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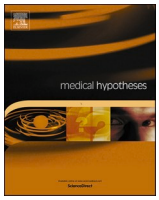

Snoring may transmit infectious aerosols from the upper to the lower respiratory tract

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ABSTRACT

Migration to the lungs of an initial upper airway infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) or other respiratory pathogens can lead to pneumonia, associated with progression from mild to severe symptoms. Chemical pneumonitis or bacterial pneumonia may be caused by the 'macroaspiration' of large volumes of oropharyngeal or gastroesophageal secretions into the lower respiratory tract. 'Microaspiration', *i.e.*, a similar mechanism but involving much smaller amounts of oropharyngeal secretions, is considered the pathogenetic mechanism for most pneumonias, including that associated with COVID-19. Here, we hypothesize an alternative mechanism: Rather than by microaspiration, these fluids enter the lungs as microdroplets that are generated by snoring and then carried by the inspired airstream. Laboratory measurements indicate that snoring generates (a) comparable numbers and sizes of oral fluid droplets as loud speaking and (b) total fluid quantities that are similar to those reported for microaspiration. Snoring propensity is strongly correlated to known risk factors for severe COVID-19, including male gender, age, obesity, diabetes, obstructive sleep apnea, and pregnancy. Therefore, more research is urgently needed to determine if various methods that decrease snoring can prevent progression to pneumonia after initial infection of the upper airways.

Introduction

The pathogenesis of coronavirus disease 2019 (COVID-19) pneumonia most commonly involves initial infection of the upper airways followed by seeding of the lung [1,2]. The current paradigm to explain this spreading in COVID-19 and most pneumonias is 'microaspiration', a subclinical type of aspiration where microscopic quantities of fluids are aspirated into the lungs [1,3–5]. Here, we hypothesize an alternative mechanism: Rather than by microaspiration, these fluids enter the lungs as microdroplets that are generated by snoring and then carried by the inspired airstream. We also provide laboratory measurements to support our hypothesis.

The transfer of small amounts of oral fluids into the lung is supported by evidence for microbial immigration from the oral cavity into the lung in many but not all healthy adults [6]. However, the concept of microscopic amounts of secretions flowing down into the lung against the 'mucociliary escalator', which normally clears the airways, defies the physics of fluids: Because of their large surface to volume ratio, such micron-sized quantities of fluid will rapidly merge with, and cannot move independently from, the hygroscopic mucosal surface layer to which they are anchored. 'Microaspiration' also does not adequately explain the rapid development of diffuse or multi-lobar pneumonia caused by a wide range of respiratory viruses that indicates the presence of infection sites deeper in the lung.

However, it is a well-documented phenomenon that microliter quantities of fluids are transferred into the lower respiratory tract (LRT) of healthy adults at night during sleep: Using radionuclides placed in the pharynx overnight, the presence of radioactive tracers in the lung the following morning has been established by nuclear medicine imaging [4,5]. Unfortunately, neither these nor other studies of microaspiration included data on whether or not the subjects were snoring.

Airborne transmission of respiratory diseases is mediated by micron-sized aqueous particles or droplets consisting of saliva, mucus, airway lining fluid, and other matter covering the surface of the respiratory tract [7]. These droplets are produced by activities such as breathing, coughing, sneezing, and talking, which also includes singing, laughing and other vocalizations [8]. All but breath droplets are solely generated during expiration and are released into the atmosphere. There, their aqueous fraction evaporates while non-volatile material, including potential pathogens, remains as aerosol and can transmit disease when inhaled by others.

To date, snoring has not been recognized as a mechanism for producing respiratory droplets, probably because the droplets are generated during inspiration and therefore not readily observed by standard aerosol detection technology. However, the same physical mechanisms responsible for the generation of speech droplets [9] apply to snoring,

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strongly suggesting that snoring is a droplet producing activity. Here, we present preliminary experimental data supporting the abundance of respiratory droplets generated by snoring and discuss their quantities in terms of the dose required for infection of the LRT.

