especially at risk for patients with cardiovascular comorbidities [39]. The reciprocal relationship between RAAS and catecholamines remains to be studied, knowing that Ang II acts on brain Ang II type 1 receptor (AT1), thereby inducing the secretion of adrenaline [40], whereas upregulation of ACE2 in specific brain areas have beneficial effects on cardiovascular circulation [41]. Viral infection promotes hypoxia in corresponding infected lung areas, a process which induces local vasoconstriction and redirects the blood flow towards more oxygenated and vascularized territories [42]. This regulation matches perfusion to ventilation in order to maximize the oxygen saturation of the venous blood within the lungs.

In infected lung areas, hypoxia promotes enhancement of glycolysis in cells with lactic acid production. This so-called “Warburg effect” could likely sustain the replication of the SARS-CoV-2 virus in alveoli and endothelial cells, as it supports the replication of this virus in both cultured colon cancer cells [43] and blood monocytes [44]. Of note, the Warburg effect supports the replication of many other respiratory viruses, including Middle East Respiratory Syndrome Coronavirus (MERS-CoV), which shares many similarities with SARS-CoV-2 [45]. The replication of MERS-CoV is attenuated *in vitro* by inhibitors of PI3K/AKT/mTOR and MAPK/ERK

signaling pathways [46], two pathways which are key drivers of the Warburg effect. If the pro-inflammatory response - a process also sustained by the Warburg effect [45] - is not arrested and censored at adequate time by control mechanisms (such as p53, AMP-activated protein kinase (AMPK), nitric oxide (NO) and itaconate production) [43,45], hypoxic pneumonia may develop extensively, and lung destruction may lead to acute respiratory distress syndrome (ARDS) [47].

It is noteworthy that atheroma deposits in micro-vessels reduce the blood flow in corresponding tissues, and it promotes hypoxia and the Warburg effect in vascular smooth muscle cells, with a chronic state of vascular inflammation [48,49]. Chronic arterial pulmonary hypertension is also associated with the Warburg effect in vessels [50]. Platelet thrombosis is also dependent of aerobic glycolysis activation [51]. Thus, patients with atherosclerosis, a common pathological denominator associated with aging and most comorbidity factors of COVID-19, should be especially sensible to cold-vasoconstriction and the cascade leading to aerobic glycolysis sustaining viral replication and extensive pneumonia [52]. In addition, as shown in mice, acute lung edema and injury are favored by Ang II and AT1a, in contrast to ACE2 and Ang1-7, which are protective [53]. Lung edema and airway inflammation alter tight junctions in alveoli and increase glucose permeability. Interestingly, the higher glucose concentration in pulmonary alveoli sustains the development of germs, in particular of gram-negative bacteria [54].

To summarize, cold induces Ang II induced-vasoconstriction, a process known to promote hypoxia and aerobic glycolysis in lung, a metabolism sustaining viral replication. We hypothesize that a similar cascade could occur also in the case of SARS-CoV-2 infection (Fig. 1). As suggested above, cold could favor the survival of SARS-CoV-2 virus and its passage through the upper respiratory tract, where the immune defenses would be paralyzed. Also, by inducing vasoconstriction, cold could favor hypoxia and thus local pneumonia, which could exacerbate further the progression of COVID-19 disease. In addition, hypoxia may induce a metabolic rewiring towards the Warburg effect in lung cells. Since it is known that such a Warburg effect favor the replication of viruses and that it improves SARS-CoV-2 replication using *in vitro* models (see Refs. [43,44]), we hypothesize that this could be an additional cold-induced effect influencing the progression COVID-19 disease. However, additional in vivo studies should be performed to firmly establish this point. Consequently, we also suggest that patients with hypertension, atheroma, and low expression of ACE2 could be particularly at risk to develop extensive pneumonia after cold exposure.

5. A counter proof showing that cold promotes COVID-19 infection: warm is protective

As mentioned in the first paragraph, countries experiencing warm and/or tropical climate in the first semester of 2020 had low or very low incidence rate of COVID-19 infection and mortality rate. As shown in Table 1, COVID-19 infection rate was minimal during the last summer period in France, a country which experienced two heat waves with temperatures reaching 40 °C. Transmission is reduced as the virus is destroyed by high temperatures, within few minutes to half an hour at 50–60 °C, likely because the viral envelope, which contains lipids, melts [55]. At room temperature (24 °C), the virus half-life ranges from 6.3 to 18.6 h (depending on relative humidity) and is reduced to 1.0–8.9 h when the temperature increases to 35 °C [56] Although in some experiments, SARS-CoV-2 can persist on surfaces of fomites for many days, it is rapidly inactivated by sunlight, generally surviving less than 24 h at 35 °C–40 °C [57].

