SIIRI MURTOLAHTI

This study assessed upper airway function during growth and with aging. During growth, nasal resistance decreased and nasal passage and airflow rate increased but not consistently, showing gender differences. For diagnostics, age- and gender-specific guideline values are needed. Aging seems to weaken the sense of smell and the sensitivity to recognize added nasal resistance. The physiologic responses to added load were similar in adolescents and in older adults.
Age-related changes in upper airway function
SIIRI MURTOLAHTI

Age-related changes in upper airway function

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ABSTRACT:

In the upper airways, obstruction of the nasal passage often results in partial oral breathing when unheated and unfiltered air gets straight into the lower airways. Nasal obstruction may be part of the aetiology of asthma, sleep apnoea and malocclusions, and it complicates rehabilitation of cleft palate patients. Earlier studies using varying methods in different patient and age groups do not provide enough knowledge of the upper airway growth and function in healthy population. In adults, there is a lack of studies on the effects of aging on respiratory function.

To test the hypothesis that the nasal passage increases and respiratory function changes steadily during growth, and that there are gender differences, all school children in a rural municipality with 3,800 inhabitants were examined to compare consecutive age cohorts. The two youngest age groups were followed for nine years, from 8 to 17 years of age. Pressure-flow technique was used to determine nasal-oral pressures, airflow volume and rate, minimum nasal cross-sectional area and nasal resistance. To study possible changes in nasal function with aging, in a clinical experimental study the perception and respiratory responses to added nasal resistance and olfactory stimuli were compared between 40 adolescents and 40 older adults.

The results showed that nasal resistance decreased, and airflow rate and minimum nasal cross-sectional area increased with age in children and adolescents. Annual changes showed not only increase but also decrease. Changes in nasal resistance were statistically significant between several age cohorts in females, but only from 8 to 9 years of age in males. Values of nasal cross-sectional area were statistically significantly higher in boys only at the age of 16. There were clear gender differences in airflow rate at most ages. When comparing adolescents to older adults, the older group needed a clearly higher respiratory load to detect the change. Airflow rate was systematically lower in adolescents but both groups compensated the added respiratory load by decreasing airflow rate to 300 mL/s even before they detected the change. Olfactory function was significantly weaker in older adults compared to adolescents.

In conclusion, the size of the nasal passage does not increase steadily during growth, and several variables used to measure respiratory function show gender differences, indicating a need for age- and gender-specific guideline values. An adult level of nasal airway size seems to be reached by the age of 17 in females but possibly not in males. The response of adolescents and older adults to mechanically added respiratory loads was the same but the sensitivity of older adults was clearly weaker, indicating weakened ability to detect added nasal resistance. Detection of olfactory stimuli decreased with aging, which could affect appetite and nutrition.
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TIIVISTELMÄ:

Ylähengysteissä nenäkäytävän ahtautuminen laukaisee osittaisen suuhengityksen, jolloin lämmittämätön ja puhdistamaton hengitysilma pääsee suoraan suu- ja nenäkäytäviksi. Aiemmat, vaihtelevilla menetelmissä ja eri ikäryhmissä tehdyt tutkimukset eivät anna riittävästi tietoa hengitysteiden kasvusta ja hengitystoimintojen kehittymisestä terveessä väestössä. Ikääntymisen vaikutuksista hengitystoimintoihin on niukasti tutkimuksia.


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VIII
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This study was started in 1991 at the Institute of Dentistry, University of Kuopio and continued in Vimpeli until 2003. The study was on hold for many years until it was finally reopened and continued at the Institute of Dentistry, University of Eastern Finland, Kuopio, in 2015-2017.

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Kuopio, November 2017

Siiri Murtolahti
List of the original publications:

This dissertation is based on the following original publications:


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Abbreviations

AHI  Apnoea-Hypopnea Index
BMI  Body Mass Index
CBCT  Cone Bean Computed Tomography
cm²  Square Centimetre
cmH₂O  Centimetre of Water
cmH₂O/l/s  Centimetre of Water per Litre per Second
CPAP  Continuous Positive Airway Pressure
DOB  Date of Birth
g/cm³  Gram per Cubic Centimetre
ICC  Intraclass Correlation
kg/cm²  Kilogram per Square Centimetre
ml/s  Millilitre per Second
OSA  Obstructive Sleep Apnoea
RME  Rapid Maxillary Expansion
SARME  Surgically Assisted Rapid Maxillary Expansion
SD  Standard Deviation
SDB  Sleep Disordered Breathing
SME  Slow Maxillary Expansion

Equations used:

Body Mass Index (s. 14)  \[ BMI = \frac{\text{Weight}}{(\text{Height}/100)^2} \]

The Hydrokinetic Equation (p. 15)  \[ R = \frac{\Delta P}{V} \]

Minimum Nasal Cross-Sectional Area (p. 15)  \[ A = \frac{V}{k(2 \Delta P/d)^{1/2}} \]

Weber fraction (p. 16)  \[ WF = \frac{(R_i - R_o)}{R_o} \]
1 Introduction

People usually breathe through the nose, but there are individuals who are partly or mainly oral breathers. Nasal resistance determines the mode of upper airway breathing (Watson et al. 1968, Laine and Warren 1995). Upper airway obstruction resulting in mouth breathing has proved to have several harmful effects. Mouth breathing seems to be an important factor in the aetiology and management of asthma (Hallani 2008). It is also a contributor to sleep apnoea, with increasing awareness of its harmful effects on health and quality of life (Bjornsdottir et al. 2015), reported also in children (Ikävalko et al. 2012). In cleft palate patients, management of lack of tissues and, on the other hand, oral versus nasal port constriction is critically important in estimating the need and outcome for primary and secondary surgery and in speech rehabilitation (Rautio et al. 2010).

From an orthodontic point of view, there are contradictory findings and opinions on how respiratory function influences craniofacial growth and development of occlusion. Nasal obstruction has been reported to result in mouth breathing (Linder-Aronson and Bäckström 1960), which is possibly associated with malocclusions such as anterior open bite, lateral cross bite and increased overjet (Bresolin et al. 1983, Souki et al. 2009, Harari et al. 2010). Regarding craniofacial morphology, obstruction of nasal airways has been reported to be connected with craniocervical angulation, increased anterior face height and retrognathic mandible (Solow et al. 1984, Vargervik et al. 1984).
2 Review of literature

2.1 NASAL ANATOMY AND DEVELOPMENT

The nose is part of the upper airways. Its main functions are breathing, moistening, warming, and filtering inhaled air. Two nostrils lead to the nasal cavity, which is separated into two chambers, the nasal septum being between them. The nasal cavity leads to paranasal sinuses and nasopharynx. The nose also plays a role in olfaction. In the nasal cavity there are smell-sensing cells which have hair-like cilia. The olfactory cells lead the smell perception to the olfactory plexus and the brain, particularly via the limbic system (Tucker et al. 2015).

The development of the nasal cavity begins during the 8th week of foetal life. At that time, the nasal septum is differentiated into cartilage and several ridges begin to develop into nasal turbinates. Also, several ridges develop along the lateral nasal wall; these are the earliest signs of developing nasal turbinates. Between the 9th and 10th week of gestation, cartilaginous capsule shows finger-like projections into the developing turbinates. At the 15th and 16th week, nasal turbinates are fully developed. The respiratory epithelium of the lateral nasal wall and ethmoid sinus mucosa are developed by the 17th and 18th week. During weeks 20 to 24, vascular systems are developed in the lamina propria (Kennedy et al. 2012).

2.2 RESPIRATION AND CRANIOFACIAL GROWTH

The occlusal effect of mouth breathing varies between individuals because of the different ways of adapting to nasal obstruction, and developing malocclusion depends on the individual’s craniofacial morphology and growth (NcNamara 1981). The main challenges in studying the effects of upper airway obstruction are characteristics of the study sample, including age range, and methodological problems to define nasal patency. However, mouth breathing does not seem to be limited to any specific type of malocclusions (Huber and Reynolds 1946). Higher nasal resistance has been noticed in children with long narrow face and also in children with high narrow palate (Linder-Aronson and Bäckström 1960). Mouth breathing also seems to be associated with asthma when the filtering effect of nose is lacking (Hallani 2008), as well as with sleep-disordered breathing (SDB) and obstructive sleep apnoea (OSA) (Young et al. 2001, Georgalas 2011, Ikävalko et al. 2012). Oral breathing may also complicate treatment of sleep apnoea due to difficulties of using continuous positive airway pressure (CPAP) therapy (Nakazaki et al. 2012).