Transfer of oral fluids into the lung

Mechanism of snoring droplet generation

Snoring is characterized by the generation of sounds associated with highly transient upper airway closure and associated soft tissue vibrations during inspiration in sleep. Details of the biomechanics of these motions were revealed by nasendoscopy, a method that utilizes a thin, fiberoptic endoscope to monitor the pharyngeal airway, including the soft palate, during sleep [10]. During snoring, the inspired air causes the soft palate to flap up and down, transiently touching the back of the tongue. As a result of fluid surface tension, fluid filaments transiently form between these wetted surfaces while they are parting, with the inspired airstream breaking such filaments into a multitude of microscopic droplets [9]. This process is very similar to, but goes in the opposite direction of, speech droplets that are created by acoustic modulation of an exhaled airstream by the vocal folds, tongue and teeth, or lips [9]. Snoring droplets and any pathogens they contain therefore will travel with the inspired airstream directly into the LRT.

Observation of aerosols from expiratory snoring

Preliminary data from our laboratory support the hypothesis that snoring is a prolific droplet-generating mechanism. All measurements of respiratory droplets were carried out for a single male volunteer, using five repeats, under an exemption from the Institutional Review Board of the NIH.

Because direct detection of snoring droplets in the lungs is technically not feasible, we first focused on the observation of snoring droplets that were generated during expiration while producing a sound that mimicked the saw-tooth, low-frequency modulations of inspiratory snoring sounds. Generating expiratory snoring sounds that involve the same airway surfaces and acoustically mimic those of inspiratory snoring sounds is uncommon and required some practice.

The size and number distributions of the resulting expiratory snoring droplets were quantified using an optical particle sizer for the smaller aerosols (≤10 μm), and by recently introduced video analysis technology of scattered light for the larger ones [11]. Numerous particles across a broad spectrum of sizes were observed upon the generation of expiratory snoring sounds (Fig. 1). Accurate sizing of these particles requires that their aqueous fraction is first removed by evaporation. The total dehydrated particle volume then was measured at *ca* 77,000 μm^3 per liter of snoring air, which for a non-volatile fraction of 1 % corresponds to *ca* 7.7 nL of oral fluid, or several μL per hour of snoring. The observed expiratory snoring particles span a broad spectrum of sizes, with the largest numbers seen for the smallest diameters. These small particles were found to be far more numerous than those generated by the underlying breathing activity (Fig. 1), indicating that they resulted from snoring. Whereas no breath aerosols larger than *ca* 5 μm were detected, snoring particles extend in size to over 30 μm, with the distance they can descend into the LRT inversely correlated to their size. Only particles smaller than *ca* 5 μm can reach the deep lung, *i.e.,*the terminal, gas-exchanging branches of the bronchial tree [12].

Observation of aerosols from inspiratory snoring

The above observations refer to expiratory snoring. Inspiratory snoring droplets are generated by the same physiological mechanism and therefore expected to be comparable in both number and size distribution. While the larger size fraction of such droplets will rapidly sediment in the LRT, smaller particles can remain present in

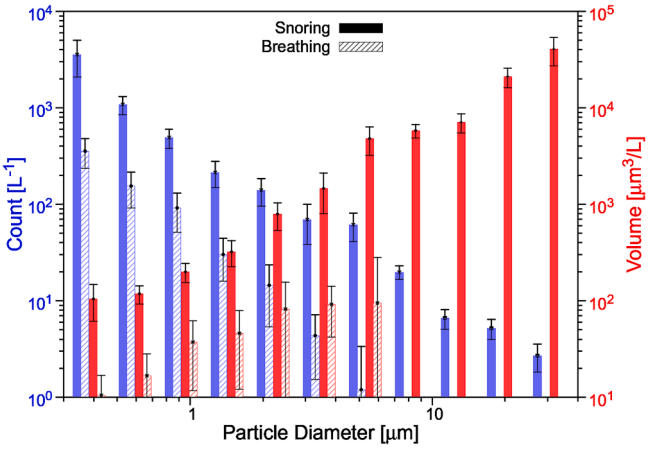

Fig. 1. Size distribution of respiratory particles. Solid bars correspond to expiratory snoring; hashed bars represent silent exhalation. Particle counts (blue, left axis) are reported for binned diameter ranges, per liter of expired air, and correspond to the dehydrated state. Particle sizes and counts were detected by a TSI-3330 optical particle sizer for the range of 0.3–10 μm, and by laser light scattering for particles > 10 μm, after they were entered into a low-humidity dehydration chamber [11]. Error bars correspond to the standard deviation over five repeats. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

subsequently exhaled air (Fig. 2) [13], analogous to a smoker exhaling cigarette fumes. This allowed us to monitor the fraction of non-deposited snoring droplets in the exhaled air of the volunteer. Indeed, we observed an approximately fourfold increase in exhaled particle count when expiration is preceded by an inspirational snoring sound that generates the oral fluid droplets. This fourfold excess essentially vanishes when inserting a 10-s breath-hold prior to expiration, allowing the particles more time to sediment or 'rain out' in the LRT (Fig. 2).

