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REVIEW

Laryngoscope Investigative Otolaryngology

Influencing factors of particle deposition in the human nasal cavity

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Abstract

Objective: To review the existing literature on the application of computational fluid dynamics methods to study nasal particle deposition and to summarize and analyze the factors affecting nasal particle deposition in order to provide theoretical references for the development of future transnasal drug delivery devices and the prevention of respiratory-related diseases.

Data Source: PubMed and CNKI databases.

Methods: A search of all current literature (up to and including February 2023) was conducted. Search terms related to the topic of factors influencing nasal particle deposition were identified, and queries were conducted to identify relevant articles.

Results: Both the properties of the particles themselves and the environmental conditions external to the particles can affect particle deposition in the nasal cavity, with particle deposition showing a positive correlation with particle size, particle density, and airflow velocity, with increasing subject age leading to a decrease in deposition, and with the relationship between airflow temperature and humidity still requiring more research to further explore.

Conclusions: With the popularity of computational fluid dynamics, more and more scholars have applied computational fluid dynamics technology to explore the influence of different parameters on particle deposition. By summarizing and analyzing the influence law of various factors on deposition, it can provide a theoretical basis for the future development and application of transnasal drug delivery devices and the prevention of respiratory-related diseases, which makes a significant contribution to the optimization of clinical disease prevention and treatment.

Level of Evidence: NA.

KEYWORDS
computational fluid dynamics (CFD), nasal cavity, numerical simulation, particle deposition

1 | INTRODUCTION

Chronic respiratory diseases have become a widespread public health problem worldwide and are now one of the leading causes of death globally; most chronic respiratory diseases are caused by long-term airway inflammation, which can be exacerbated by environmental factors such as cigarette smoke, industrial pollutants, and pollen.[1] The nasal cavity serves as both the gateway organ for respiratory airflow into the body, and the primary structure for particulate matter entrained in the airflow to enter the body. The mucosa lining the nasal cavity provides a protective barrier system for the host.[2] Nasal hairs, the nasal vestibular flexure, and the nasopharynx work together in a filtering role to block some of the harmful particles from being deposited in the nasal passages that can lead to disease.[3] A range of respiratory diseases such as paranasal sinus cancer can be induced when the airways are damaged or when there is an excessive amount of particulate matter in the environment (including industrial dust, pollen, etc., as mentioned above) that is inhaled through the nasal passages and stays in or passes through the nasal passages into the lungs and other structures. In addition, nasal inhalation therapy has been increasingly used in respiratory diseases due to the advantages of a large absorption area, abundant capillaries, low local enzymatic activity, and the avoidance of first-pass effect and intestinal metabolism by transnasal administration[4–7] which makes the nasal cavity an ideal site for drug absorption (refer to Figures 1 and 2).[8,9] Common forms of nasal drug delivery include sprays, drops, powders, and gels.[4] Common areas of nasal drug therapy include antimicrobial, cardiovascular, pain, Parkinson, Alzheimer, cancer, osteoporosis, anticoagulation and many more.[10]

Since the dimensions of cadaveric models are usually too large in relation to the cavity, it is more appropriate to use a living nose as the corresponding nasal model. A living nose model can be obtained by computed tomography (CT) scanning, which allows the internal dimensions of the nose to be accurately modeled.[10] Human experimentation are greatly limited by the invasive and dangerous nature of

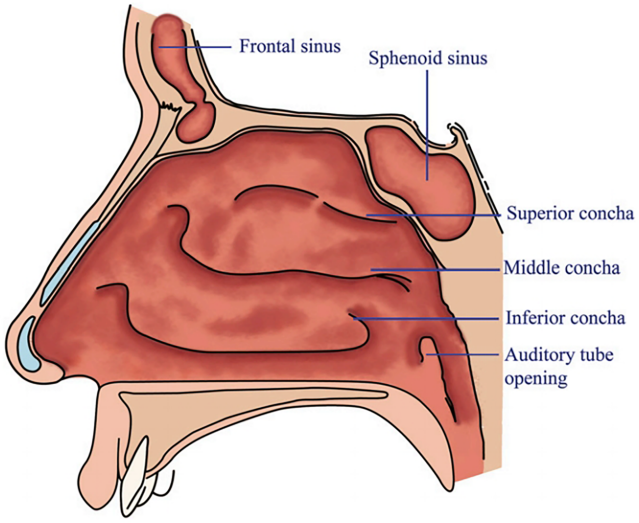


FIGURE 2 View of the lateral wall of the nasal cavity.[9]

