THE UNIVERSITY OF CHICAGO BIOLOGICAL SCIENCES

Anosmia -
The forgotten sense takes the center stage

Jayant M. Pinto, M.D., F.A.C.S.
Professor of Surgery, Director of Research
Section of Otolaryngology-Head and Neck Surgery

Deans for Faculty Affairs, Biological Sciences Division

The University of Chicago

Disclosures

- Research: NIH
- Advisory boards: Genentech, Sanofi-Genzyme/Regeneron, Optinose, GSK, Connect
- Clinical trials (site investigator): Sanofi Genzyme/Regeneron, Optinose, Connect
- Speakers Bureau: Sanofi-Genzyme/Regeneron, Optinose
- No other financial conflicts (stock, etc.)

"What's in a name? That which we call a rose
By any other word would smell as sweet."
-William Shakespeare, Romeo and Juliet

- Special sense of olfaction is critical to human quality of life
- Early warning system
- Sensation of pleasure
- Potential role in kin recognition, pheromone detection, mood, central nervous system physiology, and other processes

Great impairment in quality of life

- Impaired activities of daily living:
  - Detection of spoiled foods, smoke, gas leaks
  - Eating, cooking
  - Personal hygiene
  - Cleaning, buying fresh food
  - Socializing
- Increased symptoms of depression
- Reduced weight, appetite, & psychological well-being
- Overall decline in pleasure, quality of Life

Olfactory loss is associated with major health problems

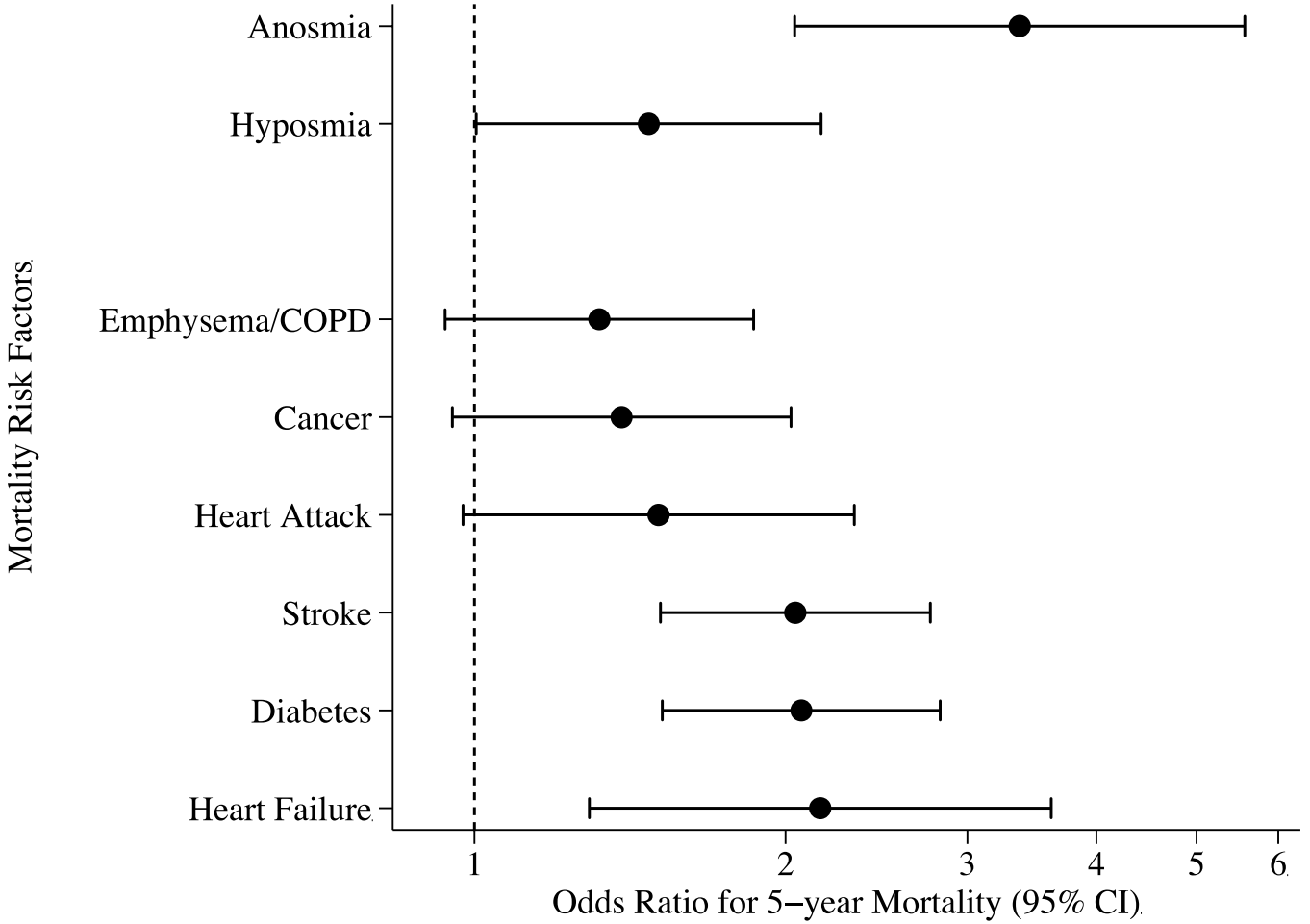
- AD and its precursor[1], mild cognitive impairment[2]
- Brain pathology at autopsy[3]
- Future cognitive decline[4]
- Predates Parkinson's disease by ~4 years[5]
- Impaired in Lewy body dementia[6]
- A marker for neurodegeneration[7]
- Diabetes[8], renal disease[9], epilepsy[10]

[1]Schubert CR, 2008, Murphy C, 1990, [2]Devenand DP, 2010; [3] Attems J,1995; [4]Wilson RS, 2007; [5]Sobel N, 2001; [6]Williams SS, 2009; [7]Hawkes C, 2003; [8]Weinstock RS, 1993; [9]Tung TH, 2005; [10]Kohler CG, 2001

Decreased sense of smell predicts mortality

Olfactory dysfunction predicts 5-year mortality in older adults.
Pinto JM, Wroblewski KE, Kern DW, Schumm LP, McClintock MK.
PLoS One. 2014