Voluntary versus natural snoring

Droplets observed in our measurements resulted from voluntary,

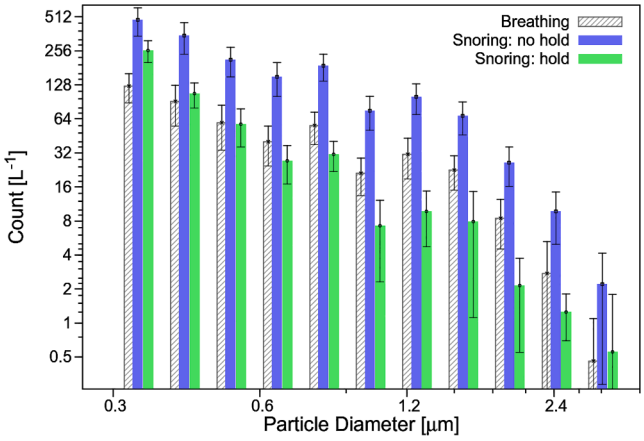

Fig. 2. Size distribution of respiratory particles in exhaled breath after inspiratory snoring. Blue bars represent particle counts when exhalation immediately follows inspiration of 1.6-L of air while making a loud snoring sound; green bars are the corresponding values when inserting a 10-s delay between the inspiratory snoring sound and expiration. For reference, hashed bars correspond to breathing of the same air volume. Note that bin widths (spaced by factors of 1.25) are twofold narrower than for Fig. 1. Particle sizes and counts were determined by a TSI-3330 optical particle sizer after entering a low-humidity dehydration chamber [11]. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

simulated snoring, which likely differs from natural snoring in involved muscle tones and reflexes. However, the sounds produced in our voluntary snoring measurements mimic those of natural snoring during sleep, including the repetitive "saw tooth" sound modulation associated with the transient touching of the soft palate and the back of the tongue [10] and therefore can be assumed to generate a similar distribution of droplets. The transient touches between these wetted surfaces are at the core of speech droplet generation [9,14], and the same mechanism will apply for snoring. Although there likely will be some differences between natural and voluntary snoring as well as variability among snorers, just like speech droplets are inextricably linked to speaking, snoring invariably generates droplets.

Fluid transfer by snoring and obstructive sleep apnea

In contrast to the highly transient modulation of the inspired airstream by snoring, obstructive sleep apnea (OSA) involves prolonged, complete occlusions of the upper airway, followed by its sudden opening associated with gasping. The adverse health effects of OSA are well recognized [15]. Both OSA and snoring are caused by the relaxation during sleep of muscles that support the soft tissues in the throat. However, while increased incidence of snoring among OSA patients is well recognized, in contrast to OSA, snoring is generally considered a mostly benign activity associated with deep sleep [15]. Quantities of fluids transferred overnight into the central airways of OSA patients are in the single digit milliliter range [16], thus too voluminous for aerosolization. We speculate that these fluids are aspirated from the surface of the occluded passage by the sudden burst of air during the gasp that terminates the blockage. Although generation of small, airborne droplets is likely to occur simultaneously by the same mechanism that is responsible for breath droplets [17,18], their total liquid volume will be much smaller than the large aspirated quantities observed by Beal et al. [16].

Similarity of the microbiome of the lung and the oral cavity

A well-documented observation that is consistent with our proposed snoring mechanism to transfer pathogens to the lung relates to the physical origin of 'microaspirated' fluid. In healthy adults, quantitative PCR analysis of the bacterial community present in the lung showed strong overlap with that of the mouth, but not the nose [6]. This finding indicates that microbial immigration into the lung, attributed to microaspiration during sleep, predominantly originates from the oropharynx, despite nighttime breathing mostly occurring through the nose. Substantial inter-subject differences of the quantity of microbial import from the mouth to the lungs were also noted [6]. Both these observations are consistent with snoring, which involves mouth breathing, as a mechanism for the transfer of the microbe-containing fluids, with the substantial inter-subject differences putatively consistent with their varying snoring propensities. Unfortunately, data on snoring among the study subjects were not collected.