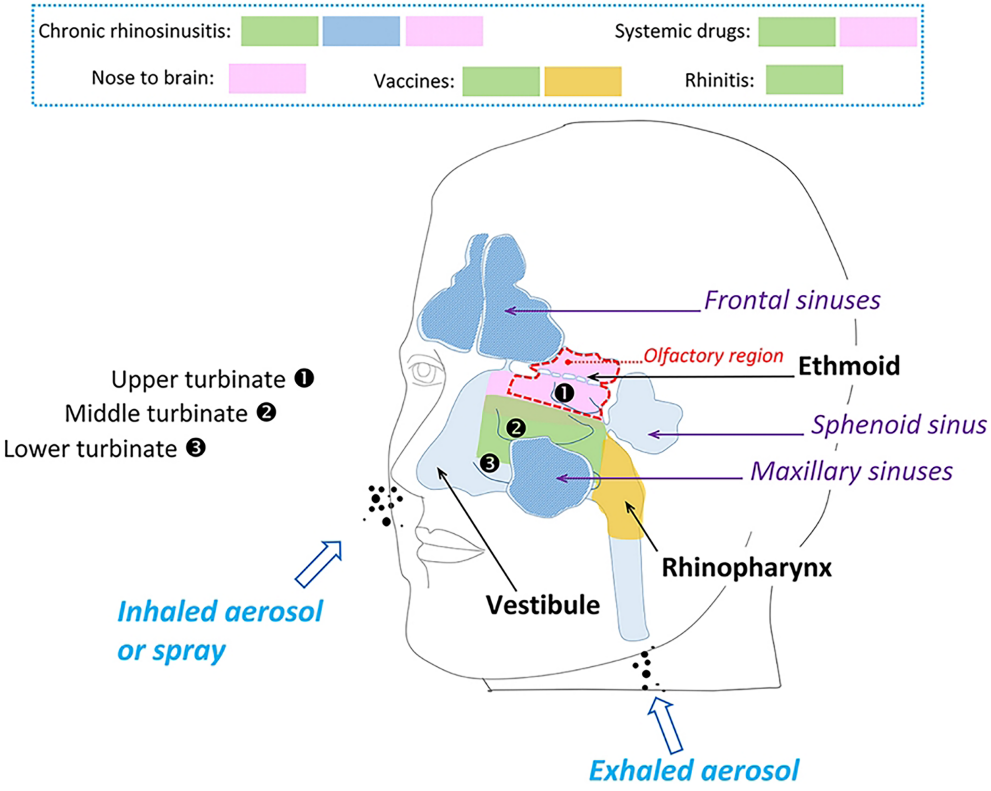


FIGURE 1 Schematic representation of adult nasal cavities and theoretical therapeutic target regions for nasal drug deposition.[8]