Poor sense of smell predicts mortality better than major common diseases

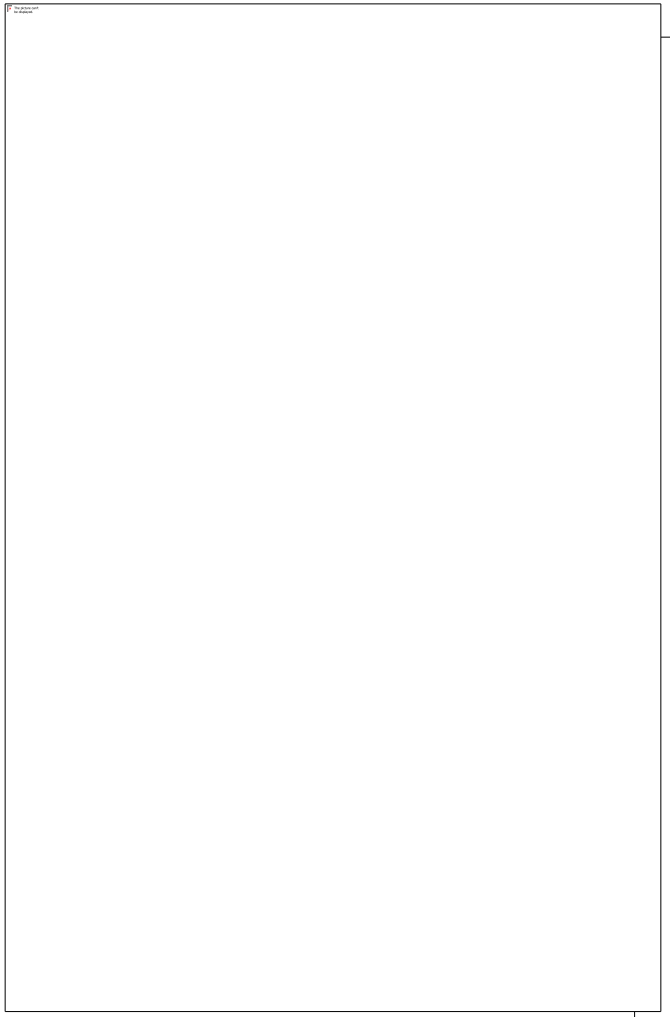


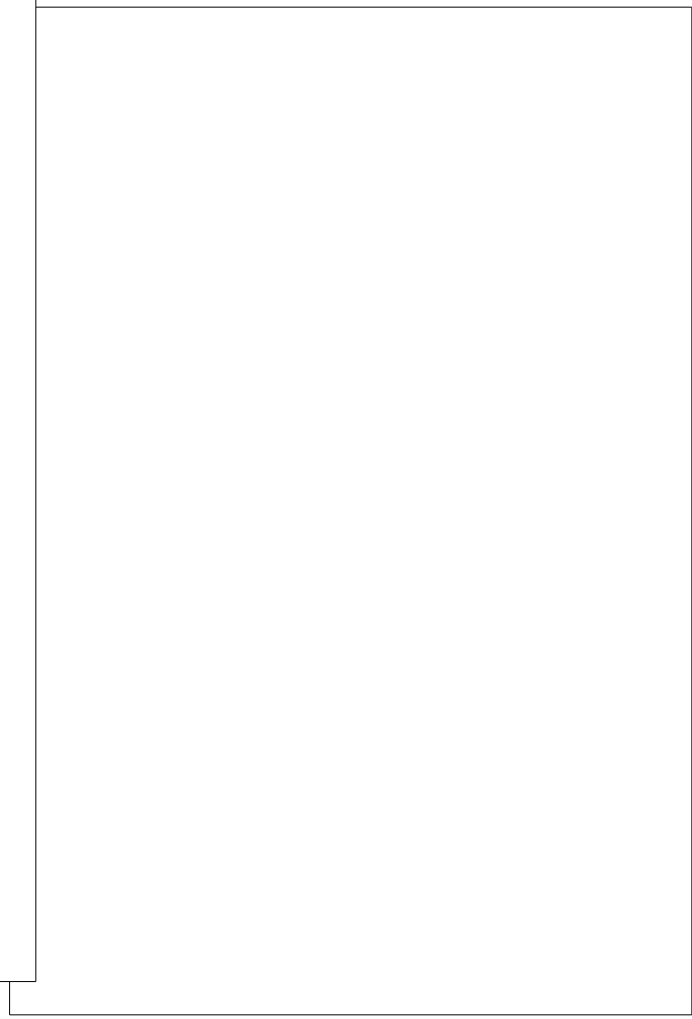
Olfactory physiology

- Odorants diffuse up to roof of the nasal cavity
- Olfactory epithelium comprises the receptor surface
  - Superior portion of middle turbinate, superior turbinate, septum, cribiform plate
- Bathed in a blanket of mucus produced by Bowman's glands which protect and carry escort molecules
- Only portion of the body where nerve tissue is directly exposed to the environment
  - Susceptible to injury, effects of airborne allergens, pollutants, viruses
  - Conduit to the CNS

Olfactory epithelium

- Neuronal receptor cells (Cranial Nerve I)
- Supporting or sustenacular cells
- Stem cells





THE UNIVERSITY OF CHICAGO MEDICINE & BIOLOGICAL SCIENCES

http://education.vetmed.vt.edu/Curriculum/VM8054/Labs/Lab25/EXAMPLES/EXOLFACT.HTM

Olfactory receptors neurons

- 6 – 10 million ciliated receptor neurons in each nasal cavity
- Large surface area to detect odorants
- Binding of odorants to the receptors at the cell membrane activate the signaling cascade

How do we smell?

- Sniffing
- Odorants diffuse into the mucus and are transported to the olfactory receptor by chaperones called odorant binding proteins
- Receptor binding then induces signaling

Olfactory Receptors

Axel and Buck 1991

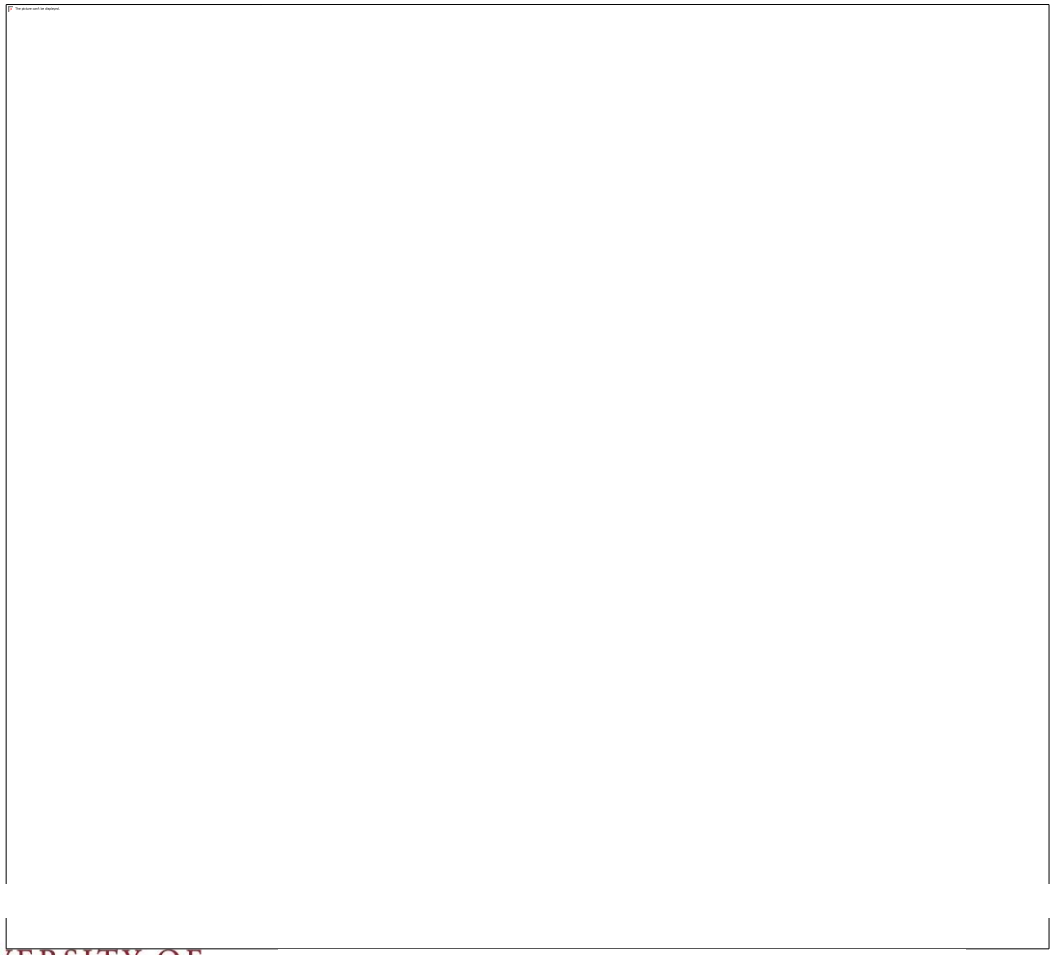
Discovery of Olfactory Receptor Gene Family

Ancient, large gene family

A physical and coding basis for the sense of smell

http://nobelprize.org/medicine/laureates/2004/

ORs are present on every chromosome: An ancient part of our physiology



Genetic variation can affect olfactory function and perception.

(Keller, Pinto, others)

D. Lancet Mamm Genome. 2000 Nov;11(11):1016-23.

Pathology of the olfactory system

- Numerous causes of olfactory dysfunction
  - Inflammatory
  - Trauma
  - Congenital
  - Degenerative
  - Endocrine
  - Neoplastic
- Disease in the nose, the nervous system, or systemic disease

- Conductive
  - Hindered access of odorants to neuroepithelium
- Sensorineural
  - Perturbation of neuronal elements
- Central
  - Brain disease

Nomenclature of olfactory dysfunction

- General or total anosmia
  - Inability to detect any qualitative olfactory sensation
- General or total hyposmia
  - Decreased sensitivity to all odorants
- Specific anosmia
  - Inability to detect a specific odorant
- Dysosmia
  - Distorted sensation
- Phantosmia
  - Phantom sensation
- Hyperosmia
  - Increased sensitivity

Common causes

- Most common
  - Age
  - *URI
  - *Rhinosinusitis
  - *Trauma
- Others
  - Surgery
  - Neurodegenerative disease
- Rare
  - Chemical injury/toxin exposure
  - Endocrine disease
  - Tumors