Experimental studies also showed that physical training - a body condition which warms up and makes sweating as tropical climate

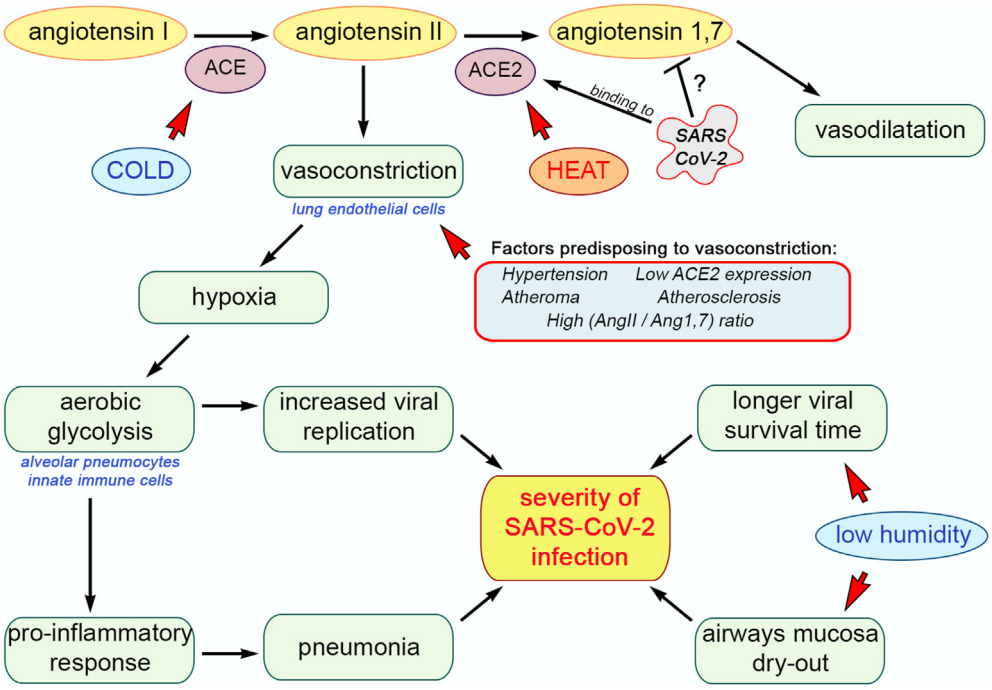

Fig. 1. The sequence relying cold exposure with SARS-CoV-2 replication and extensive pneumonia. Cold induces vasoconstriction and secretion of Ang II, a process promoting hypoxia and activation of aerobic glycolysis, a metabolism sustaining the replication of the virus in lung territories. The pro-inflammatory response is also sustained by aerobic glycolysis and factors promoting vasoconstriction may therefore promote deregulated pro-inflammatory response, and extensive pneumonia. Low humidity favors SARS-CoV-2 infectivity, by promoting its stability on surfaces, and/or its entry in airway tract. Although, Ang 1–7 secreted by ACE2 counteracts the deleterious effect of Ang II, the virus binding to ACE2 likely alters Ang 1–7 production.

- promotes activation of ACE2 / Ang 1–7 axis with vasodilatation, and a shift of the balance against Ang II [58]. Therefore, although the entry of the virus could be theoretically favored by the increase expression of ACE2, we suppose that the vasodilatation instituted by a « warm climate » in airways may counteract the virus entry, this condition likely thinning the mucus and preserving the metabolism of cells ensuring the defense barriers, in contrast to cold. Additionally, if an infection occurs, the higher production of Ang 1–7 can reduce the severity of the disease.

However, countries with warm climate have been also affected, in particular Brazil which has a subtropical climate. Data collected from February 27th to April 1st, 2020 in various cities of Brazil showed a negative linear relationship between temperature and daily confirmed cases from 16.8 °C to 27.4 °C, while the curve flattened at a threshold of 25.8 °C, with no evidence of a decline for temperatures above 25.8 °C [59]. Even if cold cannot be strictly studied independently of the other factors impacting transmission of the virus, in particular population densities, social distancing and protective measures, this study suggested that each 1 °C rise in temperature was associated with a decline in the number of daily confirmed cases (−4.89%, $p = 0.0226$) [59].