2.3 CHANGES IN NASAL PATENCY DURING GROWTH

Nasal patency can be measured with different methods, such as rhinomanometry, acoustic rhinometry or plethysmograph. The techniques are described more precisely in Chapter 2.11.

In infancy, growth of the nasal airway is significant during the first year of life, especially during the first months of life. This has been explained by the rapid increase of head circumference right after birth (Djupesland and Lyholm 1998). The breathing mode of infants is entirely through the nose, and they are also able to breathe while swallowing (Paul et al. 1996, Kelly et al. 2007). The respiratory tract is closed during swallowing by the age of 6 months (Kelly et al. 2007), and rest breathing passes through the nose. The sagittal nasopharyngeal airway seems to be narrowest in childhood at the age of five. The pharyngeal airway size seems to increase in childhood and the beginning of puberty, the changes being most significant between the ages of 5 and 10 and after the age of 11 (Linder-Aronson and Leighton 1983). In children, the nasal cross-sectional area seems to increase during growth when measured in different age groups (Warren et al. 1990, Laine and Warren 1991, Vig and Zajac 1993, Laine-Alava and Minkkinen 1997, Ho et al. 1999, Straszek et al. 2007). There are varying results on at what age upper airways reach their adult size as well as on changes with age and differences between genders (Laine and Warren 1991, Crouse et al. 1999, Kim et al. 2007, Abramson et al. 2009). Laine-Alava and Minkkinen (1997) concluded in their cross-sectional study that an adult airway size and stability of naso-respiratory function may be reached by the age of 16, but Crouse et al. (1999) speculated that the adult size of nasal airways may already be reached by the age of 13 in both girls and boys. In children, gender does not seem to correlate with nasal airway size (Laine and Warren 1991). Also, Abramson et al. (2009) found that there were no differences between boys and girls in nasal and pharyngeal airway sizes when measuring airway parameters in computed tomography images. Ronen et al. (2007) reported that upper airway length in the midsagittal plane, defined as the length between the lower part of the posterior hard palate and the upper edge of the hyoid bone, was significantly lower in prepubertal boys than girls. Instead, in postpubertal children, boys seemed to have longer airway length in proportion to body height compared to girls at the same age. At puberty, the changes in upper airway growth seem to differ from each other in girls and boys.

2.4 PHYSIOLOGIC CHANGES IN NASAL PATENCY

Body position has been reported to affect nasal airway morphology and resistance. The perception of nasal obstruction and breathing difficulty occurs more readily in the supine position and is associated with oral and sleep-disordered breathing (Battagel et al. 2002). Nasal airway size has been shown to be smaller and nasal resistance higher in supine position compared to standing or sitting position (Cole and Height 1986, Roithmann et al. 2005, Van Holsbeke et al. 2014). This may be explained by a greater effect of gravity on airway muscles in supine position (Van Holsbeke et al. 2014). In subjects with unilateral nasal obstruction, resistance seems to be higher in the obstructed side of the nasal cavity (Cole and Height 1986). Hasegawa (1994) noticed that changes in body position did not affect nasal resistance in healthy subjects, but in subjects with allergic rhinitis there was a significant increase in nasal resistance in dorsal and lateral supine position when compared to sitting position. Huggare and Laine-Alava (1997) studied head posture and respiratory function and noted an association between extended head posture and increased nasal cross-sectional area.

In addition to temporary nasal airway impairment, under some physiological conditions, such as breathing in cold air (Fontanari et al. 1996), breathing mode changes to an oral-nasal pattern in individuals who are normally nasal breathers. Fontanari et al. (1996) studied the effects of breathing cold dry air on airway resistance, measuring values in the lower airways. They found out that when breathing cold air, resistance values increase more during nasal breathing.
compared to mouth breathing. Resistance returned to normal values in five minutes after ceasing the cold air inhalation. Laine et al. (1994) found that during inspiration of cooled air, the nasal cross-sectional area decreased significantly, evidently due to mucosal swelling and increased blood circulation. The correlation between environmental temperature and nasal patency has been investigated in the past ten years. Nasal mucosal temperature seems to be influenced by nasal patency. It has been suggested that nasal thermoreceptors might be the key in perception of nasal patency (Lindemann et al. 2007), but Dipak et al. (2011) showed that tactile sensation of nasal mucosa is not involved in the sensation of nasal patency. During exercise nasal patency has been shown to increase (Cole et al. 1983).

2.5 NASAL PATENCY AND AGING

Results by Edelstein (1993) and Abramson et al. (2009) indicated that age was not associated with nasal airway parameters in adult population. Instead, Kim et al. (2007) found that the nasal cross-sectional area increased with age both with and without decongestion in adults. They reported also that nasal resistance decreased, and airflow increased with age.

2.6 OLFACTORY FUNCTION AND AGING

Olfactory function has been observed to decrease with age in adults (Doty 1989, Murphy et al. 2002, Guthoff et al. 2009, Doty et al. 2011, da Silva et al. 2014, Hori et al. 2015, Guido et al. 2016). During aging, there appear some changes in olfactory and brain structures such as olfactory receptor cells, bulb, and tract, and moderate loss of neurons and nerve fibres (Liss and Gomez 1958). Smell loss associated with aging may be also due to neurological diseases such as Alzheimer’s disease, in which the olfactory structures are affected by disease and the smell loss seems to be associated with apolipoprotein E ε4 allele (Murphy et al. 2009, Hori et al. 2015), or Parkinson’s disease, in which Lewy bodies are seen in the olfactory bulb and anterior olfactory nucleus before nigral involvement (Wilson et al. 2008). Olfactory impairment has also been related to Down’s syndrome where the changes in the brain seem to be similar to those seen in Alzheimer disease (Nijjar and Murphy 2002), schizophrenia, which may be explained by changes in the orbital frontal cortex (Moberg et al. 1997, Brewer et al. 2003), and diabetes mellitus (Guthoff et al. 2009). Regarding genetic influence, in diabetes, the Kv1.3 gene seems to regulate both insulin sensitivity and olfactory bulb neurons (Guthoff et al. 2009).

2.7 FACTORS AFFECTING UPPER AIRWAYS

2.7.1 Structural factors
The individuals with airway obstruction associated with atypical craniofacial growth often have open-mouth posture, extended head posture, increased anterior facial height, small nostrils and prominent maxillary incisors (Quick and Gundlach 1978, McNamara 1981). Septal deviations (Subtelny 1980, Garcia et al. 2010, Gogniashvilli et al. 2011) and deviated external nose (Zhu et al. 2013) may increase nasal resistance. Septal perforations have been found to affect nasal resistance only minimally (Cannon et al. 2013).

2.7.2 Concha bullosa
Concha bullosa is a pneumatisation of the middle turbinate. It can cause nasal obstruction and other nasal symptoms (Badran 2009). Operative treatment of isolated concha bullosa can relieve the sinonasal symptoms of patients (Badran 2009).
2.7.3 Smoking habit and respiratory function

Virkkula et al. (2007) reported that smokers with nasal symptoms are troubled by snoring at younger age than non-smokers. They reported also that smoking increases nasal obstruction and nasal resistance. In children, parental smoking was found to be associated with increased nasal resistance (Montaño-Velázquez et al. 2011) and with symptoms of perennial rhinitis (Virkkula et al. 2011). Schick et al. (2013) investigated the effects of short exposure to cigarette smoke. They noticed that second-hand smoke increased nasal resistance. Smoking and impaired nasal breathing may also have a negative impact on weight reduction when treating obstructive sleep apnoea (Blomster et al. 2011).

2.8 SLEEP APNOEA

Obstructive sleep apnoea syndrome (OSAS) is usually related to overweight, structural factors, or obstruction of upper airways due to enlarged tonsils or adenoid (Saaresranta et al. 2010). Nasal resistance in patients with OSAS is reported to be higher than that of normal controls (Lu et al. 2014). Earlier studies tend to report that sleep apnoea is not necessarily influenced by nasal anatomic obstruction but rather by the narrowed pharyngeal area (Lu et al. 2014). Nasal obstruction is common among OSAS patients with difficulties of using CPAP (Nakazaki et al. 2012). In obese people (BMI ≥ 30) (WHO 2000), higher nasal resistance has been shown to be in relation with apnoea-hypopnea index (Tagaya et al. 2010). High nasal resistance may also contribute to snoring, which is one of the symptoms of OSAS (Georgalas 2011).