Measuring olfaction

- Many people are unaware of deficits: **you must perform objective testing**
- Tests allows
  - Assessment of degree of loss
  - Establishment of validity of disease (rule out malingering)
  - Monitoring of changes over time
- A variety of methods
  - Odor identification
    - UPSIT, Sniffin' Sticks most commonly used
    - Cross cultural versions (some not validated)
  - Threshold testing
  - Odor Discrimination (research)
  - Neurophysiologic techniques (research)

University of Pennsylvania Smell Identification Test (UPSIT)

- 40 item scratch and sniff smell test
- Validated in cross-cultural populations
- Test-retest reliability > .90
- Cheap(ish), but not reusable
- Age and sex norms available

http://www4.parinc.com/Products/Product.aspx?ProductID=SIT

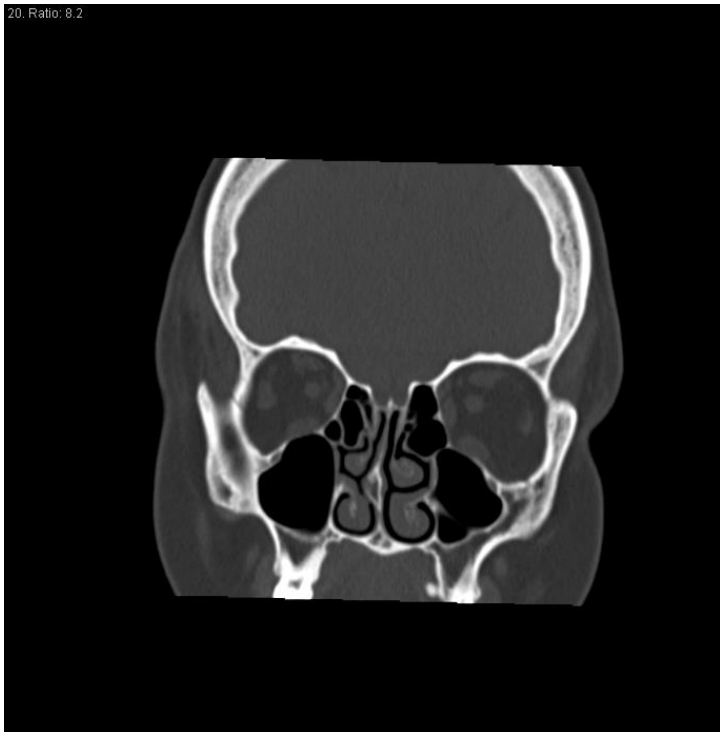
RL Doty. Laryngoscope. 1984 Feb;94(2 Pt 1):176-8.

Relevant history

- History
  - Onset, rate of decline, duration
- Nasal symptoms
  - Inflammatory disease
    - AR, CRS
  - Facial or head trauma
  - Prior surgeries (sinus, brain)
- Neurologic symptoms
- Family history for genetic syndromes
  - Kallmann's syndrome
  - Bardet-Biedl syndrome
  - Extremely rare
- New/current/past medications
- Viral infection
- Occupational exposures
- Diet (malnutrition)
- Use of tobacco, alcohol
- Drugs
  - Medication side effects (psychiatric, anti-cancer, statins)
  - Illicit drugs (cocaine, heroin)
  - Intranasal zinc preparations

Physical examination/testing

- Thorough nasal examination including endoscopy
  - Inflammatory disease (CRS, nasal polyposis)
  - Nasal tumors (esthesioneuroblastoma, etc.)
- Careful Head and Neck
- Complete neurologic exam
  - Cranial nerves
  - Memory



Treatment of olfactory dysfunction

- Best outcome: Conductive disease
  - Allergy therapy
    - Immunotherapy
    - Systemic (antihistamines, antileukotrienes, decongestants)
    - Intranasal (steroids, antihistamines)
      - Nebulized or vertex to floor delivery is better
  - Surgery
    - Septoplasty, Endoscopic Sinus Surgery

Treatment of olfactory dysfunction

- Sensorineural dysfunction is very difficult to treat
- Treat associated diseases
  - Autoimmune disease, diabetes, renal dysfunction, etc.
- Nutritional support
  - Vitamin A, b carotene, Thiamine (few are deficient)
  - No good studies, but probably no harm
- Olfactory training may be helpful
  - Daily exposure to odors may stimulate olfactory stem cell growth/brain plasticity

Treatment of olfactory dysfunction

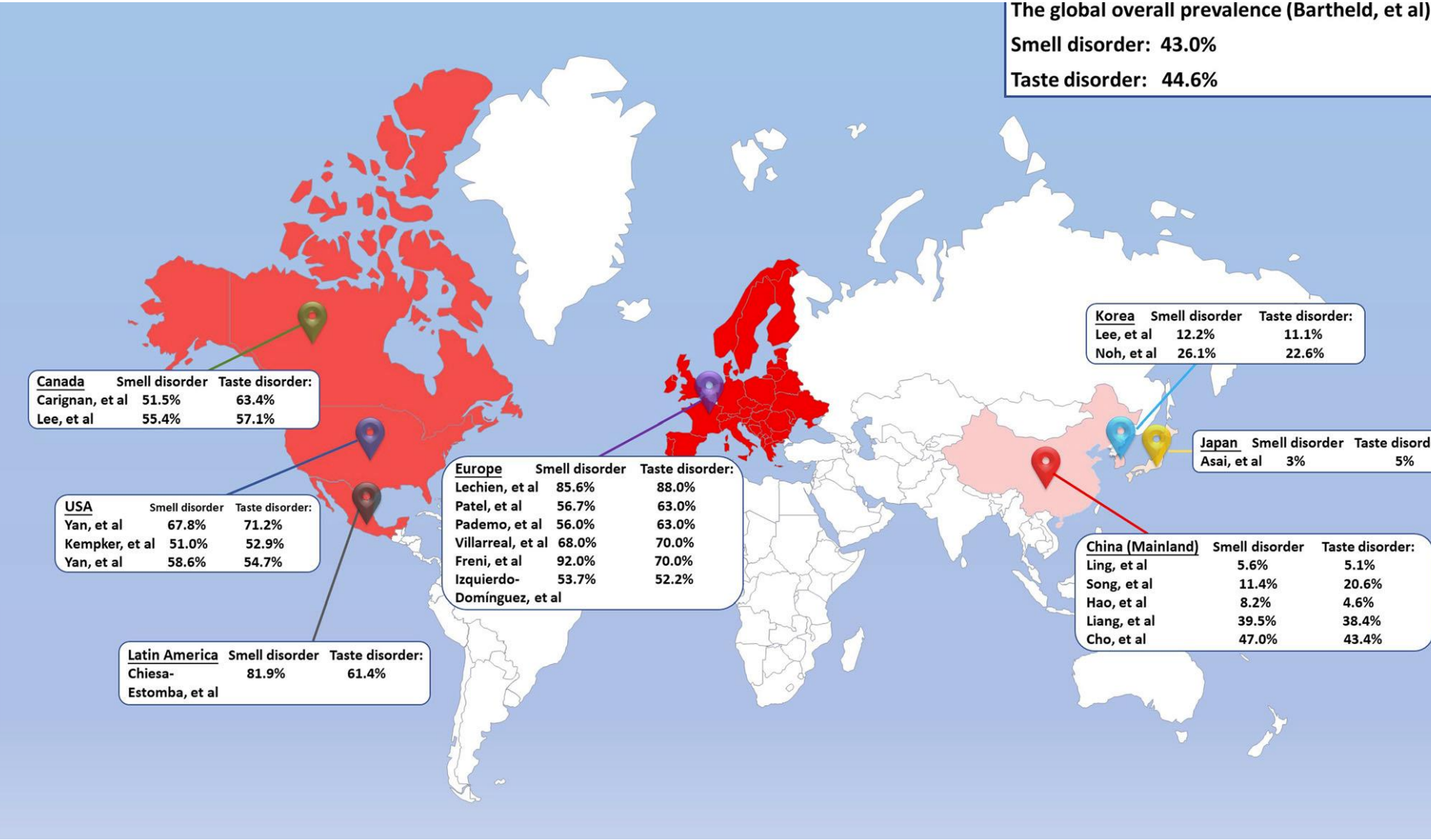
- Counseling regarding detection of spoiled food, installation of smoke detectors and monitoring for gas leaks
- Emphasize other characteristics of foods
  - Texture, temperature, visual appeal