6. Discussion

As we have seen, cold appears as a key factor in increasing infectivity of viruses, this very likely by altering the defense barriers in the airway tract and favoring viral replication and fitness. We speculate that the same could apply also for SARS-CoV-2. Furthermore, cold also promotes vasoconstriction, in particular of micro vessels, a process which can sustain the development of pneumonia, by inducing hypoxia and further stimulation of aerobic glycolysis in cells. We believe that this metabolism may also sustain the replication of SARS-CoV-2 in lung cells, as it does for many other respiratory viruses. This sequence from the exposure to cold to the occurrence of pneumonia is likely favored in patients with atherosclerosis, arterial hypertension, high Ang II/Ang 1–7 ratio, and downregulation of ACE2. Of note, atherosclerosis, a common factor of comorbidities encountered in severe COVID-19 disease (arterial hypertension, diabetes, obesity, cardiovascular disorders), is associated with aerobic glycolysis in cells of vessels [48,60]. This metabolism also sustains the acute pro-inflammatory response against microbes [45,61,62] and the chronic inflammation, as showed in asthma [63].

Thus, we suggest that cold temperature could have been a key driver of the spread of the first waves of COVID-19 infection in the northern hemisphere in 2020, especially in European countries. Sensitivity to this natural factor should be further studied, considering the possible different responses of the RAAS among various ethnicities [64], and the impact of gene polymorphisms in the expression of ACE2 and/or type II transmembrane serine protease (TMPRSS2) receptors, another possible entry of the virus in host cells [65–67]. The impact of cold during subsequent waves of COVID-19 in 2021 would be more difficult to be established. Indeed, several other factors are likely to have influenced the spread of COVID-19 in Europe more than climate. Among them, the implementation of preventive measures of different amplitude and length among different countries, the appearance of vaccination, and the occurrence of viral mutants could have played a major role.

In reference to Hippocrates, natural factors other than cold temperature, such as extreme weather conditions, humidity, pollution (impacting ACE2 expression [68,69]), wind, rain and sun, may also impact COVID-19, knowing that one factor is not strictly independent from the others. Furthermore, extreme weather conditions, which tend to drive people indoors and in close proximity, could likely be more relevant for the spread of SARS-CoV-2 than climactic temperature. Dry weather seems to increase the impact of cold on SARS-CoV-2 infectivity, as it does for many other respiratory viruses, including respiratory syncytial virus [70], influenza, SARS-COV, and MERS-COV [7,71]. Humidity is expressed as absolute humidity (total mass of water vapor present in a given volume of mass of air; g/m^3) or specific humidity (mass of water vapor in a unit mass of air; g/kg), and also as relative humidity (RH), which is the amount (saturation) of water vapor that the atmosphere withstands at a given temperature. Low humidity levels contribute to the dry-out of airway mucosa, compromising the functioning of the mucociliary barrier as well as the fluidity of the mucus [72]. A low specific humidity (3–6 g/kg) and a low absolute humidity (4–7 g/m^3) likely contribute with a cold temperature (between 5 and 11 °C) to a higher community transmission and infection, as seen in Paris, Madrid or Milan from January to March 2020 [7,73]. In several hundred areas of USA studied from March to August 2020, lower specific humidity and cold were also associated with increased SARS-CoV-2 transmissibility; humidity was even considered as playing a larger role than temperature [74]. Data from 10 countries of Europe studied from January to June 2020 showed that a one percent gain in humidity was associated with a decrease in the number of cases in most countries [75]. In contrast, it was calculated that a 1% decrease in RH increases the infection rate of 7–8% [76]. However, the relationship between temperature and RH and SARS-CoV-2 transmissibility and infectivity is not strictly linear [77,78], given that RH is influenced by temperature. For example, there is more water vapor in air at 30 °C and 40% RH than in air at 20 °C and 50% RH, although RH is lower in the first case. Thus, the RH percentage gap that seems to enhance viral transmission is variable, ranging from 30% to 70% RH in different studies [73,77,79,80]. Low humidity contributes to the formation of smaller aerosol droplets that remain in suspension for longer, settling more slowly on surfaces [81]. It also contributes to a prolonged survival of the virus and therefore to increase the risk of infection [56,82]. With air humidity below 30%, it was calculated that the amount of aerosolized particles in the environment was twice as high as when humidity reached levels of 60% or more [83].