2.9 TREATMENT METHODS THAT AFFECT NASAL BREATHING FUNCTION

In animal experiments, primates have shown to adapt to nasal obstruction in different ways and show different facial appearance from controls (Harvold et al. 1973 and 1981). Mouth breathing seems to be related to malocclusions such as anterior open bite, lateral cross bite and increased overjet (Bresolin et al. 1983, Fields et al. 1991, de Freitas et al. 2006, Souki et al. 2009, Harari et al. 2010). Obstruction of nasal airways has also been reported to be associated with increased anterior face height and retrognathic mandible (Solow et al. 1984, Vargervik et al. 1984).

2.9.1 Adenoidectomy and tonsillectomy

Adenoidectomy is a relevant treatment of enlarged adenoids. Adenoidectomy usually changes children’s breathing mode from oral to nasal breathing (Mattila 2010). Combining adenoidectomy with tympanostomy tube insertion does not differ from adenoidectomy alone in post-operative nasal cross-sectional area or nasal airway resistance (Niemi et al. 2015).

Tonsillectomy is used as treatment when sleep apnoea and snoring result from enlarged tonsils. After tonsillectomy, patients’ apnoea-hypopnea index (AHI) and nasal resistance values have been reported to decrease (Nakata et al. 2007).

2.9.2 Nasal turbinectomy and septal surgery

Nasal turbinectomy surgery does not always decrease nasal resistance but it also weakens olfactory function, altering the main airflow direction (Na et al. 2012). Septal surgery is used as treatment for deviated septum, but the long-term effectiveness of septal surgery has not been established (Haavisto and Sipilä 2013). Gulati et al. (2008) found that nasal airflow rate improves, and nasal resistance decreases after septoplasty. Also, Haavisto and Sipilä (2013) found that nasal resistance decreased during the first 6 post-operative months, but they also noticed it rising after
10 years. There is a surgical procedure to expand the nasal cavity. The surgery includes a series of procedures to decrease nasal resistance and relieve nasal obstruction. The target in nasal expansion surgery is to remove the obstructive structure in the airway and relieve symptoms of both nasal obstruction and obstructive sleep apnoea (Han and Zhang 2011).

2.9.3 Maxillary expansion with orthodontic appliances

In children and growing adolescents, maxillary expansion is usually performed with orthodontic appliances which are tooth-borne fixed or removable appliances. The appliances expand the maxilla from the mid-palatal suture. Nonsurgical orthodontic procedures alone can be used when the mid-palatal suture of the maxilla is still open (Haas 1970).

In young children, the most common appliances to expand the maxilla are quad-helix, hyrax appliance and fan-type appliances (Christie et al. 2010, Sökücü et al. 2010, Trindade et al. 2010, Corbridge et al. 2011, Shundo et al. 2012). The quad-helix is mainly used in expanding the maxilla in young children. The technique expands the maxilla slowly, opening the mid-palatal suture, and is known as slow maxillary expansion (SME). The quad-helix treatment increases intermolar and palatal width (Corbridge et al. 2011, Shundo et al. 2012). Also, the hyrax appliance is used for SME in growing children.

The most common non-surgical treatment to expand the maxilla is rapid maxillary expansion (RME). Because the maxillary bone is the base of the nasal cavity and also the roof of the palate, the expansion affects the nasal dimension, airflow (Babacan et al. 2006) and resistance (Enoki et al. 2006, Iwasaki et al. 2014). The hyrax appliance is usually used in RME (De Felippe et al. 2009, Christie et al. 2010, Sökücü et al. 2010, Trindade et al. 2010, Görgülü et al. 2011, Smith et al. 2012, Bouserhal et al. 2014, Figueiredo et al. 2014, Yilmaz and Kucukkeles 2015). Hyrax seems to expand the maxilla effectively, widening also the nasal floor and increasing the minimum nasal cross-sectional area (De Felippe et al. 2009, Christie et al. 2010, Sökücü et al. 2010, Trindade et al. 2010, Görgülü et al. 2011, Smith et al. 2012, Bouserhal et al. 2014, Yilmaz and Kucukkeles 2015). The same effect is seen when using the fan-type appliance (Sökücü et al. 2010). Çörekçi and Goyenç (2013) noticed that the hyrax-type appliance had a greater effect on intermolar width than the fan-type appliance.

When comparing hyrax, quad-helix, and fan-type appliances, they all seem to have similar short and long-term effects on the maxillary arch (Huynh et al. 2009, Wong et al. 2011). Godoy et al. (2011) showed that the treatment time was significantly longer when using a removable expanding plate compared to quad-helix. If needed, maxillary expansion can be performed asymmetrically, resulting in asymmetrical changes in the transversal dimensions (İleri and Başciçtcı 2014).

The long-term effects of expanding the maxilla are still under investigation. Matsumoto et al. (2010) investigated the longitudinal effects of RME with hyrax-type appliance on the nasal cavity in children aged 7–10 years. The study showed that the widening of the nasal cavity and decrease in nasal resistance were not stable, but more research is still needed to understand the long-term effects of the treatment. More studies on how the orthodontic palate widening appliances affect the nasal dimensions and respiratory function are needed, especially concerning the effects of slow maxillary expansion. The long-term effects on nasal patency are also still unknown.

2.9.4 Surgically assisted rapid maxillary expansion

Surgically assisted rapid maxillary expansion (SARME) is used in patients whose mid-palatal suture is closed to correct crossbites and to expand the maxilla. In adults, the suture of the maxilla needs to be performed with the help of surgery and then expanded by appliances (Seeberger et al. 2011). SARME seems to have an impact on nasal dimensions. The procedure results in a v-shaped widening in the lower nasal passage and seems to improve nasal airflow (Seeberger et al. 2010 and 2011). Also, an increase in the minimum cross-sectional area of the nasal cavity has been shown (Pereira-Filho et al. 2014). SARME seems to have a favourable effect on nasal function but the effect has shown to be short-term. The nasal effect seems to last longer only in patients who
have had nasal obstruction before treatment (Magnusson et al. 2011, Magnusson 2013). Magnusson et al. (2011) found that the increase in anterior minimum cross-sectional area and improvement in nasal obstruction disappeared between 3 and 18 months postoperatively. Instead, the change in posterior minimum cross-sectional area persisted 18 months postoperatively. Altug-Atac et al. (2010) compared RME and SARME but did not find any differences on nasal effects between these procedures. Bach et al. (2013) published a study about the effects of SARME on sleep pattern. They found that SARME did not have any negative effects on sleep in healthy individuals. In patients with mild sleep apnoea it normalized their breathing index during sleep when obstruction was located in the nasal area.

2.9.5 Orthognathic surgery

Maxillary surgery seems to have different effects on nasal respiratory function depending on the direction of movement. Ghoreishian and Gheisari (2009) reported that surgical advancement of the maxilla may improve nasal airflow rate and reduce nasal resistance, but setback surgery of the maxilla may have an opposite effect. In orthognathic surgery, advancement of the maxilla is a more common treatment modality while maxillary setback surgery is rarely used (Ghoreishian and Gheisari 2009). Bimaxillary surgery is a commonly used method in treatment of sleep apnoea. The surgery has been shown to decrease airway resistance and improve airflow (Gokce et al. 2012). Instead, correction of Class III occlusion may increase nasal resistance and contribute to iatrogenic obstructive sleep apnoea when Class III occlusion is corrected by mandibular setback osteotomy (Foltán et al. 2011).

2.10 SPECIAL FEATURES OF CLEFT PALATE FOR UPPER AIRWAY FUNCTION

Physiologic variables of the normal nasal airway have clinical significance because the nasal airway of patients with clefts is usually impaired (Kunkel et al. 1999, Reiser et al. 2011). In children with cleft palate, an obstructed nasal airway may be of some help in producing plosive consonants during speech (Warren et al. 1992) but nasal obstruction due to allergy has been reported to increase the risk for upper airway and ear infections (Fireman 1997). In the cleft palate patients, the tension-free cleft repair decreases the nasal cross-sectional area and increases nasal resistance (Kunkel et al. 1997, Rezende et al. 2015). Kilpeläinen (1997) reported that differential pressure and nasal resistance were higher and nasal airflow and cross-sectional area smaller in cleft patients compared with normal subjects. Nasal airflow rate and cross-sectional area were affected by the type of clefting. Scott et al. (2011) modelled geometrically the consequences of cleft repair in cleft palate patients and demonstrated that the wider the repaired cleft, the higher the postoperative nasal resistance. In adults, mean of acoustic minimum nasal cross-sectional area has been shown to be smaller in the cleft side (0.32 ± 0.2 cm²) in patients with unilateral cleft lip and palate compared to non-cleft side (0.56 ± 0.1 cm²) or controls, but total nasal volume did not seem to differ significantly from controls (Kunkel et al. 1999). Fukushiro and Trindade (2005) compared minimum cross-sectional areas of different cleft types in adults. Minimum cross-sectional area was significantly smaller in patients with bilateral cleft lip and palate, 0.47 ± 0.2 cm², while it was 0.57 ± 0.2 cm² in patients with unilateral cleft lip and palate, 0.61 ± 0.1 cm² in cleft palate patients, and 0.60 ± 0.1 cm² in controls.
2.11 MEASURING AIRWAY PATENCY