Causes of respiratory infection related smell loss

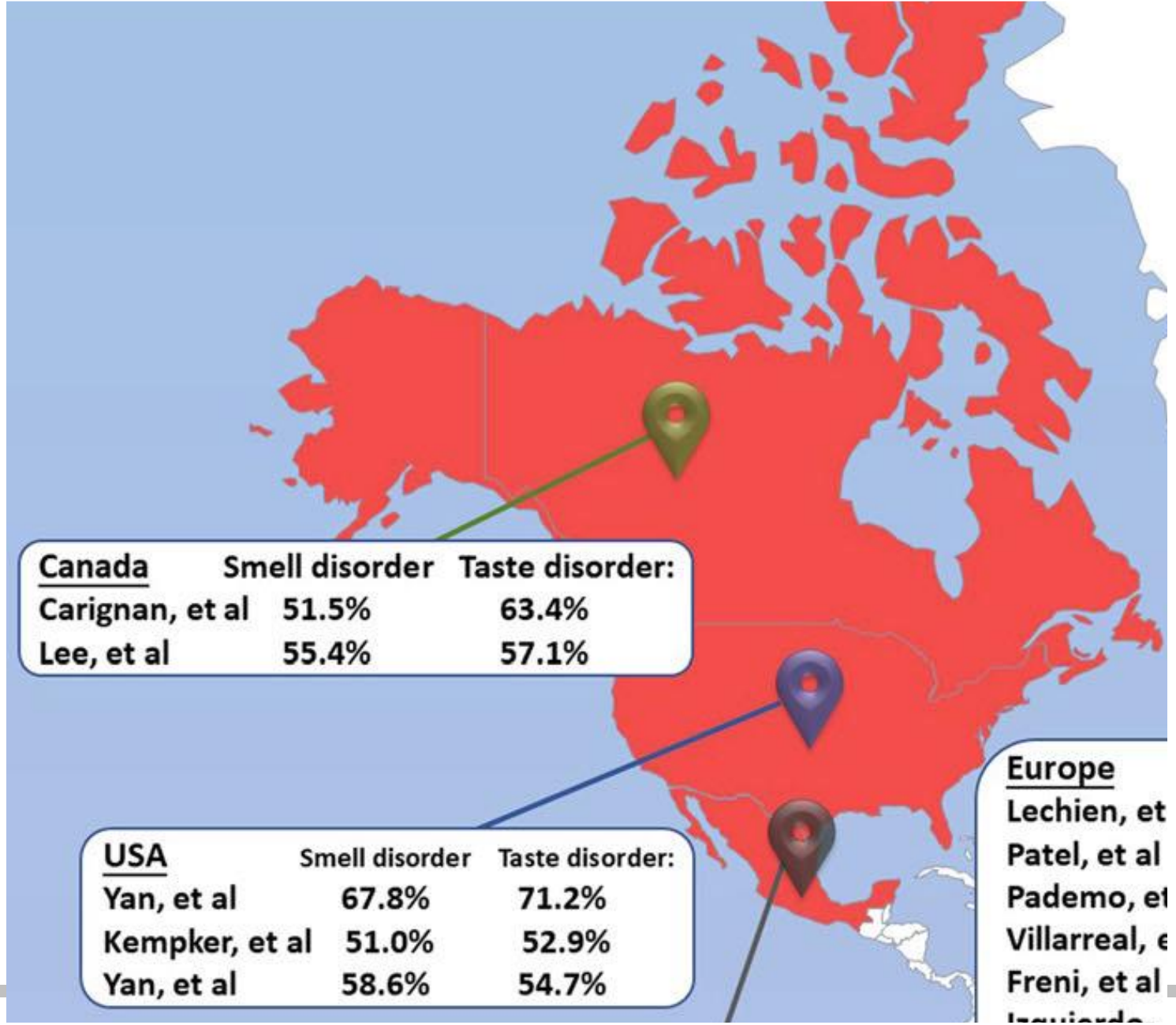
- Bacteria
- Fungi
- Rare organisms such as microfilaria

- Most commonly: respiratory viruses
  - Common cold (Rhinovirus and Adenovirus)
  - Influenza
  - And now: SARS-CoV-2

- Post-viral olfactory dysfunction/anosmia



M. Zeng. Current Allergy and Asthma Reports (2021) 21: 6



M. Zeng. Current Allergy and Asthma Reports (2021) 21: 6

Smell dysfunction is common in COVID-19, but many remaining questions

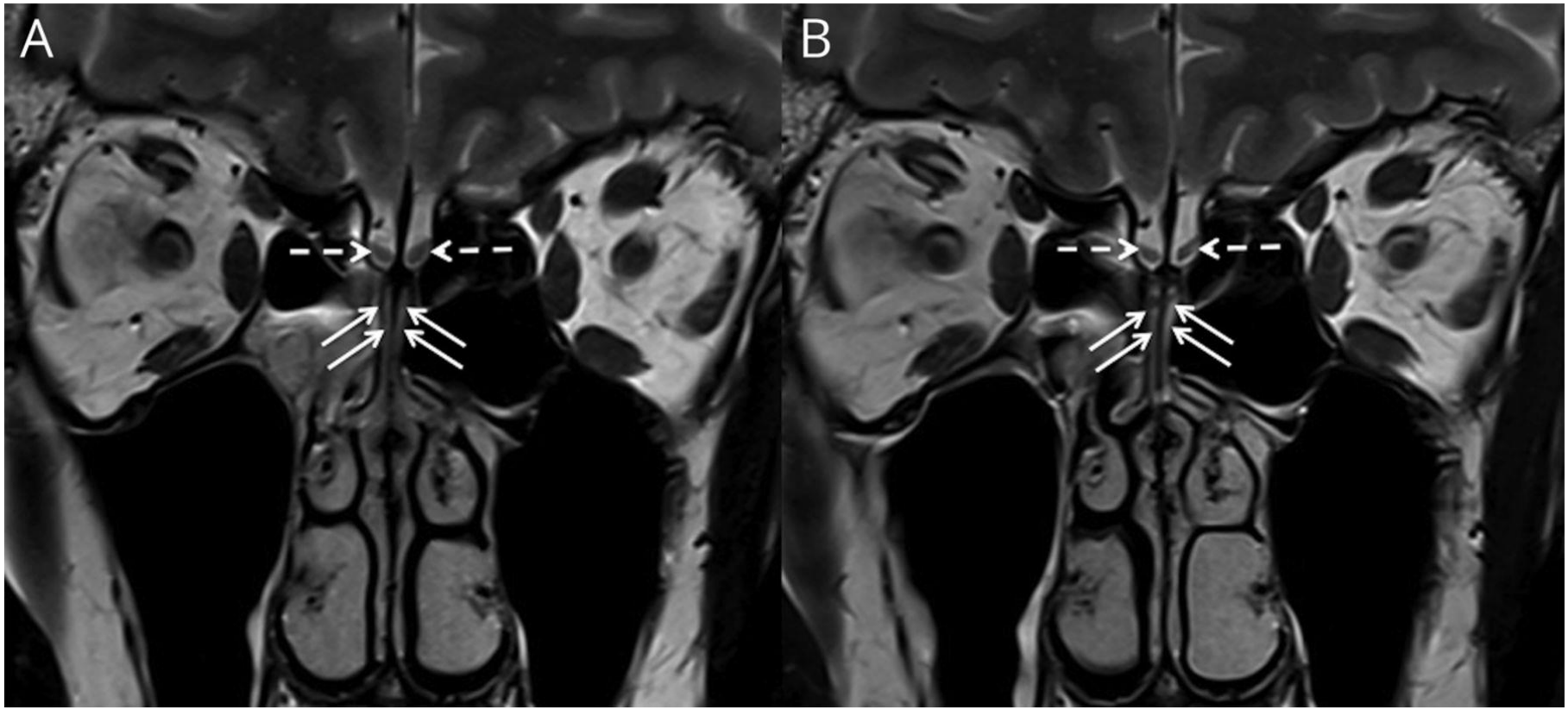
- Presence of decreased smell higher in Europe/North America vs. Asia
  - Differences in variants?
  - Differences in receptor genetic variation?
- Nearly all data is by self report (notoriously inaccurate)
- Some data show higher prevalence with objective testing:
  - 76 vs. 53%
- Confounded by disease context
  - Hospitalized vs. outpatient, sick vs. well
  - Confirmed disease vs. report
  - Many other factors
  - Cohort studies underway to study survivors with objective testing
  - Few prospective studies
    - UChicago cohort

KW Pang. Curr Allergy Asthma Rep. 2020;20(12).