However, countries or cities with subtropical climate, like Brazil, experiencing warm temperature with intermediate or high humidity, also showed a high rate of COVID-19 transmission. It is thought that high humidity stabilizes the envelope of SARS-CoV-2 [80,84]. Remarkably, in other countries with recent and serious COVID-19 outbreaks, such as India, the highest per capita incidence has been observed in warmer regions with temperatures close to 30–40 °C. However, we speculate that in these countries suffering from overpopulation, the effect of cold is presumably masked by the social and economic conditions, bringing people in close proximity to each other, frequently without effective personal protective equipment (such as masks), as well as limited access to vaccination and hospitalization. Consequently, the impact of other natural and human factors remain to be studied, considering that all factors influencing COVID-19 transmission and infection, as the natural and social environments (in particular densities of populations, daily number of testing, social distancing, hygiene, masks and hand wash), the patients' physical conditions (defined by many clinical, biological and genetic parameters …), and also viral mutations (which may increase the entrance of SARS-COV-2 in cells) should be ideally integrated in larger models calculating their respective specific impact. Indeed, it is difficult to correctly discriminate the relative contribution of single factors (such as cold and humidity) among the complex interactions of biology, environmental factors, and human behavior influencing the global and local outcomes of COVID-19 pandemic. For example, a major role in fostering the propagation of COVID-19 pandemic may have been played by seasonal events and holidays, at a time when people tend

to get together (especially indoor, such as in family or churches). In France, in Mulhouse, the evangelical gathering of the Christian Open Door, from February 17 to 24, 2020 (grouping together up to 200 people) was undoubtedly one of the routes of entry of the coronavirus into France. Similarly, big social events in the United States have been associated in 2020 with a significant local increase in the number of infections [85]. In all these cases, the effect of climatic factors could be masked by the failure to comply with the correct preventive and distancing measures. Hopefully, big data analysis will be helpful for identifying the relative importance of each factor in the future. In line with this, a Monte Carlo simulation suggests that social activities during weekends are an important factor contributing to enhance the spread of the SARS-CoV-2 virus [86]. Animal models of COVID-19, like ferret or hamster, could be also useful for a better understanding of the pathophysiology of the infection, of the metabolism supporting the viral replication in cells, and also for testing the capability of several inhibitors of the Warburg effect already well-studied in cancer (for a list see Ref. [87]) to attenuate infection and/or to increase the effectiveness of anti-viral drugs.

7. Therapeutic perspective

Hippocrates taught that medicine is an art requiring interpretation of observational signs with sagacity, while the therapeutic strategy is basically acting by opposites: hot over cold, warm beverage and balanced diet, and hygiene at individual and collective level. The thoughts of Hippocrates and Sanctorius must inspire our lifestyle, practice, and methodology, as well as our barrier measures.

From a therapeutic point of view, we suggest preventing the possible adverse effect caused by cold on COVID-19 infection by adopting simple preventive measures, such as wearing warm clothes and a mask. The latter may favor a warmer and more humid atmosphere in the upper respiratory tract, all factors potentially reducing viral fitness and improving host defense. As low humidity likely increases the risk of contamination during the cold winter months, increasing indoors humidity could limit infections transmission, particularly when window ventilation is difficult or not possible. In line with this, a study demonstrated that in indoor places a lower humidity (<40% RH) increases the chances of airborne transmission of SARS-CoV-2 compared to high humidity (>90% RH) [88]. Thus, as the authors stated, "*it is extremely important to set a minimum relative humidity standard for indoor environments such as hospitals, offices and public transports for minimization of airborne spread of SARS-CoV-2*" [88].

Strategies counteracting the deleterious effects of Ang II on pulmonary, renal and cardiac function appear attractive, using drugs blocking Ang II receptor type 1 (ATR1), or increasing angiotensin 1-7 levels [89]. Zinc deficiency should be corrected as its deprivation alters immune response [90], promotes aerobic glycolysis functioning and impacts ACE2 catalytic functioning [45]. Vitamin D deficiency - frequently observed in patients lacking sun exposure - should be also corrected because it may alter RAAS and up-regulate ATR1 [91].

8. Conclusion

On the footsteps of Hippocrates, Santorius, and Harvey the ability to link natural and clinical observations with experimental measurements could help us achieve a better understanding of the influence of cold temperature on transmission, infectivity, and virulence of SARS-CoV-2. This methodic and deductive approach illustrates that Medicine is an art of interpretation, a logical reasoning which is more and more a science at the crossroads of several disciplines. This interdisciplinary understanding has resolved a lot of mysteries about human pathologies in modern times. It is still fundamental to understand modern enigmas, such as COVID-19.

For solving puzzles, the old Masters have taught us the right lessons: being surprised by unusual facts, being curious and observe, asking the good questions, testing hypotheses by performing rigorous experiments, inventing new methods of detection, developing techniques of measurements and calculation, repeating experiences, making correct interpretations, and reintegrating the results into a holistic understanding. By doing this, the old Masters solved many difficult problems in their time. Let us continue to draw inspiration from their spirit and practice.

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Declaration of competing interest

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Code availability

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Authors' contributions

PI and MA were responsible for design and contributed to manuscript writing. LS contributed to manuscript revision, editing and made the figure. JR, LF and VDP contributed to editing and searching of references. All authors read and approved the final manuscript.

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