2.11.1 Airway size

Lateral cephalogram is one of the routine examination modalities for orthodontic treatment. Formerly, cephalograms were also used in measuring airway size and the size of adenoid (Holmberg and Linder-Aronson 1979, Sørensen et al. 1980). The validity of cephalograms in diagnosing nasopharyngeal airways has been questioned. The cephalogram is a 2-dimensional image of 3-dimensional structures. Pirilä-Parkkinen et al. (2011) compared the capability of 2-dimensional cephalogram to the golden standard, 3-dimensional magnetic resonance imaging (MRI), and clinical observation. They found that cephalogram is a valid method in measuring dimensions in the nasopharyngeal and retropalatal region but not in the oropharyngeal area. Clinical assessment of tonsillar size seems to be a relatively reliable method when evaluating the size of the oropharyngeal area (Pirilä-Parkkinen et al. 2011).

A 3-dimensional cone-beam computed tomography (CBCT) scan shows a 3-dimensional image of the nasal airway morphology, valuable in assessing the size and function of the nasopharyngeal airways (Aboudara et al. 2009). Also, three-dimensional computed tomography (CT) has been used in assessing upper airways (Abramson et al. 2009, Stratemann et al. 2011). In using CBCT or CT, radiation hygiene needs to be considered. The radiation dose is high, therefore using those examination methods needs to be justified. CBCT has been used for measuring the pharyngeal airway in patients with clefts (Celikoglu et al. 2014), before and after maxillary surgery (Hatab et al. 2015), and also retropalatal and retroglossal airway changes, volume, and sagittal and cross-sectional areas in orthodontic patients treated with rapid maxillary expansion (Chang et al. 2013).

The most common method to monitor airflow in the nasal cavity is rhinomanometry. Both methods are standardized and validated for clinical and scientific use (Cheung et al. 2010). Although rhinometric methods are rarely used in orthodontic patients, they are utilized in diagnosing sleep apnoea (Thurnheer et al. 2001) and in orthognathic surgery of clefts (Kunkel et al. 1997 and 1999, Trindade et al. 2009 and 2010), and in cleft population in general to assess the need and outcome of secondary surgery and speech rehabilitation. Rhinomanometry is a non-invasive technique recording the nasal and oral pressure and airflow rate and volume over a given time period. Nasal resistance and minimum cross-sectional area can be calculated from these measurements. Most commonly used techniques are anterior, posterior, and postnasal rhinomanometries, also defined as pressure-flow technique. When using anterior rhinomanometry, the subject breathes through one nostril. Airflow is measured via a facemask or a nozzle which is held in the opening of the nostril. The total airflow measurement can be calculated from two unilateral measurements. Disadvantages of the method are that the method requires an artificial mode of breathing and it is reliable only for the decongested nose. When using posterior rhinomanometry, the total airflow can be measured directly. The nasal airflow from both nostrils is measured with nozzles or a face mask. The pressure is measured from the oral cavity by a catheter placed between the tongue and the palate. The posterior technique is useful particularly in children because it includes the nasopharyngeal airway and it can therefore be used in diagnosing nasopharyngeal obstruction. The postnasal technique is similar to the posterior technique except that the catheter measuring pressure is placed in the nasopharynx. In rhinomanometric methods, catheters in nasal and oral cavities are connected with transducers that process the analogue signals electrically, supplying the signals to the computer. The posterior technique has shown to have greater variation in measured values compared to the anterior and the postnasal techniques (Cole 1989) but also to have high intra-individual consistency (Laine et al. 1994).

Optical rhinometry is a new method to monitor nasal airflow. The method was introduced in Germany in 2004 (Hampel et al. 2004) and it is based on light extinction in optical density to assess nasal blood volume as a measure of nasal patency (Luong et al 2010). The method seems to
correlate well with acoustic rhinometry (Cheung et al. 2010) and it correlates with subjects' ratings of nasal congestion better than anterior rhinomanometry (Wüstenberg et al. 2007). Optical rhinometry also seems to be more comfortable compared with anterior rhinomanometry (Wüstenberg et al. 2007).

2.11.2 Nasal resistance
Body plethysmograph has been observed to be a usable device in assessing nasal resistance and other respiratory variables, but it is a space-requiring device. Body plethysmograph has also been used in children and small animals, it is stable and reliable, and it can be used instead of a nasal mask or a nozzle (Cole and Havas 1987, Cole 1989). “Head out” body plethysmograph can be used instead of nasal mask and its reliability has been shown to be good (Cole and Havas 1987).

Rhinomanometry is used in measuring oral and nasal pressures. Pressure is measured via a detector sealed in the other occluded nozzle. Nasal resistance can be calculated from nasal-oral pressure and nasal airflow (Laine et al. 1994).

2.11.3 Nasal cross-sectional area
Acoustic rhinometry is a non-invasive method which uses reflected sound waves in assessing the nasal cross-sectional area. A pulse generator generates sound waves and introduces them into the nasal cavity. The sound waves reflect back towards the wave tube in which they are received by a microphone and analysed by computer (Fisher et al. 1994). The technique measures the bony nasal cavity, but it does not take into account changes in the nasal mucosa.

Nasal cross-sectional area can also be measured by rhinomanometry. The area is calculated from the formula with nasal airflow rate, density of air, and nasal-oral pressure as variables (Laine et al. 1994).
3 Aims of the study

1. To relate changes in nasal airway size and respiratory functions to age in children and adolescents.
2. To find out when nasal size reaches adult size.
3. To find out if there are gender differences.
4. To assess nasal patency and respiratory function in relation with age.
5. To compare perception and compensatory behaviours to added respiratory loads in adolescents and older adults.
6. To determine whether sensitivity changes with age.
7. To assess perception of olfactory stimulus.
4 Materials and Methods

4.1 ETHICAL CONSIDERATIONS

The data of this study were collected between the years 1991 and 2003, and the permission for the study was applied from the Ethical Committee of the Kuopio University Hospital District Municipal Federation and Kuopio University Hospital in 1986. Participation in the study was voluntary, and the informed consent forms were signed by the participants or the children’s guardians.

4.2 STUDY SUBJECTS

The study groups included cross-sectional (Study I), longitudinal (Study II) and clinical experimental (Studies III and IV) study design. Age and gender distribution of the study populations is listed in Table 1. All participants volunteered to participate in this study. All children and adolescents were clinically healthy and free of nasal symptoms at the time of the measurements. In the clinical experimental study, 13 older adults had chronic diseases controlled by medications.

To assess annual changes in nasal airway size and respiratory function, consecutive age cohorts (N = 927) among all school children from the 1st to the 9th grade in a rural municipal of 3,800 inhabitants of homogeneous Caucasian population were compared with each other (Study I). The number of the studied subjects per age cohort varied from 45 to 113. All children and adolescents who were present at school at the time of examinations were included in the study, except for individuals attending special schools due to severe handicaps.

In the longitudinal study (Study II), characteristics of naso-respiratory function of the two youngest age cohorts, that is children in the 1st and 2nd grades, were examined annually from 8 to 17 years of age. The study population consisted of 115 children, 63 girls and 52 boys. The results from 9 to 13 years of age have been published (Crouse et al. 1999 and 2000, Crouse 2001). The present study reports the findings from 8 to 17 years of age.

In the clinical experimental studies (Studies III and IV), two different age groups of homogeneous Caucasian origin were compared with each other: 40 adolescents and 40 older adults. The younger group included 21 girls and 19 boys with a mean age of 17.6 years (SD 2.1, range 11.2–20.3 years) and older adults, 29 women and 11 men, on average 69.9 years of age (SD 5.9, range 59.0–82.8 years). In Study IV, three of the study subjects in the older group could not detect the same concentration of olfactory stimulus consistently and they were excluded from the study. Thus, in the older group, the number of participants included in the study was 37.

Power analysis showed that a study sample with a minimum of 36 individuals per study group was large enough for this study. Our study sample was 40 individuals per group.