Mechanisms for COVID-19 smell loss

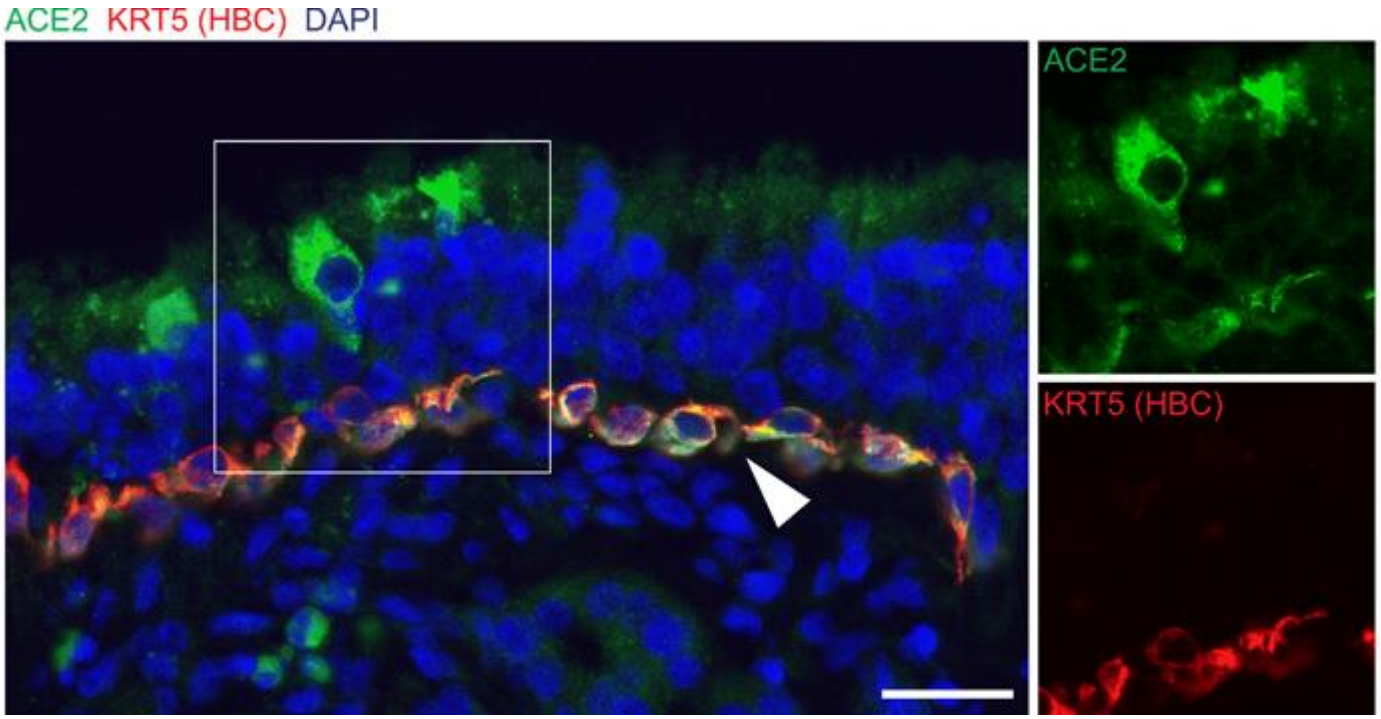
- ? sensorineural vs. conductive cause
- No correlation of olfactory severity with other symptoms
- Many patients have olfactory loss without other nasal symptoms
- Edema of the olfactory clefts (OC) on MRI
  - impair odorant access to the sensory epithelium
  - without obvious nasal obstruction
- IL-6 is associated olfactory neuron dysfunction
- Olfactory epithelium of COVID-19 patients in autopsy
  - prominent leukocytic infiltration
  - possible cause of neuritis and axonal damage of olfactory nerve

Wang H. Ann N Y Acad Sci. 2009;1170(1):596–603.
Kirschenbaum D. The Lancet. 2020;396(10245).



Michael Eliezer et al. Neurology 2020;95:e3145-e3152

Genomic studies show SARS-CoV-2 receptor expression on support cells, not olfactory neurons



ACE2 protein (green) is detected in sustentacular cells and KRT5-positive HBCs (red; white arrowhead). Nuclei were stained with DAPI (blue).

DH Brann. Sci Adv. 2020 Jul 31;6(31):eabc5801

Effects on regeneration

- Damage to the olfactory epithelium via olfactory sensory neuron apoptosis
- Inhibition of olfactory neurogenesis and thus poor recovery
- Transition to respiratory epithelium
- An important model of post-viral smell loss from SARS-CoV-2

Yee KK.. Am J Rhinol Allergy 2010;24:110–20.
Victores AJ. Int Forum Allergy Rhinol 2018;8:415–20.
DH Brann. Sci Adv. 2020 Jul 31;6(31):eabc5801

Treatment of COVID-19 olfactory dysfunction

- No pharmacologic treatments for post-viral smell loss
  - systemic steroids
  - intranasal steroids
- Smell training
- Supportive care
- Testing
  - Best chance of recovery at 1 year
  - Some recover event at 2-3 years
  - Objective testing allows better counseling
    - patient resilience/relief

Inflammatory disease and the sense of smell

- Sinonasal disease: one of the most common causes of olfactory impairment
- The prevalence of chronic sinusitis approaches 20 percent of US adults (defined by > 12 weeks of classic symptoms)
- The prevalence of allergic rhinitis is 10-30% in US, similarly high prevalence in industrialized countries
- For clinicians that treat olfactory disorders, this is an exciting area because the problem is reversible and we have treatments
- Thus, taking a ‘looking for the keys under the light’ approach, asking patients about inflammatory disease is a key first step in approaching patients with this problem

Loss of olfaction is a cardinal symptom in CRS

- 60-80% of patients report some form of olfactory dysfunction
  - Typically hyposmia, but can be dysosmias also
- Prevalence is high using objective testing
  - 67% using 40-item UPSIT
  - 78% using Sniffin' Sticks (TDI)
- Up to 25% of patients do not recognize the loss
  - Gradual nature?

Reden J. Eur Arch Otorhinolaryngol 2007;264:139–44.
Jiang R. Am J Rhinol 2008;22:445–8.
Soler ZM. Am J Rhinol 2008;22:297–301.

Key mechanism in CRS: Inflammation

- Consequently, factors that increase sinonasal inflammation are highly associated with olfactory impairment in CRS
- These include:
  - Smoking
  - Nasal polyposis (most severe form of CRS)
  - Asthma
  - Tissue eosinophilia

Litvack JR.. Am J Rhinol Allergy 2009;23:139–44.
Apter AJ. J Allergy Clin Immunol 1992;90:670–80.
Alt JA.. Laryngoscope 2014;124:259.
Frasnelli J, Hummel T. 2005;262:231–5.

Conundrum: conductive vs. sensorineural?

- Physical obstruction of the olfactory cleft by nasal polyp or mucosal edema impairs airflow to the olfactory cleft.
- However, increased tissue eosinophilia appears to have a local, damaging impact by release cytotoxic substances to the olfactory neuroepithelium.
  - Direct effects on olfactory neurons/support cells
  - Consistent with this, disease features which mark heightened inflammation are associated with higher rates of olfactory impairment
    - Serum eosinophilia
    - Asthma
- Other forms of inflammatory disease (CRS without nasal polyposis) affect the sense of smell less commonly (only 17% by objective testing) and less severely
  - Less responsive to medical therapy