Researcher	Model	Result
S.M. Wang et al.	3D model of upper airway of a healthy adult male.	The deposition of nanoparticles in the nasal cavity was relatively uniform. Most of the micron particles were deposited near the nasal valve area, and some micron particles were deposited on the nasal septum wall in the turbinate area.
Jinxiang Xi et al.	3D model of upper airway of a 5-year-old child.	There are significant differences in inhaled aerosol deposition between children and adults. At the same flow rate, the amount of particles deposited in the nasal cavity of children is much higher than that of adults.
Pejman Farhadi Ghalati et al.	3D model of upper airway of a healthy adult female.	There are four main hot spots for the deposition of micro-particles, namely, nasal valve region, the top of middle meatus, the nasopharynx and the larynx. The results of regional deposition of nanoparticles showed that the highest percentage of nanoparticles were deposited in the nasal cavity, pharynx, trachea and larynx. The deposition pattern of nanoparticles was more uniform.
T. Wang et al.	3D models of upper airway of 20 patients with severe anterior nasal cavity stenosis, including one case of bilateral stenosis.	The anterior part of the inferior turbinate, especially the nasal valve area, has the most significant effect on the airflow gradient distribution, and the operation can not only improve the local nasal structure and resistance, but also provide bilateral airflow pressure uniformity, thus improving nasal respiration.
XiaoBing Chen et al.	3D model of upper airway of a healthy adult was established, and the transverse area of the inferior turbinate was reduced twice respectively, resulting in a normal nasal cavity, a moderate nasal obstruction (with the transverse area of the inferior turbinate reduced by about 1/3), and a severe nasal obstruction (with the transverse area of the inferior turbinate reduced by about 2/3) model was obtained.	Patients with nasal obstruction need to be assured of a moderate inspiratory flow rate when using nasal sprays in order to obtain a high escape rate. For patients with moderate or severe nasal obstruction, the effect of variations in nasal flow rate, initial particle velocity, particle diameter and tilt angle of the head for administration is limited to negligible.

FIGURE 3 Some key findings in CFD.[11,13–16]

toxic aerosols.[11] In addition, in vivo experiments cannot provide precise and detailed information about the initial particle condition and its relationship to specific deposition sites in the nasal tract.[12] With the continuous development of computer technology, a serious of scholars have conducted in-depth studies on particle deposition in different regions of the human nasal cavity using computerized fluid dynamics (CFD). Some scholars have already discovered laws related to particle deposition through CFD studies, which provide great clinical help (Figure 3).[11,13–16] The CFD method is based on the application of CT images of the human nasal cavity, which can safely simulate the structure of the nasal cavity in vivo, avoiding the drawbacks associated with cadaveric and in vivo experiments. The

common anatomical structures in the nasal cavity include the nasal vestibular region, three groups of turbinates (upper, middle, and lower turbinates), four groups of sinuses (frontal, sieve, pterygoid, and maxillary), the olfactory region, and the nasopharynx.[8,17] In applying CFD to study particle deposition in the nasal cavity, scholars usually divide the nasal structure into different anatomical regions for calculation purposes, and these partitions are based on the importance of each part of the nasal cavity (importance is rated based on the tissue type, location, or specific function of each region).[18] Numerous anatomical and pathological studies have shown that the impact of particulate matter on human health depends mainly on the site and amount of deposition in the human respiratory system (namely, the amount of particulate matter deposited in a specific respiratory site over a certain period of time)[19]; therefore, it is crucial to clarify the effect of various factors on the deposition of particulate matter in different nasal compartments for the improvement of nasal drug delivery devices and the prevention of respiratory diseases.

Computational fluid dynamics (CFD), a growing sophisticated engineering technology that investigates the motion of fluids (liquids and gases) by utilizing computers to solve mathematical equations that describe the motion of fluids.[20] The application of CFD techniques in the study of nasal issues is becoming even more popular with the rapid advancement of computer technology, the upgrading of modeling software, and the growing interaction between industry and medicine. Past studies have shown that particle deposition patterns are majorly influenced by (1) particle self-properties such as particle size, shape, density, charge and hygroscopicity, (2) airway geometry in relation to individual gender, age and disease status, and (3) breathing patterns such as respiratory rate and tidal volume and so on.[21] Due to the complexity and risks associated with the implementation of human experiments, CFD technology is becoming a vital tool for researching the deposition of respirable particles in the human nasal cavity, and CFD makes it more convenient to study the effects of the aforementioned variables (particle size, particle density, airflow rate and so forth) on particle deposition.

This paper aims to present the results of recent studies by scholars on the factors influencing nasal particle deposition in humans to guide experiments on nasal respirable particle deposition, as well as to provide certain literature references and guidance values for further systematic and in-depth studies on the application of nasal inhalation drugs in the future.