The study subjects or the guardian of the participating child filled in a questionnaire (Appendix 1) each time before the day of examination. The questionnaire for children and adolescents included questions about medication, allergies, allergic symptoms, orthodontic treatment, and whether their adenoid and/or tonsils had been removed. For the clinical experimental study, the subjects filled in a semi-structured dichotomous questionnaire (Appendix 2) with information about the use of medication and presence of allergies, nasal symptoms and smoking habit as well as medical history of the presence of heart diseases and other chronic diseases including rheumatism, diabetes, lung, thyroid gland and biliary diseases.
Height (cm) and weight (kg) of the study subjects were asked in the questionnaire but were also verified during the examination. The measured values were used for analyses and to calculate body mass index \[\text{BMI} = \text{Weight}/(\text{Height}/100)^2\].

Table 1. Age and gender distribution of the study groups (Studies I–IV).

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Age (years)</th>
<th>Females (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study I</td>
<td>923</td>
<td>8–17</td>
<td>51–70</td>
</tr>
<tr>
<td>Cross-sectional study</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study II</td>
<td>115</td>
<td>8–17</td>
<td>53</td>
</tr>
<tr>
<td>Longitudinal study</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study III</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical experimental study</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adolescents</td>
<td>40</td>
<td>11–20</td>
<td>50</td>
</tr>
<tr>
<td>Older adults</td>
<td>40</td>
<td>59–82</td>
<td>73</td>
</tr>
<tr>
<td>Study IV</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical experimental study</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Adolescents</td>
<td>40</td>
<td>11–20</td>
<td>50</td>
</tr>
<tr>
<td>Older adults</td>
<td>37</td>
<td>59–82</td>
<td>70</td>
</tr>
</tbody>
</table>

4.3 METHODS

4.3.1 Respiratory function
Respiratory function was measured using the pressure-flow technique, originally developed and described in detail by Warren (1984) with software Perci-PC and Perci-SARS (Microtronics Co., Chapel Hill, NC) (Fig. 1). The method has good reproducibility (ICC 0.80, 95 %, CI 0.58–0.94) (Laine et al. 1994). The equipment was calibrated before each measurement session. For calibration, airflow rate of 500 ml/s was used. Respiratory function was registered in January and/or February to avoid the pollen season, with the study subject in a sitting position, after at least 30 minutes’ acclimation to the room temperature. A period of 10 seconds of respiratory function was saved for each study subject.

Nasal airflow rate (ml/s) and oral-nasal differential pressures (cmH\(_2\)O) were measured using a well-fitted nasal mask as follows: The pressure-drop (oral minus nasal pressure) across the nasal airway was measured by differential transducers connected to two catheters. One catheter was placed midway in the mouth and another catheter within a well-fitted nasal mask. Nasal airflow was measured with a heated pneumotachograph connected to the nasal mask. During measurements, the study subject breathed through the nose and the lips were closed. Nasal airway resistance was determined using the hydrokinetic equation:
\[ R = \frac{\Delta P}{V}, \]

where \( R \) = resistance (cmH\(_2\)O/l/s), \( \Delta P \) = oral pressure minus nasal pressure (cmH\(_2\)O) and \( V \) = airflow rate (ml/s).

In addition to nasal resistance, minimum nasal cross-sectional area was calculated based on these measurements as follows:

\[ A = \frac{V}{k(2 \Delta P/d)^{\frac{1}{2}}}, \]

where \( A \) = minimum nasal cross-sectional area (cm\(^2\)), \( V \) = airflow rate (ml/s), \( k = 0.65 \), \( d \) = density of air (g/cm\(^3\)), and \( \Delta P \) = oral - nasal pressure (cmH\(_2\)O).

In measuring children and adolescents (Study I and II), the measurements were made at schools using portable equipment, calibrated before each measurement session.

**Figure 1.** Pressure-flow technique (redrawn from Crouse et al. 1999).

### 4.3.2 The device used to create resistance loads

In Study III, the pressure-flow technique was used to record rest breathing and respiratory function with added respiratory loads. The device used to create resistance loads (Study III, Fig. 1) was modified from precision iris diaphragm (Model no. N36.624, o.d. 60 lever bridge). The maximum opening was 8.0 mm in diameter, corresponding to an area of 0.50 cm\(^2\). The device could be opened and closed at 0.2-mm increments in the diameter. The diaphragm was set between the nasal mask and the pneumotachograph. As a preliminary part of the study, resistance values of the diaphragm aperture at different aperture openings were calculated using a respiratory pump and the pressure-flow instrumentation (Study III, Table I).

The device to create added resistances was added after the rest breathing measurements, and the aperture size was manually set in a random sequence of different loads. The load condition was compared to a control condition, with a maximum opening of 0.50 cm\(^2\) of the diaphragm. Following each change in aperture size, the subjects were asked whether they detected a change in the airway resistance. The measurements at the unloaded condition and with added load just prior to detection and at detection were included in the data. The study subjects had to detect the same value three times consecutively to be accepted as a threshold value. In Study III, the
The increment threshold for detecting a difference in nasal resistance was calculated for each individual as Weber fraction, indicating just noticeable difference. The increment threshold for detecting a difference in nasal resistance was calculated for each individual as follows:

\[ WF = \frac{(R_i - R_o)}{R_o} \]

where \( R_i \) = the resistance of the system corresponding to the just noticeable resistance during added load plus nasal resistance during rest breathing, and \( R_o \) = the resistance of the system corresponding to the diaphragm setting maximally open plus nasal resistance during each individual’s rest breathing.

**4.3.3 Detection of olfactory stimulus**

Detection of olfactory stimulus was studied using 0.00002% butanol concentration (Study IV, Table 2) with a threshold score of 1–10 to find out the threshold of each individual to detect the stimulus. The stimuli were given in a random order, and an individual had to detect the same value three times consecutively before it was accepted as a threshold value, and they also had to detect the next concentration.

**4.4 STATISTICAL METHODS**

For all analyses, the level of significance was set at \( p \leq 0.05 \).

The Mann-Whitney U-test was used to compare differences in median values of airflow rate (ml/s) (Study I) and also differences in oronasal pressures and nasal resistance between boys and girls (Study II). Student’s t-test was used in comparing mean values of minimum nasal cross-sectional area (cm\(^2\)) between girls and boys at each age. Paired t-test was used in analysing changes in nasal resistance between consecutive ages. For significance of the annual changes between two consecutive ages, Wilcoxon test was used for the airflow rate and paired t-test for the nasal cross-sectional area, separately for boys and girls.

In the clinical experimental study (Study III), paired t-test was used in assessing differences between inspiratory and expiratory resistance (cmH\(_2\)O/l/s) and airflow rate (ml/s) within each age group. To estimate associations of resistance (cmH\(_2\)O/l/s) and airflow rate (ml/s) according to age groups and gender, linear regression models were used, with the use of medication, presence of any diagnosed medical condition, smoking habit, upper airway allergies, seasonal nasal symptoms and height (cm) as confounding factors.

The connection between the perception of the intensity of olfactory stimulus defined as threshold score (1–10) and age group, gender, BMI (kg/cm\(^2\)), smoking habit, and medical history was analysed using linear regression models (Study IV). Due to high correlations between the respiratory variables, nasal airflow rate, minimum nasal cross-sectional area and resistance during inspiration were included separately in the analyses.
5 Results

5.1 CHANGES IN NASAL PATENCY AND RESPIRATORY FUNCTION DURING GROWTH

5.1.1 Changes in airflow rate during growth (Study I)
The median value of inspiratory airflow rate increased in girls from 339 to 493 ml/s from the age of 8 to 17, except that it decreased on average 20 ml/s from the age of 10 to 11 years as well as from 13 to 14 years of age (Study I, Table 2). For boys, airflow rate increased from 406 to 563 ml/s from the age of 8 to 17 but decreased from 9 through 10 to 11 and from 14 to 15 years of age (Study I, Table 2). The only statistically significant changes between consecutive ages were from 11 to 12 years of age for girls and from 11 to 12 and from 15 to 16 years for boys (Table 4). There were statistically significant differences between genders for airflow rate at most ages (Table 5).

5.1.2 Growth of minimum nasal cross-sectional area across age cohorts (Study I)
The mean of minimum nasal cross-sectional area increased in girls from 0.38 cm$^2$ to 0.58 cm$^2$ from the age of 8 to 17, but there was some inconsistency (Table 2). The mean value decreased from 10 to 11 and from 14 to 15 years of age. The annual changes were statistically significant between ages 8 and 9 years ($p = 0.05$) and 11 through 12 to 13 years of age ($p < 0.01$ and 0.05). In boys, minimum nasal cross-sectional area increased from 0.40 cm$^2$ to 0.68 cm$^2$ from the age of 8 to 17, and decreased slightly from 9 to 10 and from 14 to 15 years of age (Table 3). The annual changes were statistically significant between 11 and 12 years of age ($p = 0.02$), 13 to 14 ($p = 0.03$), from 15 to 16 ($p = 0.05$) and from 16 to 17 years of age ($p = 0.03$). Across genders, the only statistically significant difference occurred at age 16.