Alt JA.. Laryngoscope 2014;124:259.
Frasnelli J, Hummel T. 2005;262:231–5

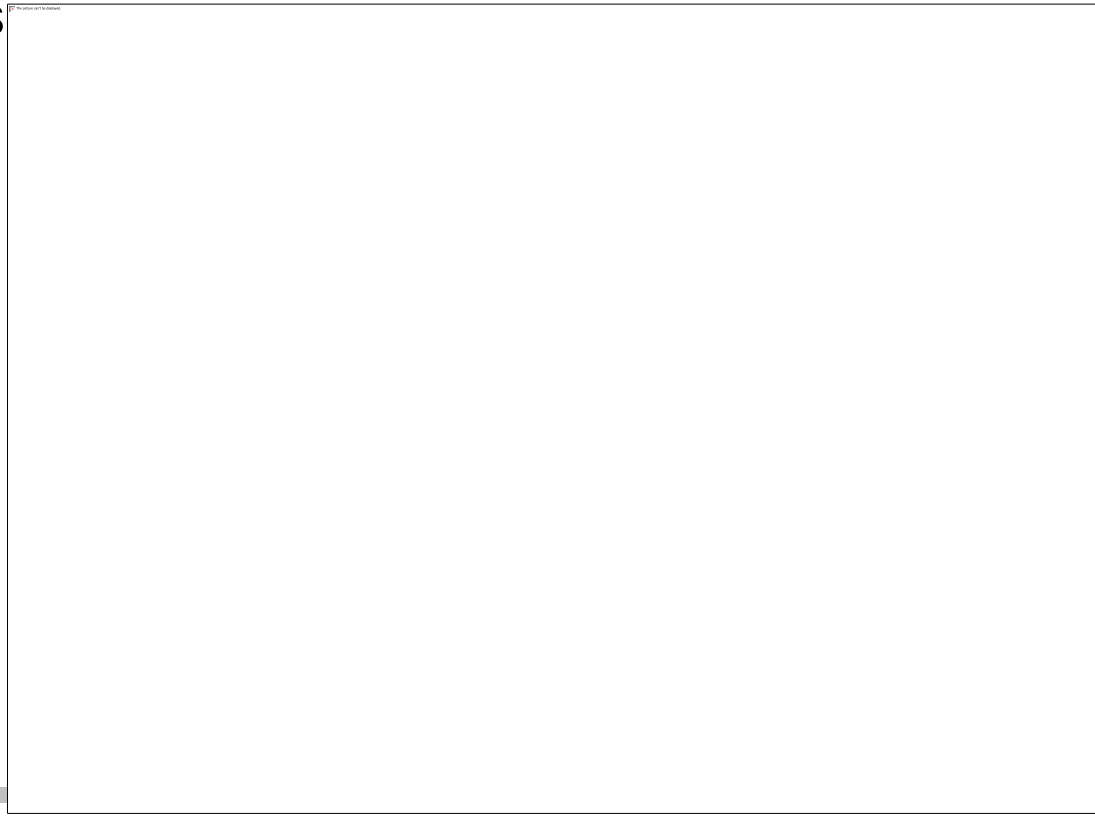
How does CRS cause olfactory impairment?

- Both conductive and sensorineural components
  - Decreased odorant signaling, reduced detection of odors
- Specific inflammatory mediators appear important
  - Eosinophils and their products (ECP, etc.)
  - Cytokines: IL-2, IL-5, IL-6, IL-10, and IL-13
- This inflammatory environment may stimulate the intracellular tumor necrosis factor-a/c-Jun-N-terminal kinases pathway
  - Deleterious effects on neuronal function
  - Leads to apoptosis and cell death
  - Inhibition of this pathway may have neuroprotective effects
- Structural effects on the olfactory system
  - Decrease in size and function of the olfactory bulb (similar to post viral anosmia)
  - Cause or effect?

Hummel T. Rhinology 2016;56:1–30; Kern RC. Laryngoscope 2000;110:1071–7. Yee KK.. Am J Rhinol Allergy 2010;24:110–20.' Stevens MH. Laryngoscope 2001;111:200–3; Wu J,. Laryngoscope 2018;128: E304–10; Victores AJ. Int Forum Allergy Rhinol 2018;8:415–20; Rombaux P. Rhinology 2009;47:3–9.

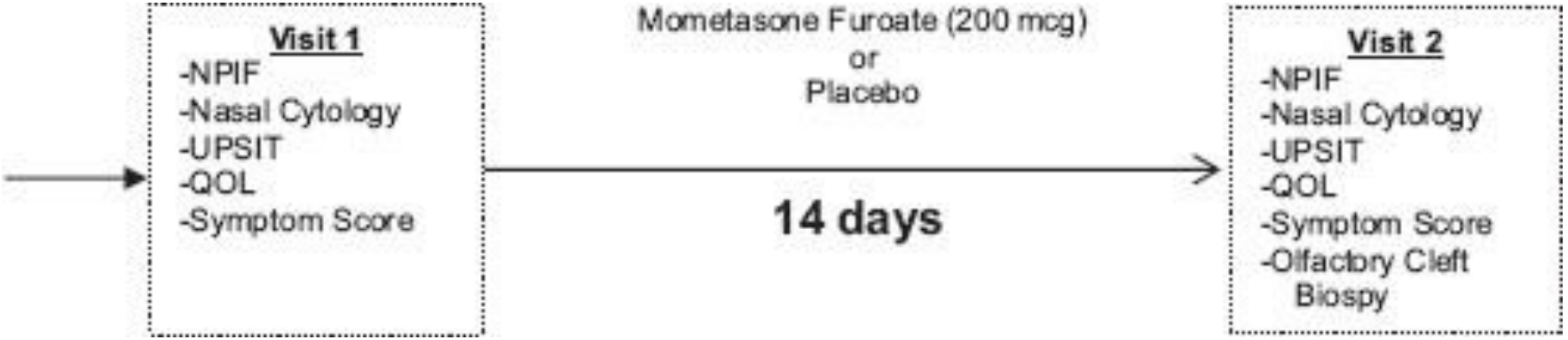
Assessing what's happening in the olfactory cleft

- Mucus from sampled from patients with CRS and controls
- Proteome measured by liquid chromatography and mass spectrometry
- Pathway enrichment analysis
- Significant differences were found between patients with normosmia and those with dysosmia for a number of **odorant binding proteins** and **metabolizing enzymes**



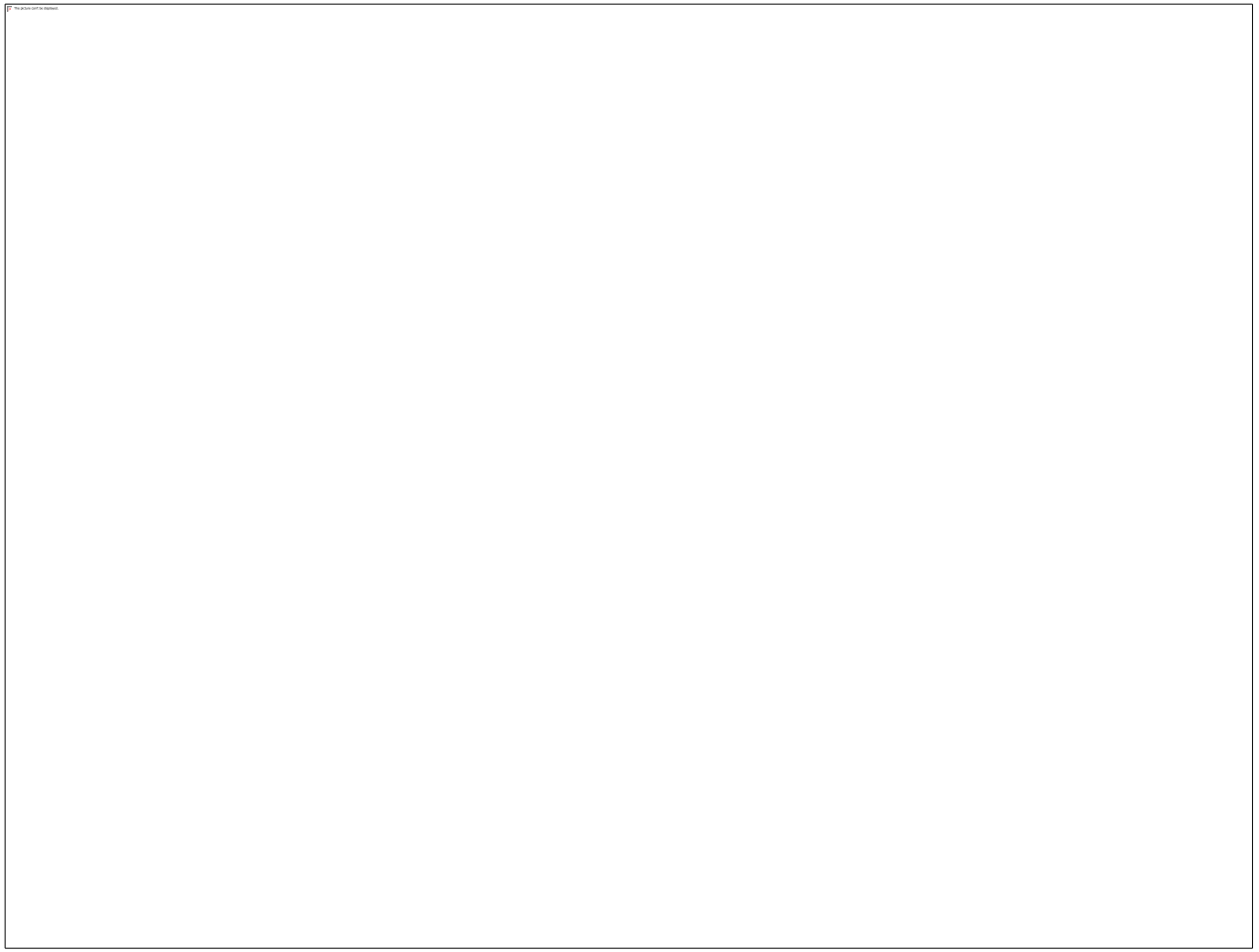
Soler ZM. Int Forum Allergy Rhino 2021.