2 | METHODS

A search was conducted in PubMed and CNKI databases for literature up to and including February 2023, without any restrictions on language. The search was organized around the following terms and their various combinations and variants: "nasal particle deposition influencing factors, nasal computerized fluid dynamics, nasal numerical models, particle size, particle density", and further literature cited in the included articles was searched to screen for literature that fit the theme of this review for inclusion in the reference. Literature that investigated the effects of various variables on nasal particle deposition by applying computerized fluid dynamics to model the nasal cavity was eligible for inclusion. Literature prior to 2000 was excluded to ensure the advanced nature of the study results. Based on the above criteria, 39 literatures were finally screened.

3 | RESULTS

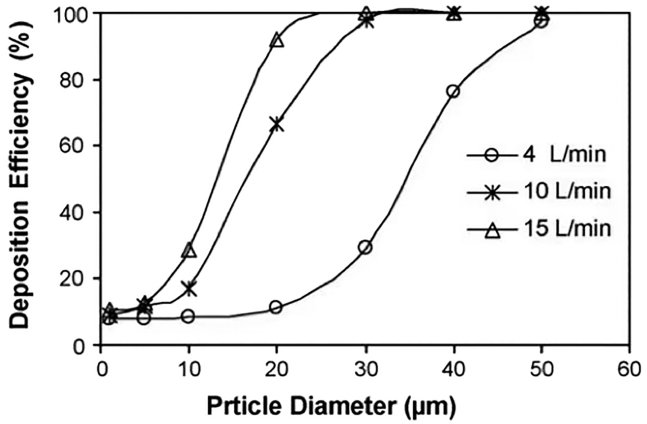
3.1 | Particle self-properties

3.1.1 | Particle size

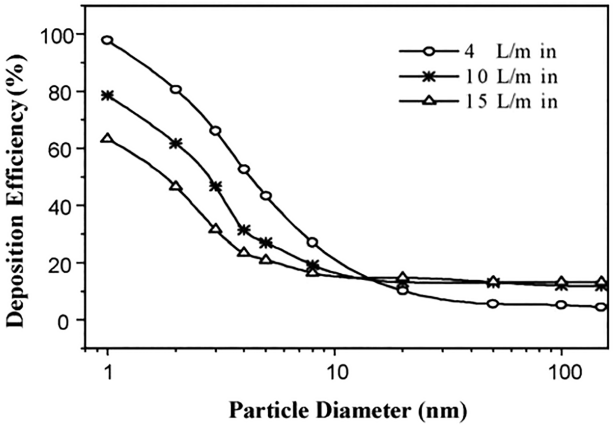
It is widely believed that the deposition of particulate matter in the nasal cavity increases with the increase of respirable particle size, and this idea has been confirmed in numerous experimental and numerical studies by scholars.[22] Cheng et al. studied the deposition pattern of droplets from nasal sprays in the nasal cavity and found that when spray droplets were larger, deposition in the anterior region of the nasal airway increased as a result.[23] By comparing the deposition of particles with particle sizes of 2, 10, and 20 μm in the nasal cavity, Calmet et al. found that due to inertia, 10 μm particles were deposited mainly in the superior turbinate region, whereas 20 μm particles were deposited mainly in the anterior turbinate region, and with increasing particle size, more than 50% of 10 μm particles and more than 90% of 20 μm particles were deposited in the nasal cavity, respectively. In addition, when the airflow velocity is low, particles with larger particle size are deposited more in the anterior part of the nasal cavity.[24] Li et al. found that the deposition efficiency of micron particles is much higher than that of nanoparticles, and the number of micron particles deposited increases rapidly with particle size, while the effect of size on nanoparticle deposition is relatively weak and the pattern is different, namely, the deposition concentration of nanoparticles tends to decrease and then increase with decreasing particle size.[25] Shang respectively chose 2.5, 10 and 20 μm particles to represent low, medium and high inertia particles and showed that the deposition of low inertia particles was more uniformly distributed under different respiration patterns, while the deposition of high inertia particles was more concentrated in specific "hot" areas. The number of deposited low inertia particles was much less than that of medium and high inertia particles and did not appear to be deposited in the region of the nasal vestibule, whereas high inertia particles were deposited on the entire nasal wall except for the inferior nasal tract. In the active breathing condition, only a few high inertia particles were deposited on the nasal vestibule, and deposition of medium inertia particles was extremely pronounced in the nasal vestibule; moreover, medium-inertia particles were deposited in all regions of the nasal cavity. Different inhalation conditions do not lead to much change in the pattern of low and medium inertia particle deposition, but significantly affect high inertia particle deposition.[26] The study by S.M. Wang et al.[11] compared the deposition characteristics of micron particles and nanoparticles. They investigated the deposition patterns of particles with diameters of 0–50 μm and 1–150 nm at a particle density of