5.1.3 Oral-nasal pressure and resistance during growth (Study II)
In children and adolescents, the differences between oral and nasal pressures were almost constant during growth in both genders (Study II, Fig. 1 and 2). Median values of differential pressure ranged from 0.72 to 1.13 cmH$_2$O in girls and from 0.92 to 1.44 cmH$_2$O in boys at different ages (Study II, Table 1). Differences in oral-nasal pressures between girls and boys were statistically significant at several ages (Table 5; Study II, Table 1). Mean nasal resistance decreased from age of 8 to 17, in girls from 4.0 (SD 3.27) to 2.4 (SD 2.30) cmH$_2$O/l/s and in boys from 3.3 (SD 2.48) to 1.5 (SD 0.81) cmH$_2$O/l/s, but not consistently (Tables 2 and 3). Nasal resistance had a tendency to increase in girls from 10 to 11 and from 14 to 16, and in boys from 9 to 10, 11 to 12 and 14 to 15 years of age (Study II, Table 2). The differences were statistically significant only between 11 and 12 and between 12 and 13 years of age ($p = 0.01$ and $p = 0.03$, respectively) in girls but only from 8 to 9 years of age ($p = 0.02$) in boys. Girls had a general tendency towards higher values for upper airway resistance than boys, the difference being statistically significant only at age 13 ($p = 0.05$).
Table 2. Changes in minimum nasal cross-sectional area (cm$^2$), airflow (ml/s) and nasal resistance (cmH$_2$O/l/s) during inspiratory phase of rest breathing from 8 to 17 years in girls.

<table>
<thead>
<tr>
<th>Age (y)</th>
<th>Girls</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cross-sectional area</td>
<td>Airflow rate</td>
<td>Nasal resistance</td>
</tr>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td>8</td>
<td>0.38 (0.12)</td>
<td>349 (103)</td>
<td>4.0 (3.27)</td>
</tr>
<tr>
<td>9</td>
<td>0.42 (0.15)</td>
<td>368 (107)</td>
<td>3.7 (2.92)</td>
</tr>
<tr>
<td>10</td>
<td>0.44 (0.15)</td>
<td>388 (118)</td>
<td>3.1 (2.21)</td>
</tr>
<tr>
<td>11</td>
<td>0.41 (0.11)</td>
<td>372 (82)</td>
<td>3.3 (1.55)</td>
</tr>
<tr>
<td>12</td>
<td>0.49 (0.12)</td>
<td>409 (101)</td>
<td>2.5 (1.17)</td>
</tr>
<tr>
<td>13</td>
<td>0.53 (0.14)</td>
<td>428 (103)</td>
<td>2.2 (1.67)</td>
</tr>
<tr>
<td>14</td>
<td>0.56 (0.16)</td>
<td>415 (92)</td>
<td>1.9 (0.93)</td>
</tr>
<tr>
<td>15</td>
<td>0.51 (0.14)</td>
<td>417 (104)</td>
<td>2.3 (1.14)</td>
</tr>
<tr>
<td>16</td>
<td>0.53 (0.16)</td>
<td>442 (110)</td>
<td>2.4 (1.61)</td>
</tr>
<tr>
<td>17</td>
<td>0.58 (0.23)</td>
<td>471 (108)</td>
<td>2.4 (2.30)</td>
</tr>
</tbody>
</table>

Table 3. Changes in minimum nasal cross-sectional area (cm$^2$), airflow (ml/s) and nasal resistance (cmH$_2$O/l/s) during inspiratory phase of rest breathing from 8 to 17 years in boys.

<table>
<thead>
<tr>
<th>Age (y)</th>
<th>Boys</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cross-sectional area</td>
<td>Airflow rate</td>
<td>Nasal resistance</td>
</tr>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td>8</td>
<td>0.40 (0.14)</td>
<td>434 (125)</td>
<td>3.3 (2.48)</td>
</tr>
<tr>
<td>9</td>
<td>0.44 (0.13)</td>
<td>420 (98)</td>
<td>2.8 (1.82)</td>
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<tr>
<td>10</td>
<td>0.42 (0.14)</td>
<td>391 (90)</td>
<td>3.3 (3.92)</td>
</tr>
<tr>
<td>11</td>
<td>0.42 (0.14)</td>
<td>394 (110)</td>
<td>3.2 (3.11)</td>
</tr>
<tr>
<td>12</td>
<td>0.50 (0.18)</td>
<td>460 (151)</td>
<td>3.3 (6.36)</td>
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<tr>
<td>13</td>
<td>0.52 (0.16)</td>
<td>458 (101)</td>
<td>2.5 (1.53)</td>
</tr>
<tr>
<td>14</td>
<td>0.57 (0.15)</td>
<td>484 (108)</td>
<td>1.8 (1.03)</td>
</tr>
<tr>
<td>15</td>
<td>0.56 (0.17)</td>
<td>506 (135)</td>
<td>1.9 (1.50)</td>
</tr>
<tr>
<td>16</td>
<td>0.63 (0.24)</td>
<td>548 (138)</td>
<td>1.8 (1.09)</td>
</tr>
<tr>
<td>17</td>
<td>0.68 (0.16)</td>
<td>579 (139)</td>
<td>1.5 (0.81)</td>
</tr>
</tbody>
</table>
Table 4. Statistically significant annual changes in respiratory variables (+ = increase, - = decrease) separately for genders (F = females, M = males) (p ≤ 0.05).

<table>
<thead>
<tr>
<th>Age cohorts (yrs)</th>
<th>Airflow</th>
<th>Minimum cross-sectional area</th>
<th>Resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>F</td>
<td>M</td>
<td>F</td>
</tr>
<tr>
<td>8 vs. 9</td>
<td>+</td>
<td>M</td>
<td>-</td>
</tr>
<tr>
<td>9 vs. 10</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 vs. 11</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11 vs. 12</td>
<td>+ +</td>
<td>+ +</td>
<td>-</td>
</tr>
<tr>
<td>12 vs. 13</td>
<td></td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>13 vs. 14</td>
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<td></td>
<td>+</td>
</tr>
<tr>
<td>14 vs. 15</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15 vs. 16</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>16 vs. 17</td>
<td></td>
<td>+</td>
<td></td>
</tr>
</tbody>
</table>

Table 5. Statistically significant gender differences in respiratory variables (F = females, M = males) (p ≤ 0.05).

<table>
<thead>
<tr>
<th>Age (yrs)</th>
<th>Airflow</th>
<th>Minimum cross-sectional area</th>
<th>Differential pressure</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
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5.2 RESPIRATORY AND OLFACTORY FUNCTION WITH AGING

5.2.1 Nasal patency in older adults and adolescents (Study III)
During rest breathing, in older adults the mean of the inspiratory nasal cross-sectional area was 0.59 (SD 0.17) cm$^2$, ranging from 0.17 to 0.85 cm$^2$. In adolescents, mean value was 0.56 (SD 0.14) cm$^2$ and varied from 0.22 to 0.78 cm$^2$. The differences between the study groups were nonsignificant. Minimum nasal cross-sectional area was smaller during the inspiratory phase than during expiration in both groups, 0.64 (SD 0.19) cm$^2$ and 0.58 (SD 0.16) cm$^2$, respectively.

5.2.2 Changes in perception and respiratory responses to added nasal resistance with aging (Study III)
The resistance values were lower for adolescents (Study III, Table II) at all conditions compared to older adults. The differences were statistically significant at all conditions except during rest breathing (Study III, Table IV). Among adolescents, resistance values were higher (Fig. 2–3) during inspiration compared to expiration at all conditions, the differences between the phases being statistically significant at all conditions (Study III, Tables II and III). Among older adults, mean values of nasal resistance were higher during inspiration than during expiration at rest breathing and at the unloaded condition, but lower at all other conditions. Gender had a statistically significant effect only on differential resistance just prior to detection of added load (p = 0.026).
Figure 2. Means and SD of inspiratory and expiratory resistance (cmH₂O/L/s) during rest breathing in 40 adolescents and 40 older adults.
Values for the Weber fraction, the just noticeable difference in added upper airway resistance, varied between -0.02 and 1.16 in the younger group and between 0.01 and 2.48 in the older group. The mean values of Weber fraction were 0.23 (SD 0.26) for adolescents and 0.84 (SD 0.79) for older adults, (p < 0.001). The Weber fraction seems to have a constant nature (Study III, Fig. 1) among adolescents while there was wider inter-individual variation among older adults (Study III, Fig. 2). In older adults, higher added loads were needed to detect the change.