Do intranasal steroids affect the olfactory cleft in allergic rhinitis?



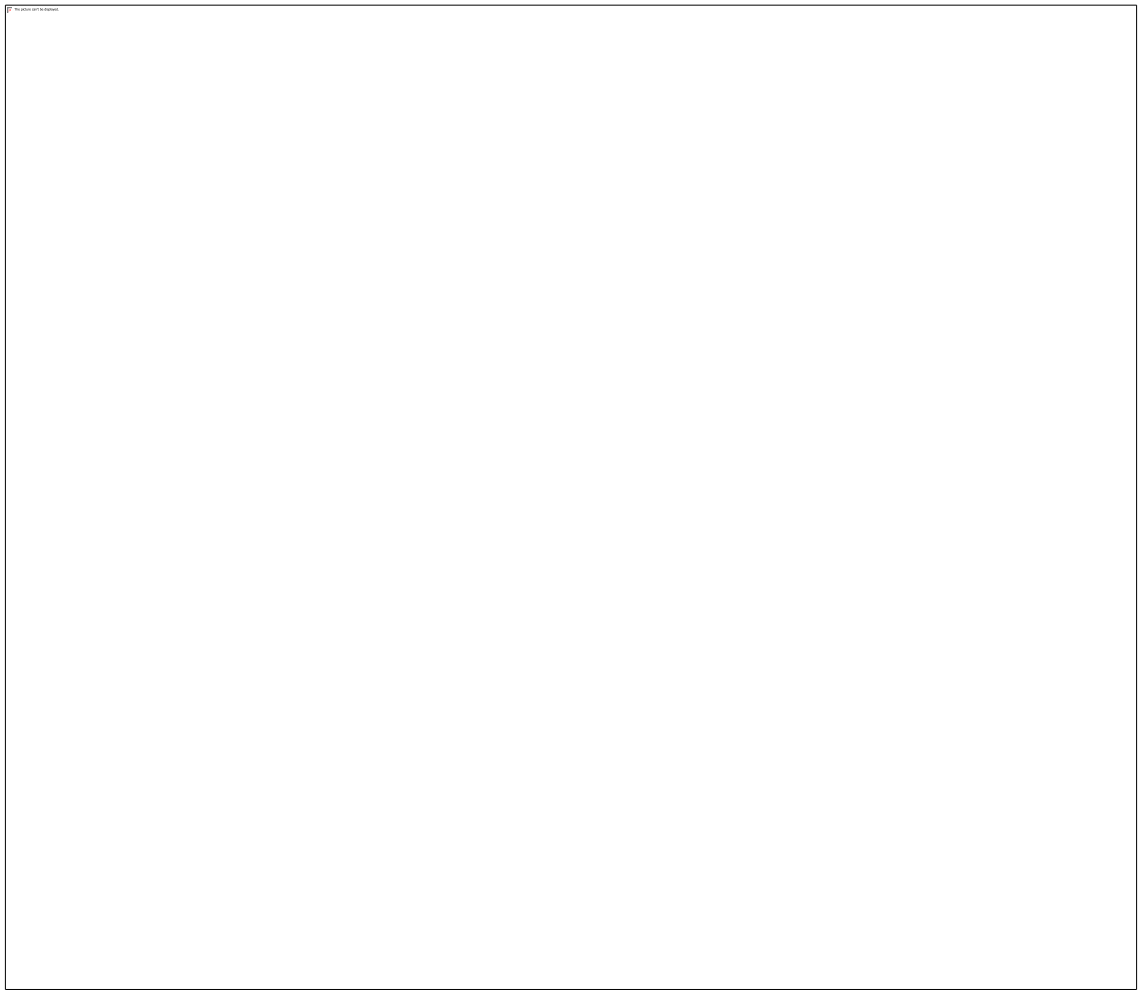
A. Sivam. AJRA. Jul-Aug 2010;24(4):286-90.

A. Sivam. AJRA. Jul-Aug 2010;24(4):286-90.



A. Sivam. AJRA. Jul-Aug 2010;24(4):286-90.

Similar results in CRS when examining superior turbinate eosinophilia



BK Tan. Laryngoscope. 2017 Oct; 127(10): 2210–2218.

Machine learning as a tool to study predictors of olfactory function in CRS

- Examination of 4 ML methods used to analyze 611 adults with CRS in a prospective, multi-institutional, observational cohort study
- Predictors included: objective disease measures (CT and endoscopy scores), age, sex, prior surgeries, socioeconomic status, steroid use, polyp presence, asthma, and aspirin sensitivity
- In a prospective cohort study, 37 parameters from four categories were recorded from 60 men and 98 women before and four months after endoscopic sinus surgery
  - endoscopic measures of nasal anatomy/pathology, assessments of olfactory function, quality of life, and socio-demographic or concomitant conditions. Parameters containing
- Changes in the endoscopic Lildholdt score allowed separation of baseline from postoperative data accurately.
- Another method of analyzing complex data!

VR Ramakrishnan. Chemical Senses. September 2021. Jörn Lötsch . J Clin Med. . 2021 Sep 18;10(18):4245..

Workup of olfaction in the context of CRS

- Subjective measures
  - Visual analogue scales
  - Sinonasal outcome test (SNOT-22)
  - Rhinosinusitis disability index (RSDI)
  - Olfactory-specific, QOL measures
    - Questionnaire of olfactory disorders-negative statements (QOD-NS)
    - Good internal consistency and test-retest
- But, essentially all are subjective measures
  - Poor correlation with testing
- Psychophysical testing is the gold standard (discussed in other parts of this meeting)
  - Orthonasal is common

Hummel T. Position paper on olfactory dysfunction. Rhinology 2016;56:1–30.

Novel measures: Imaging

- Imaging of the olfactory cleft/olfactory bulb can be helpful diagnostic tools to assess olfactory dysfunction in CRS
- Computed tomography (CT) imaging is a standard tool to assess sinonasal mucosal inflammation in patients with CRS and plan surgery
  - The degree of radiologic opacification in the olfactory cleft on CT correlates with the degree of olfactory loss in CRS
  - Stronger in patients with CRS with nasal polyposis compared those without
- Other methods of assessing olfactory cleft inflammation: validated endoscopic scoring system that reliably correlates with objective olfactory function
  - Easily performed in routine evaluations for patients with CRS

Kohli P. Am J Rhinol Allergy 2016;30:402–6.
Soler ZM. Int Forum 2016;6:293–8.

Imaging the olfactory system in CRS

- MRI is useful for viewing the central olfactory system
  - Detailed imaging of the olfactory apparatus: the olfactory bulb (OB), olfactory tract, sulcus, and the central olfactory projection areas
- OB size correlates with olfactory loss in patients with CRS
- This appears to be plastic: changes in size of the OB in accordance with the current olfactory status in patients with CRS
  - Patients with CRSwNP undergoing endoscopic sinus surgery (ESS) had objectively improved olfaction and postoperative increase in olfactory bulb volume size
  - Some hope!

Gudziol V. Brain 2009;132: 3096–101.
Rombaux P. Rhinology 2009;47:3–9.

Patients with CRS with severe olfactory dysfunction show differences in central olfactory regions

Reduced GMV in the gyrus rectus, orbitofrontal cortex, thalamus, and the insula.

Pengfei Han, IFAR 2017 Jun;7(6):551-556.