1000 kg/m^3 at flow rates of 4, 10, and 15 L/min, respectively (results are shown in Figure 4). It was found that for micron particles in the above ranges, the particle deposition efficiencies at all flow rates were low when the particle size was <10 μm; when the particle size was >20 μm, the particle deposition efficiencies at all flow rates increased significantly with the increase of particle size; and the deposition efficiencies of micron particles of a given size also increased significantly with the increase of flow rate (Figure 4A). While for a given range of nanoparticles, the nanoparticle deposition efficiency decreases at all flow rates when the particle size increases from 1 to 15 nm; the three curves for different flow rates converge when the particle size approaches 15 nm; and for particles of 15–100 nm, the deposition efficiency decreases only slightly as the particle diameter increases (Figure 4B). Based on the above deposition results of nanoparticles, it was predicted that a particle diameter of 15 nm could be the critical value to distinguish the type of deposition involved; as the particle size increases, the effect of diffusion becomes less prominent; as for the flow rate, its increase decreases the deposition efficiency, which is only slightly higher for nanoparticles at high flow rates than at low flow rates, which is quite different from the effect of the air flow rate on micrometer particles. In addition, they found that the dominant effect on the deposition of nanoparticles is particle diffusion, the effect of flow rate on deposition is secondary, and the density-induced changes are negligible, by comparing a large amount of data. Ali Farnoud et al. evaluated the deposition characteristics of particles in the range of 1 nm–30 μm in various parts of the nasal cavity and found that, for nanoscale aerosols, the deposition dose increased with decreasing aerosol size, whereas for microaerosols, the deposition dose increased with increasing aerosol diameter, and furthermore, as the aerosol particle size increased, more aerosols tended to be deposited in the lower part of the nasal airways[27] (Figure 5). J. Dong et al. studied nanoparticles in the range of 3–150 nm under low to moderate breathing conditions (4–20 L/min) and showed that for nanoparticles in this range, the total deposition efficiency was inversely proportional to the size of the particle diameter and the inhalation flow rate, that is., the larger the particles, the larger the inhalation flow rate and the lower the deposition efficiency[28] (Figure 6).

The current literature reports investigating the deposition characteristics of particles of various particle sizes in the nasal cavity model under computerized fluid dynamics simulations show different deposition pattern, as particles increase in size, their deposition in the nasal cavity will also increase. Specifically, the deposition efficiency of micron particles is much higher than that of nanoparticles, and the deposition quantity of micron particles increases rapidly with the increase of particle size, but the effect of particle size on the deposition of nanoparticles is relatively weak, and the deposition concentration decreases and then increases with the decrease of particle size; under different respiration patterns, the deposition distribution of smaller particles is more uniform than that of larger particles, and the deposition distribution of larger particles is more uniform than that of larger particles. Under different respiration modes, the deposition distribution of smaller particles is more uniform than that of larger ones, and the deposition of larger particles is more inclined to be concentrated in specific "hot spots."



(A) micron particles with the density of 1000 kg/m^3



(B) nano particles with the density of 1000kg/m^3

FIGURE 4 (A, B) Simulated deposition efficiency as function of diameter using different inspiratory flow rate.[11]

3.1.2 | Particle density

Particle density is also one of the critical factors affecting particle deposition. Scholars have found that the effect of density and particle size on deposition of respirable particles has a similar pattern, namely, as the density of respirable particles increases, their deposition efficiency also increases.[29] However, for different density ranges, the deposition efficiency of particles exhibits different characteristics with the degree of particle density variation. Liu et al. studied the deposition efficiency of particles with particle sizes of 2.5, 5, and 10 μm in the nasal septum under different density conditions by setting five different density values between 950 and 2150 kg·m^{-3}. The deposition efficiency of particles with a particle size of 2.5 μm increased slowly with increasing particle density; for particles with a particle size of 5 μm, the deposition efficiency increased significantly in the density range of 1250–1850 kg·m^{-3}.[30]