Respiratory response manifested as changes in airflow rate. Airflow rate values were systematically lower (Fig. 4–5) for the younger group than for older adults (Study III, Table II) but differed statistically significantly only during rest breathing (Study III, Table IV). With added respiratory loads, nasal airflow rate decreased in both groups to about the same value of 300 ml/s just prior to detection and at detection of the added load.

When comparing airflow between inspiration and expiration (Study III, Table II), in the younger study group, mean values of airflow rate were slightly higher during inspiration compared to expiration except at detection of the added load when it was almost the same, 302 and 303 ml/s. However, the differences were small and nonsignificant except during rest breathing, 431 and 387 ml/s, respectively (p < 0.001). Among older adults, airflow rate had lower mean values during inspiration compared to expiration except during rest breathing, the difference being statistically significant only at the unloaded condition (Study III, Table II). Linear regression models, including other studied variables and confounding factors, showed that the difference between inspiratory and expiratory airflow rate differed significantly between the groups only at the unloaded condition (Study III, Table III).
Figure 4. Means and SD of inspiratory and expiratory airflow rate (ml/s) during rest breathing in 40 adolescents and 40 older adults.
a) Error Bars: 95% CI
5.2.3 Changes in sense of smell with aging (Study IV)

For olfactory function, the present results (Study IV, Table 4) showed a statistically significant difference \((p = 0.000)\) in means of threshold for smell detection between adolescents and older adults, 3.03 (SD 1.70) and 5.59 (SD 1.21), respectively. Backward linear regression analyses (Study IV, Table 5) showed a positive association between the threshold and age group, which indicates that adolescents are more sensitive to olfactory stimuli. Gender, BMI, medication, smoking habit, allergies, and nasal symptoms were not related to olfactory function. Relationship between nasal resistance and olfactory threshold almost reached the level of statistical significance \((p = 0.054)\) but other respiratory variables, namely cross-sectional area or airflow rate, were not related to olfactory identification ability.

5.3 ASSOCIATION BETWEEN GENDER AND UPPER AIRWAY FUNCTION

In children and adolescents, there were statistically significant differences between genders in airflow rate (Study I, Table 2) at most ages except the ages of 10, 11 and 13 years. The minimum cross-sectional area values had a general tendency of higher values for boys than girls from the age of 14 on, but the difference was statistically significant only at the age of 16 \((p = 0.03)\). The values of oral-nasal pressure (Study II, Table 1) differed between the genders statistically significantly at the ages of 8, 10, 13, and 14 years \((p = 0.01, 0.03, 0.02, \text{ and } 0.01, \text{ respectively})\). Gender differences in nasal resistance (Study II, Table 2) were statistically significant only at the age of 13.
In the adult population, gender did not have any statistically significant effects on resistance, differential pressure, or airflow values at any test conditions, nor on olfactory function.

5.4 OTHER ASSOCIATED FACTORS

Because none of the adolescents but 13 individuals among the older adults had chronic diseases, controlled by medication, linear regression models were performed also separately for the older group (Study III). The results indicated that in older adults, a history of chronic diseases had an increasing effect on nasal airflow only at unloaded condition (p = 0.035).

Body size, medication, smoking habit, upper airway allergies, or other nasal symptoms did not have a statistically significant effect on respiratory variables.
6 Discussion

6.1 SUBJECTS

The study subjects to determine age-related growth changes in the upper airways and in respiratory function included all school children and adolescents (N = 923) from the 1st to the 9th grade from the municipality of Vimpeli, Finland, who were present at school at the time of examination. Children or adolescents with severe handicaps attending special schools were not included in the study. Also, children and adolescents had to be free from nasal symptoms to participate. Therefore, the measurements were performed in early winter to avoid the pollen seasons. This rural area was chosen for two reasons. First, the inhabitants represented a homogeneous population, and thus the results can be applied to the original Finnish population. Second, for the longitudinal part of the study, it is vitally important to have an area with a minimal amount of people moving in or out of the area. In fact, this study project had been initiated in a town of 80,000 residents and lost one third of the sample in three years, and had to start again in this rural area where none of the children moved out and actually two children moved into the area within nine years.

In clinical experimental studies, 40 adolescents and 40 older adults were examined to determine age-related changes in respiratory function. In the study of olfactory function, three of the older adults could not detect the olfactory stimulus, so they were excluded. This may have biased the results slightly if the reason for the inconsistent perception was poor sense of smell. All study subjects were clinically healthy and free of nasal symptoms at the time of examination, and information of history of medical conditions and smoking habit were included in the statistical analyses.

6.2 METHODS

The pressure-flow technique was chosen because it provides a non-invasive method to measure upper airway function. Nasal decongestants were not used because that would affect the nasal mucosa; assessing response of the nasal mucosa to temperature and different stimuli is fundamental knowledge for respiratory physiology. One benefit of the method is that the equipment allows measuring the right and left sides separately, which is important with cleft palate patients. Although the method has shown to have not only high intra-individual but also almost as high inter-individual consistency (Laine et al. 1994), the same examiners (RM, MTLA, UC) with extensive experience in the use of the method performed all the measurements throughout the study. Calibration of the equipment needs to be done before every session it is used, and is of special importance when using the equipment outside hospital or laboratory conditions, as was the case when studying the children. The limitations of the method are its limited availability and that it is not suitable for very young children due to their short attention span and immature fine motor control of the lips and tongue. Clinical and research conditions for our group provided the equipment for use not only in research laboratories but also in hospitals, public health care centre and craniofacial centre, the latter being the most common place to utilize the pressure-flow technique.
6.3 RESULTS

One aim of the study was to develop age- and gender-specific values for nasal airway size and respiratory function. The guideline values are especially important in diagnostics and treatment of children with craniofacial anomalies, mainly individuals with cleft palate, and also in some orthodontic patients. In general, the present results showed that nasal airway size and airflow rate increased, nasal resistance decreased, and differential pressure remained nearly constant during growth.

Regarding changes in respiratory variables with age and gender in children and adolescents, differential pressure showed small changes. However, gender differences were statistically significant at most ages. The nasal airflow rate increased between the ages of 8 and 17, and was significantly higher in boys at most ages. Because determining minimum cross-sectional area and nasal resistance are dependent on oral-nasal pressure values and airflow rate values, respiratory variables need to be determined separately for girls and boys.

Minimum cross-sectional area increased during growth, which is in accordance with earlier studies (Warren et al. 1990, Laine and Warren 1991, Vig and Zajac 1993, Ho et al. 1999). Nasal passage was larger in males from the age of 14 on, but statistically significantly only at the age of 16. However, it did not increase steadily but decreased from 10 to 11 in girls, from 9 to 10 in boys, and from 14 to 15 years of age in both genders. The growth of the nasal passage seems to follow general growth and may also be regulated by hormonal factors. The size of adenoid seems to be related to changes in nasal function. In adults, Crouse and Laine-Alava (1999) found that gender seems to correlate with airway size and airflow rates, the values being higher in males.

With increasing nasal airway size, nasal resistance values decreased with age. Earlier studies have shown that adult level of nasal resistance is reached by the age of 16-17 years (Saito and Nishihata 1981, Laine-Alava and Minkkinen 1997). The present results suggest that adult level is reached by the age of 17 in females but possibly not in males because of ongoing growth. Resistance values were higher in females than in males, but differed statistically significantly only at the age of 13. On the contrary, Kobayashi et al. (2012) did not find any differences in nasal resistance between genders in children. Abramson et al. (2009) did not find any differences between genders in upper airway size of children and adults, but Janosević et al. (2009) found gender differences in nasal resistance values in adult population.

If the nasal airway is congested, the response to increased nasal resistance is to part the lips and open the mouth slightly, changing the breathing route from nasal to a combination of oral and nasal breathing to lower the resistance (Watson et al. 1968, Warren et al. 1984). Threshold values to switch from nasal to oral breathing differ due to individual responses (Laine and Warren 1995). Earlier studies have shown that shifting from nasal to nasal-oral breathing seems to begin at a nasal resistance of 4.5 cmH2O/l/s in children and adolescents aged 9 to 17 (Watson et al. 1968) and 4.7 cmH2O/l/s, measured at 0.5 l/s, in a plastic model illustrating an adult airway (Warren et al. 1984). In our experimental study, the values when individuals detected nasal loading were 2.26 cmH2O/l/s in adolescents and 4.55 cmH2O/l/s in older adults. Interestingly, individuals changed their breathing mode before they detected the change. The proportion of oral breathing compared to total volume is difficult, if not impossible, to measure accurately. In assessing upper airway obstruction, clinical evaluation alone is not always sufficient and actual measurements of rest breathing and guideline values based on healthy population are necessary.