Discussion

Infectious dose required for SARS-CoV-2 infection

The number of virions required to cause a new infection in a susceptible person remains difficult to determine. Thus, for airborne virus transmission the concept of a "quantum" is commonly used, which corresponds to the inhaled dose of pathogens required for a 63 % infection probability [19,20]. Analysis of various superspreading events indicated *ca* 10–1000 quanta per 1000 L of air expired by the index case [19], depending on their respiratory activity, with the highest value corresponding to singing at the Skagit Valley Chorale [21]. In other words, for a highly infectious person, a quantum of pathogens can be present in a single liter of exhaled breath when singing or otherwise loudly vocalizing. However, because only a small fraction of these pathogens will be inhaled by others, the likelihood of generating a new infection scales with the number of quanta emitted. By contrast, for inspired snoring droplets, nearly all pathogens will deposit directly in the LRT and a single quantum of pathogens can suffice to infect the lung. In fact, even fewer pathogens may be required for in-host transmission from the pharynx to the lungs because snoring droplets, carried from the back of the mouth into the lungs, are not subject to the dehydration/rehydration cycle in the atmosphere, which has been shown to inactivate the viability of SARS-CoV-2 by as much as tenfold [22]. On the other hand, lower levels of angiotensin converting enzyme 2 (ACE2) receptor in the lower compared to the upper respiratory tract [1], combined with effective mucociliary clearance in the LRT (Fig. 3), may offset the increased viability of snoring-generated virus. Considering that the quantities of oral fluid aerosolized by snoring (Fig. 1) approach values reported for loud speaking, measured by the same instrumentation [11], as little as a few liters of inspired snoring air may suffice to self-infect the lungs. Taking into account that only the smallest snoring droplets that can penetrate the deep lung [12], several hundred liters of inspired snoring air, may be required, *i.e.*, as much as half an hour of snoring.

Infectious dose contained in snoring droplets

A recent SARS-CoV-2 human challenge study showed that high viral loads in the throat precede those in the nose and reach a peak of *ca* 4×10^7 copies per milliliter [23]. At the above estimated 7.7-nL volume of

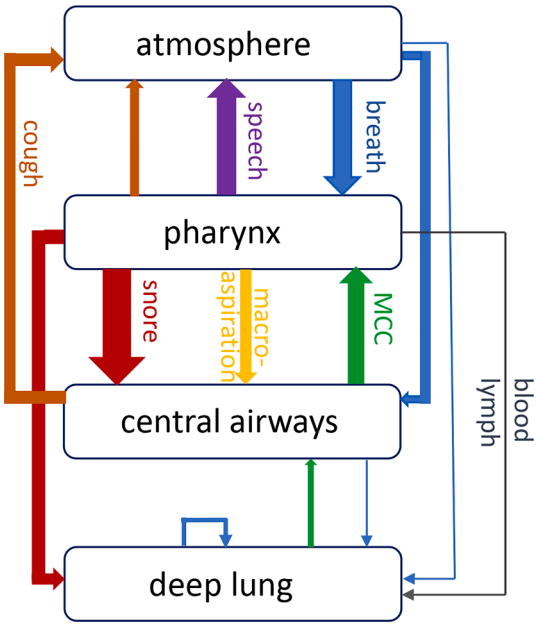

Fig. 3. Flow diagram for pathogen transfer pertinent to development of pneumonia. Arrow thickness qualitatively reflects the efficiency of each process. Inspired breath (blue) delivers pathogens primarily to the pharynx and the central airways, where relatively high speed [27] of mucociliary clearance (MCC, green) reduces the probability of infection. Only a very small mass fraction of inspired particles is sufficiently small to reach the deep lung [12]; inspired breath may dislodge fluid particles from the central airways and carry them into the deep lung [28]. Snoring (red) generates an abundance of fluid particles that are carried into the central airways and the deep lung. Expired breath, coughing/sneezing (brown) and speaking (purple) transfers pathogen-laden particles to the atmosphere that upon rebreathing can reach the deep lung in a process referred to as self-infection [27,41]. Pathways that involve the external atmosphere are subject to partial virus inactivation due to dehydration [22], whereas the snoring and macroaspiration (yellow) pathways are not. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