Outcomes of olfaction with medical therapy

- Meta-analysis of randomized controlled trials (RCTs) evaluating olfactory outcomes after oral steroid treatment in patients with CRSwNP
- 4 RCTs found that a subjective improvement in olfaction compared with placebo out to 6 months max, so durability of response could not be assessed
- 2 RCTs demonstrated short-term smell improvement with a 2-week follow-up
- Evidence also suggests that the degree of olfactory response following the use of oral glucocorticoids correlates with the degree of olfactory improvement following ESS
- These medicine have major side effects in the long term, however,
- One protocol is oral steroids, followed by topical
- New steroid delivery systems and biologics offer new opportunities

Gudziol V. Brain. 2009;132: 3096–101.
Banglawala SM. Int Forum Allergy Rhinol 2014;4:986–94.
Alobid I. Ann Intern Med 2011;154:293–302.
Alobid I. Rhinology 2006;44:8–13.
Kroflic B/ Eur Arch Otorhinolaryngol 2006;263: 767–71.

New treatments for CRS that improve olfaction

- Novel steroid delivery systems
  - Optinose (Xhance)
- Biologics
  - Anti-IL4Rα (Dupilumab)
  - Anti-IgE (Omalizamab)
  - Anti-IL-5 (Mepolizumab)
  - Anti IL-5Rα (Benralizumab)
  - Others coming:
    - Anti-TSLP (Tezepelumab)

Outcomes with surgery

- Functional endoscopic sinus surgery for CRS results in improved olfaction as measured objectively
  - Greatest improvement for women, patients with nasal polyps, and those with aspirin intolerance
  - Consistent with greatest improvement with increased T2 immune responses
- Similar olfactory related quality of life improvements
  - Soler demonstrated a significant improvement in postoperative QOD-NS scores.
  - Baseline severity of disease scores by imaging predicted postoperative changes in QOD-NS scores
- A recent meta-analysis demonstrates postoperative improvements in measures of olfaction in 23/24 studies
  - either objective or subjective testing
- These results vary by patient factors, extent of disease, extent of surgery, differences in postoperative treatment, and others

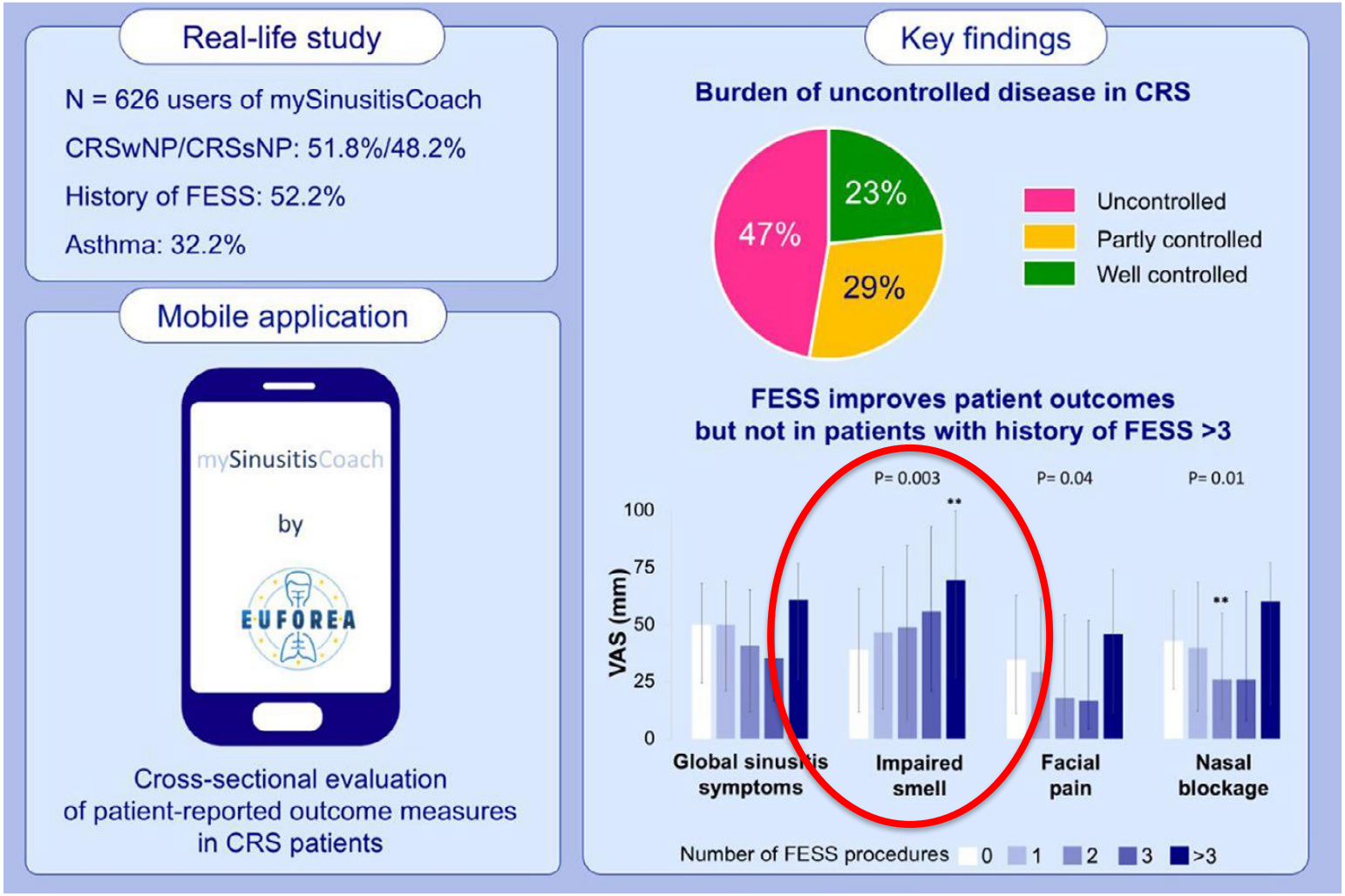
Minovi A. Eur Arch Otorhinolaryngol 2008;265:57–61; Ling FTK. Laryngoscope 2007;117:1090–3; Haxel BR. Laryngoscope 2019;129:1053–9; Randhawa PS. Clin Otolaryngol 2016;41:15–20; Schriever VA. Eur Arch Otorhinolaryngol 2013;270:107–11;

Results after sinus surgery

- Improvement of olfaction specific QoL was also established in a multi-center prospective study
- Preoperative lesions in the olfactory cleft are associated with poor olfactory outcomes
- Overall, 65% will realize a clinically meaningful improvement in QoL after ESS
- Patients undergoing their first sinus surgery are twice as likely to improve as patients undergoing revision

Smith TL. Otolaryngol Head Neck Surg. 2010;142(1):55–63.
Soler ZM. Int Forum Allergy Rhinol. 2016;6(4):407–13.
Akiyama K. Int Forum Allergy Rhinol. 2020;10(2):208–216.
Hopkins C. Laryngoscope. 2015;125(8):1779–84.

New data collection tools: MySinusitisCoach



Sven F. Seys. Allergy. 2020 Nov;75(11):2867-2878

Comparison of medical versus surgical management

- Deconde examined 281 medically refractory CRS patients who were candidates for ESS.
- 20% of patients elected to continue medical management, whereas 80% chose to undergo ESS
- Both groups experienced statistically significant improvement in objective testing for olfactory dysfunction
- Prior ESS was the only risk factor associated with failure of postoperative olfaction
  - An indicator of refractory disease, elevated inflammation, or consequence of surgery?

DeConde AS. Int Forum Allergy Rhinol 2014;4:725–33.

Conclusions

- We can exploit our ability to manipulate disease in patients with CRS to study olfaction in humans
- New tools (therapies, surgeries, technologies, analytic methods) offer the ability to improve our ability to reverse olfactory dysfunction in these patients
- Human disease may be a model to under how inflammation affects the olfactory systems
- Perhaps we can use this information to design therapies for other forms of olfactory disorders

Acknowledgments

The University of Chicago
The Olfactory Research Group (The ORG)

Psychology/Comparative Human Development
Martha K. McClintock

Public Health Sciences
Kristen E. Wroblewski
L. Philip Schumm

Geriatrics/Palliative Care
Megan Huisingh-Scheetz
William Dale (now City of Hope)

Pritzker School of Medicine
Yazan Eliyan
Matthew GoodSmith

Otolaryngology-Head and Neck Surgery
Dara Adams

Boston University
Jennifer Weuve

Rush University
David A. Bennett

Michigan State University
Honglei Chen

Funding
NIA: AG030481, AG036762, AG029795
NIEHS: ES022657

THE UNIVERSITY OF
CHICAGO
MEDICINE &
BIOLOGICAL
SCIENCES