The present results on the effects of added respiratory loads in adolescents and older adults showed that during rest breathing, the older group had statistically significantly higher values for airflow rate but not for nasal airway size and nasal resistance. Our results, as well as some earlier studies (Crouse and Laine-Alava 1999, Kim et al. 2007, Abramson et al. 2009), show that age does not seem to be an important factor for nasal airway size in adults. Kim et al. (2007) noticed that nasal resistance still decreased until the third decade. They did not notice differences in adults aged 30–70. With added load, adolescents detected resistance differences at lower values than older adults. As a compensatory response, individuals slowed down airflow rate, resulting
in the same level of 300 ml/s, not only at the time they detected the added load but prior to the
detection. This finding supports the assumption that breathing function is controlled for the
purpose of maintaining the balance of nasal aerodynamics. The airflow is kept stable by changing
the breathing mode from nasal to oral-nasal when nasal resistance is too high.

Olfactory function seems to decrease with age, which is parallel with the results of several
effect of age on olfactory perception may be explained by age-related changes in neural systems
(Liss and Gomez 1958). In contrast to this finding, previous studies have shown gender
2012, da Silva et al. 2014, Jin et al. 2016). Neither medical conditions nor smoking habits were
related to olfactory function. Increased nasal resistance may make it easier to detect olfactory
stimuli. Smell detection ability seems to decrease with aging. Olfactory detection may weaken
one’s appetite and affect dietary choices (Boesweldt and de Graaf 2017).

There are only few studies about the possible correlation between body mass index (BMI) and
nasal airway values in adults. Crouse and Laine-Alava (1999) reported in their study that BMI
correlates with nasal airflow rates and nasal and oral pressures. Their study sample was quite
large, 332 subjects. Because earlier studies (Laine and Warren 1991, Laine-Alava and Minkkinen
1997) indicated that there were no associations between BMI and upper airway function, BMI
was not included in studies about growing children. Janosević et al. (2009) found that height
seemed to be associated with total nasal resistance in healthy adults. Findings on association
between body size and variables measuring respiratory function in children are contradictory.
Raza et al. (2010) did not find any association between BMI, height or weight and acoustic
rhinometry findings. The present study found no relation between stature, estimated as height,
and respiratory function, which is in line with the study of Saito and Nishihata (1981). In cross-
sectional studies, Zapletal and Chapulova (2002) reported linear correlation between inspiratory
resistance and body height in 2- to 19-year-olds, and Kobayashi et al. (2012) made the same
finding in school children aged 6–12 years.

Laine-Alava and Minkkinen (1999) studied the effects of the history of nasal symptoms on the
nasal-breathing function. They found some differences between individuals with and without
allergic rhinitis, and between smokers and nonsmokers, but the differences were too small to be
clinically important. The measurements in the present study were performed in early winter to
avoid pollen seasons and the effects of allergic symptoms, and subjects with nasal symptoms at
the time of measurements were excluded. Among the study groups in the clinical experimental
study, only older adults had a history of medical conditions. Multiple regression analyses for that
group separately indicated that the only significant effect on respiratory variables was related to
airflow rate at the unloaded condition where the appliance to create added loads was in place but
not yet in use. Medical conditions were not related to rest breathing or to respiratory response on
added loads. Also, medication was not related to nasal airway function in adults. Smoking habit
was registered in the analysis in both age groups but was not related to nasal function. On the
contrary, some earlier studies have reported an increase in nasal obstruction and nasal resistance
in smokers (Virkkula et al. 2007, Stround et al. 1999). The study of olfactory function showed that
smoking habit was not related to olfactory impairment, which is contradictory to the study of
Murphy et al. (2002) who found an association between smoking and smell loss. Smoking has
decreased during the last ten years. In 1997, 30% of adults aged 20–64 years smoked, whereas the
corresponding number in 2015 was 19% (National Institute for Health and Welfare 2015).
Therefore, the results about the effects of smoking on respiratory function cannot be directly
generalized to the population of this day.
7 Conclusions

It is suggested that minimum nasal cross-sectional area and nasal resistance values are useful for evaluating nasal impairment but should be assessed by comparing age- and gender-specific values obtained from healthy children and adolescents.

On the basis of Studies I–IV,

- There were statistically significant differences between genders in airflow rate at most ages and in oral-nasal pressure at several ages.
- Nasal patency was systematically larger in males from 14 years of age on. Nasal cross-sectional area did not increase steadily during growth. The gender difference in nasal airway size was statistically significant only at the age of 16 years.
- Nasal resistance decreased with age but was inconsistent just before puberty as well as during the final years of growth. Hormonal changes might be one reason for the gender differences in nasal resistance just before puberty due to changes in nasal mucosa. The annual changes were statistically significant from 11 through 12 to 13 years of age in females, but only from 8 to 9 years of age in males.
- The adult size of nasal airways seems to be reached by the age of 17 in girls but possibly not in boys because of ongoing growth.
- Adolescents and older adults had a similar response to added nasal load although the sensitivity was lower in the older group. Aging significantly decreases the sensitivity to the recognition of changes in upper airway resistance.
- Olfactory function seems to decrease with aging, older adults having weaker sense of smell than adolescents.
References


Bjornsdottir E, Keenan BT, Eysteinsdottir B, Arnardottir ES, Janson C, Gislason T, Sigurdsson JF, Kuna ST, Pack AI, Benediktsdottir B. Quality of life among untreated sleep apnea patients compared with the general population and changes after treatment with positive airway pressure. J Sleep Res. 2015;24: 328–338.


Appendix 1

Name: ________________________________________________________________
DOB: __________________________
Address: ____________________________________________________________
Height (cm): ___________________ Weight (kg): ____________________________

Are you currently taking any medication? ______________
What kind? ________________________________________________
Do you have allergies? ______________
What are you allergic to? ____________________________
What kind of symptoms do you have? ____________________________
Have you had your adenoid removed? ____________________________
Have you had your tonsil removed? ____________________________
Have you had orthodontic treatment? ____________________________

___ / ___ _______ _________________________________
Signature

___ / ___ _______ _________________________________
Parent’s signature

Thank you for your co-operation!
### Appendix 2

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**YES  NO  I don’t know**

- In your opinion, is your health good at the moment?  
- Have you recently been receiving continuous medical care by a physician?  
- Are you taking any medication regularly?  
- Describe what kind: __________________

- Do you have any chronic disease diagnosed by a physician?  
Describe what kind: __________________

- Are you allergic to certain medicine or other substances? (For example: Penicillin, sulfa, aspirin, iodine, food ingredients)?  
Describe what kind: __________________

- Do you smoke?  
- How long have you been smoking? ______ years  
- Do you often have any of the following symptoms?  
- Sneezing  
  - Stuffy nose  
- Increased nasal secretions  
  - Is secretion Clear in color?  
- Cloudy?  
- Crusted?  
- Do you have asthma?  
- Do you have skin rash?  
- Describe the nature and location of the rash:  

- Your nasal symptoms occur mostly  
  - Year around  
  - During spring  
  - During summer  
  - During fall  
  - During winter  
- The months during which the symptoms are worst:  

---
- Do your symptoms get worse due to
  - Pollen
  - Animal hair, scurf, or feathers?
  - Dust?
  - Tobacco smoke?
  - Temperature change?
  - Stress?
  - Other substances?
  - Describe what kind: ____________________________

- Do you suffer from recurrent
  - Sinus pain?
  - Sore throat?
  - Bronchitis?
  - Ear infections?
  - Periodontitis or caries?
  - Other infections?
  - Describe what kind: ____________________________

- Have you had your adenoids removed?
- Do you have headaches often?
- Have you been in orthodontic treatment?
- Do you grind or clench your teeth?
- Do you have any TMJ symptoms such as popping and clicking?
- Do you feel pain in the muscles of your face or TMJ, and it is difficult for you to open your mouth?
ORIGINAL PUBLICATIONS (I-IV)
This study assessed upper airway function during growth and with aging. During growth, nasal resistance decreased and nasal passage and airflow rate increased but not consistently, showing gender differences. For diagnostics, age- and gender-specific guideline values are needed. Aging seems to weaken the sense of smell and the sensitivity to recognize added nasal resistance. The physiologic responses to added load were similar in adolescents and in older adults.