fluid per liter of inspired snoring air, this viral load corresponds to *ca* 300 virions per liter of inspired snoring air, of which only a small fraction is competent to infect a cell [24,25]. Although genetic deep-sequencing of the SARS-CoV-2 viral genome in transmission pairs showed that a single virion most commonly is responsible for a new infection [26], the probability that any single virion enters a host cell and successfully creates progeny is very low. However, even for as little as 10 min of snoring, which corresponds to *ca* 60 L of inspired snoring air, the total number of inhaled virions (~18,000) is likely to exceed the infectious dose. While *ca* 93 % of the snoring droplet volume, and therefore the majority of inhaled pathogens, is contained in the larger (≥5 μm) droplets (Fig. 1, right axis), numerically the number of small snoring droplets that can reach the respiratory bronchioles is high. Slow mucociliary clearance in these terminal branches of the bronchial tree extends the duration of virus exposure in these regions of the lung and thereby the probability of infection [27].

Viral spread within the lung

Once an infection occurs deeper in the lung, computational modeling has shown that diffusion of newly generated virions in the airway lining fluid is a very slow process, suggesting that many separate loci of infection are needed to impact a substantial fraction of the lung [27]. By contrast, in the central airways, advection of mucus associated with mucociliary clearance is much faster than virus diffusion and gives rise to outwards-streaked infection patterns, away from the deep lung, but consistent with bronchial symptoms [27].

Below, we argue why a limited number of infection sites in the lung may suffice to rapidly spread through the entire lung. In addition to slow diffusion of virions in airway lining fluid, a second airborne mechanism for spread of virus in the lung has been proposed [28], which does not require wide-spread seeding throughout the lung by the initial exposure to pathogens contained in inhaled snoring or other respiratory droplets. This alternate spreading mechanism within the deep lung (Fig. 3) involves breath droplets that are generated upon re-opening of small airways that transiently closed during expiration [17,18]. Because airway inflammation at the site of infection results in tissue swelling, which narrows the airway passage at the site of infection, such inflammation promotes the transient closure of the infected airway. Its subsequent re-opening during breathing results in the generation of breath-droplets [17,18], precisely at the site where virus is produced, promoting viral spread throughout the lung. This scenario is supported by a *ca* 1000-fold increase in exhaled breath particle counts observed in nonhuman primates that had been deliberately infected with SARS-CoV-2, with the increase in breath particles matching their severity of COVID-19 [29]. Such breath droplets, generated at the infection site and laden with virus, will be carried by respiratory air throughout the lungs and can greatly accelerate the spread of virus within the lungs [28]. The effectiveness of inhaled budesonide in preventing severe COVID-19 supports this mechanism.. In addition to its wide range of modulatory effects on the immune response [30], its anti-inflammatory action limits tissue swelling at the infection site, thereby preventing the production of infectious breath droplets and their spread within the lungs [31]. Such a mechanism for inhaled budesonide in preventing severe disease may contribute to its observed high effectiveness in patients with mild-to-moderate but not severe COVID-19 [30,32].

Risk factors

Obesity, male gender, and obstructive sleep apnea are all positively correlated with snoring propensity [33–35] and are recognized as strong risk factors for developing severe COVID-19, which usually includes pneumonia [36,37]. It therefore appears likely that the increased snoring propensity in such individuals is a contributing factor to these elevated risks, in particular, by generating snoring microdroplets that can penetrate the lung much deeper than aspirated fluids. Pregnant and recently pregnant women with COVID-19 also are more likely to require invasive ventilation than non-pregnant women of reproductive age [38]. The observation that pregnancy increases chronic snoring propensity in the third trimester by nearly fourfold [39] suggests that snoring may play an important role in the elevated risk for severe COVID-19 in late pregnancy or postpartum.

Many respiratory viruses other than SARS-CoV-2 are also known to spread from the upper respiratory tract (URT) to the LRT, including respiratory syncytial virus, measles, influenza, and many more. It appears likely that, rather than microaspiration, snoring may be a significant pathway for carrying these pathogens into the lung. For instance, for influenza, it was demonstrated that the soft palate, which plays a key role in generating snoring droplets, becomes remarkably enriched in virus concentration during the early stages of infection [40].