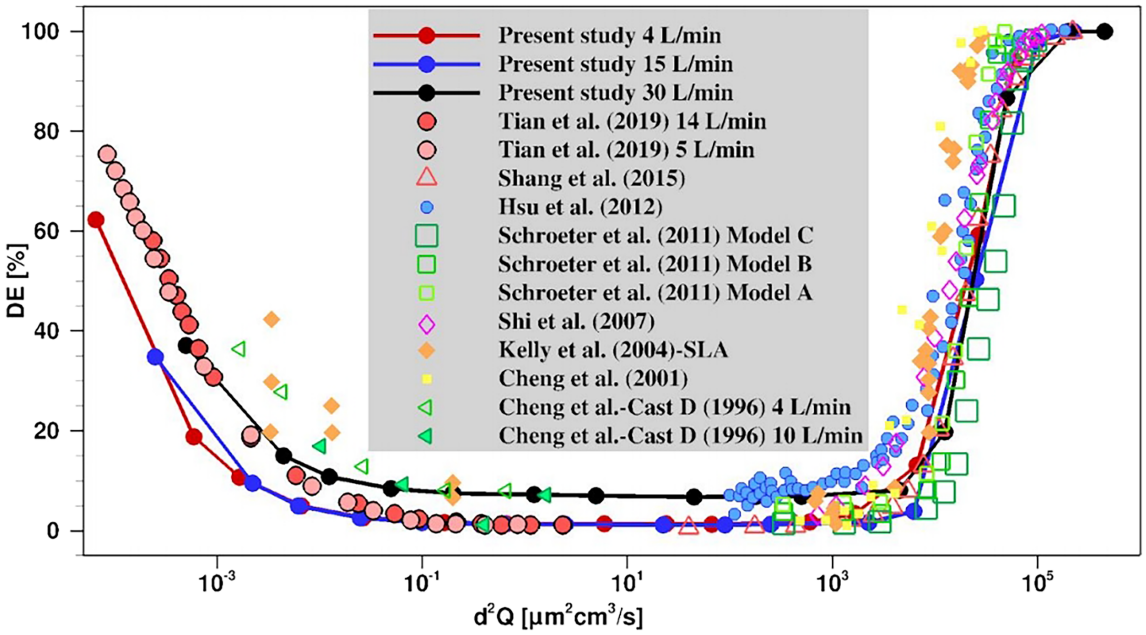


FIGURE 5 Comparison of the aerosol deposition efficiency (DE) inside the present nasal cavity and the other realistic nasal cavities reported in the literature scaled by Stokes number for unity density aerosol (d^2Q).[27]

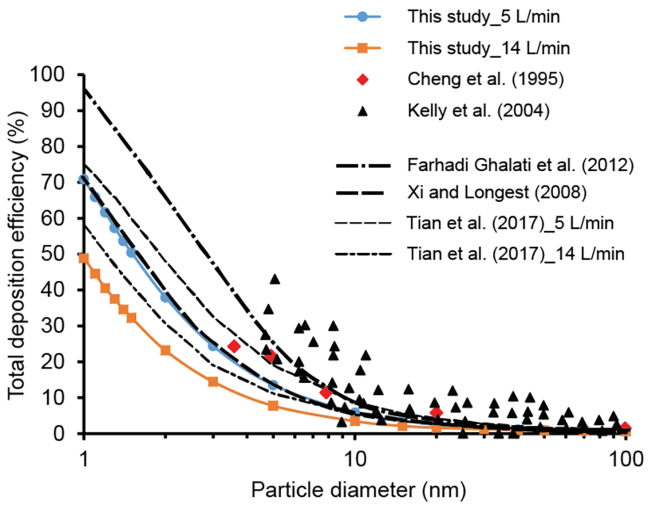


FIGURE 6 Overall deposition efficiency profiles of the present model and their comparison with data in the literature.[28]