Other mechanisms for infecting the lung

We do not propose that snoring is the only mechanism for infecting the LRT with virus. Pathogen-laden respiratory aerosols carried by inspired air can enter the lungs directly, *e.g.*, in tuberculosis, but at least for SARS-CoV-2, this probability is much smaller than generating an initial infection of the URT (Fig. 3).

The substantial volumes of fluid associated with aspiration, commonly seen for OSA patients [16] not on continuous positive airway pressure (CPAP) therapy, can carry large quantities of pathogens into the central airways. Although fluid mechanics suggest that initially such large volumes of fluid cannot enter the lung deeply, they may result in occlusion of bronchial airways and thereby cause airborne droplet generation when such channels burst open during breathing (Fig. 3).

Next to snoring, a second route for self-infecting the lungs involves inhaling one's own speech or cough droplets. Because any person with a SARS-CoV-2 infection of the URT is invariably at the center of their own speech or cough aerosol cloud for the entire day, the probability of self-infecting the lungs is far higher than for person-to-person transmission [27,41]. However, because such potential self-infection through speaking or coughing includes the virus-inactivating dehydration/rehydration cycle [22], and only a modest fraction of these aerosols will be inhaled, the effectiveness of this self-infection pathway is likely to be much lower than for snoring (Fig. 3).

Testing and implications of the snoring hypothesis

Our hypothesis that snoring rather than microaspiration, or some other unidentified mechanism, is responsible for transfer of pharyngeal fluids into the LRT can be tested by repeating the radionuclide tracer studies that monitor the transfer of fluids into the lung during nighttime sleep [4,16] while closely tracking the snoring activity of the subjects.

Determining whether or not snoring propensity correlates with the probability to develop viral pneumonia in subjects infected with SARS-CoV-2 is challenging due to the many confounding factors, including age, gender, and obesity. A large patient survey that, besides information on the regular risk factors, also includes snoring propensity therefore will be needed to clarify whether snoring represents a dominant, independent risk factor for progression of COVID-19 to viral pneumonia.

Snoring is a preventable activity. The use of a CPAP device, widely prescribed for reducing OSA, also effectively eliminates snoring [42,43]. Our hypothesis therefore predicts that use of CPAP will correlate with improved COVID-19 outcomes, despite the CPAP patient population being subject to elevated risk factors that overlap for OSA and COVID-19. A challenge in preventing snoring-mediated transfer of oral fluid droplets to the lungs is posed by the high efficiency of this mechanism. Our above analysis suggested that, in the worst case, inhalation of just a few liters of snoring air may suffice to transfer an infectious dose of virus into the LRT. Therefore, any study of the efficiency of CPAP on preventing severe disease must separately consider patients that never sleep without CPAP from those that use such a device often but not always, or

only occasionally. While adherence to CPAP therapy is often monitored remotely, such data is usually not part of the patient's electronic medical record (EMR). Integration of CPAP adherence data into the EMR will be needed for evaluating the extent to which use of CPAP therapy can prevent progression to pneumonia.

The snoring hypothesis implies that minimizing or eliminating snoring during the early phase of a new respiratory infection, when the pathogen is present at high concentrations in the URT, will strongly reduce the probability of infecting the lungs. Other than CPAP, a number of remedies are available to reduce snoring propensity, ranging from sleeping in a prone position to various devices, including mouthpieces and head-straps.

Concluding remarks

Our measurements indicate that oral fluid quantities dispersed into the LRT by inhalation of snoring droplets are comparable to those previously attributed to 'microaspiration' during sleep [4]. The suggestion that microaspiration is simply a microscopic analog of macroaspiration is physically flawed because any microscopic quantity of aspirated aqueous fluid will rapidly merge with the outward-bound mucosal layer to which it is tightly adhered. Thus, it appears plausible that snoring rather than microaspiration is responsible for the development of viral pneumonia in those infected with SARS-CoV-2 or other respiratory viruses, in particular in the elderly, pregnant, and obese, who are more prone to snoring.

If a conclusive link between snoring and pneumonia can be established, the burden of a wide range of viral respiratory diseases on society can be greatly alleviated by measures that prevent snoring for the duration of any upper respiratory tract infection.

Consent statement/Ethical approval

Consent statement/Ethical approval: Not required'. All measurements of respiratory droplets were carried out for a single volunteer under an exemption from the Institutional Review Board of the NIH (IRB #: 000979).

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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