3.2 | External factors of particle

3.2.1 | Airflow rate

According to a number of studies, intranasal deposition rises as flow rate increases.[23] At airflow rates of 10, 20, 30, and 40 L/min, G. J. Zwartz et al. used modeling to examine the patterns of deposition of particles with a particle size of 5.5 μm. They found that at a flow rate of 10 L/min, most of the particles were deposited in the main airway portion. Besides, relative to the rest of the airway, the deposition was also evident in the nasopharynx. At flow rates higher than 10 L/min, hardly any particles were deposited in the nasopharynx. The deposition pattern was different between flow rates of 20 and 40 L/min—most of the particles were deposited in the front of the nasal cavity, and as the flow rate increased from 20 to 40 L/min, the deposition site advanced toward the olfactory region. In the condition (30 L/min), particle deposition was evenly distributed between the front portion of the nasal cavity and the main airway, with essentially little deposition in the nasopharynx.[31] According to Li's research, the deposition concentration for micron particles increased exponentially with airflow velocity, and the effect of airflow velocity on deposition was more significant than that of particle diameter. This probably because the motion of micron particles was mainly influenced by inertial impact and gravity, while Brownian forces, Saffman's lift edge effect were neglected. For nanoparticles, the deposition concentration also increases with increasing airflow velocity, but its concentration is substantially lower than that of micron-sized particles.[25]

As can be observed, there is a certain regularity in how airflow velocity affects particle deposition. First off, increasing airflow velocity causes an increase in nasal deposition. Second, at different flow rates, micro particles and nanoparticles exhibit different deposition characteristics, with nanoparticles consistently depositing at much lower concentrations than micro particles. Specifically, it seems that particle deposition has corresponding characteristics with any particular flow rate. At the rate of 10 L/min, particles are deposited not only in the main airway but also significantly in the nasopharynx. However, when the flow rate is greater than 10 L/min, particles are hardly deposited in the nasopharynx. At the flow rates of 20 L/min and 40 L/min, particles are mainly deposited in the anterior part of the nasal cavity, and as the flow rate increases from 20 to 40 L/min, the deposition site gradually shifts to the olfactory region. When the

rate is 30 L/min, particle deposition is almost uniformly distributed between the anterior part of the nasal cavity and the main airway.

3.2.2 | Airflow temperature and humidity

Longest et al. anticipated, based on CFD modeling, that total nasal-mouth-throat (NMT) particle deposition would subsequently decrease as the inhaled air temperature rose from 21°C to 35.8°C under enhanced coalescent growth (ECG) conditions.[32] Ishmatov et al. found that breathing cold air led to supersaturation of the upper airway and the effect of condensation growth, which resulted in an increase in particle deposition rates.[33] Xu et al. investigated the deposition characteristics of 100 nm and 1 μm NaCl particles under three simulated conditions, A, B, and C, based on CT image modeling of a 26-year-old adult, where A represents inhalation of warm-mild air (T = 26°C, RH = 60%), B represents inhalation of warm-humid air (T = 26°C, RH = 90%), and C represents inhalation of cold-dry air (T = 11°C, RH = 30%). It was discovered that supersaturation formed in the nasal airway under inhalation conditions of C, effectively enhancing total deposition in the airway model. The authors speculated that when the ambient temperature was lower, it would result in stronger supersaturation, which would enhance total deposition.[34] According to the studies mentioned above, inhaling low-temperature airflow can lead to supersaturation of airways and condensation growth of particles, which then enhances particle deposition. In contrast, other scholarly studies have come to substantially different results from the ones stated above.

By modeling from MRI scans of a 53-year-old adult, Xi et al. investigated the deposition features of monodisperse aerosols in the 0.2–2.5 m range under four distinct inhalation conditions defined according to the initial temperature (T) and relative humidity (RH) of the nasal intake. These four conditions included inhalation of cold dry air (Case 1: T = 23°C, RH = 30%), cold mild air (Case 2: T = 27°C, RH = 60%), warm humid air (Case 3: T = 40°C, RH = 100%), and hot humid (Case 4: T = 47°C, RH = 100%), which resulted in the following ranking of nasal deposition fraction size: Case 4 > Case 3 > Case 2 > Case 1, concluding that the likelihood of respiratory injury in humans in hot and humid environments may be much higher than previously assumed.[35] Kim et al. modeled the deposition characteristics of 200 nm particles in four different inhalation conditions based on MRI images of a 5-year-old child, which were consistent with those set by Xi et al. that is, inhalation air of cold-dry (Case 1: T = 23°C, RH = 30%), cold-mild (Case 2: T = 27°C, RH = 60%), warm humid (Case 3: T = 40°C, RH = 100%) and hot humid (Case 4: T = 47°C, RH = 100%), the results and conclusions were the same as those of Xi et al. in that The overall nasal deposition fraction was evaluated in order of magnitude: Case 4 > Case 3 > Case 2 > Case 1, suggesting that high temperatures and humidity may lead to a higher potential for human respiratory damage than previously assumed.[36] In summary, the study's findings imply that inhaling hot and humid air currents may lead to higher deposition fractions.

Scholars have reached different conclusions regarding the effect of inspiratory airflow temperature and humidity on particle deposition. On the one hand, some scholars have found that airway supersaturation and particle condensation growth will occur under low-temperature airflow conditions, thus increasing particle deposition; on the other hand, some scholars have found that inhalation of high-temperature and humid airflow may lead to higher deposition fractions. In my humble opinion, high temperatures may cause particles to expand and thus increasing particle size, while under humid condition, hygroscopic particles increase their mass by absorbing liquid in the air, and the density will increase with the increase of mass according to the density equation. Considering the effects of particle size and density on particle deposition discussed above, both of these environmental conditions will lead to the increase of particle deposition. More experiments will be required in the future to further the effect of airflow temperature and humidity on particle deposition.

3.2.3 | Subjects' ages

Significant differences in nasal anatomy and physiological function exist between children and adults, which can likewise lead to different particle deposition. Hosseini et al. established nasal models of subjects aged 2, 5, and 50 years for their study and found significant differences in deposition between the child (2 and 5 years) and adult models, while no statistical differences were found between the two child models. Moreover, the proportion of deposition in the upper turbinate region decreased with age.[37] Zhou et al. established 10-day-old neonates, 7-month-old infants and 3-year-old children to study micron particle deposition in the three models, and compared the three with previous studies performed by the authors in adult models and 5-year-old children's models, and found that micron aerosol intranasal deposition was higher in toddlers and infants than in adults under equivalent breathing conditions (for instance awake sitting)[38] Golshahi et al. further confirmed higher deposition in pediatric subjects, particularly infants, in their study by plotting particle deposition fractions versus impact parameters.[39] Golshahi and Hosseini reviewed experimental nasal deposition in three age groups including five adults (three males and two females), 13 children aged 4–14 years, and 11 infants aged 3 to 18 months, which found higher deposition fractions for a given particle size and inhalation flow rate (namely impact parameter d2aQ) in infants and children compared with adults.[22] Under the same respiratory conditions, the age of the subjects may also cause differences in deposition, with young children especially infants having higher deposition of micron particles than adults.

4 | DISCUSSION

With the rapid development of science and technology, clinicians' expectation for nasal drug delivery is also increasing day by day. Therefore, the research on the development mechanism of respiratory diseases and the mechanism of nasal drug absorption needs to be

further improved, and the deposition of nasal particles is inextricably linked to the development of respiratory diseases and nasal drug delivery. The deposition of nasal particles is inextricably linked to respiratory diseases and nasal drug delivery.

With the popularization of computerized fluid dynamics (CFD), more and more scholars are using CFD techniques to study the effects of different parameters on particle deposition, and the current findings indicate that the factors affecting particle deposition are not only reflected in the properties of the particles themselves, but also exist in conditions external to the particles. The results of the research on the factors influencing nasal deposition provide a theoretical basis for the prevention of respiratory-related diseases and the development and application of transnasal drug delivery devices in the future, making a significant contribution to the optimization of the prevention and treatment of clinical diseases.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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