Université de Montréal

*The association between physical activity parameters and olfactory function*

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*Ce mémoire intitulé*

***The association between physical activity parameters and olfactory function***

*Présenté par*

**Khoosheh Namiranian**

*A été évalué par un jury composé des personnes suivantes*

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# Résumé

Le système olfactif a un impact significatif sur la qualité de vie. Une diminution de l'odorat peut influencer la santé physique et mentale des individus, or l'activité physique (AP) pourrait améliorer la fonction olfactive. Cette thèse vise à déterminer l'association entre AP et l'olfaction et si la durée, la fréquence et le volume de l'AP d'intensité moyenne à élevée pouvaient être liés à la fonction olfactive chez l'adulte.

Les données (n = 3527) ont été extraites de l'enquête américaine *National Health and Nutrition Examination Survey* (NHANES) de 2013-2014. L'étude comprenait des participants qui ont rempli à la fois le questionnaire autodéclaré sur le niveau d'AP et des tests d'odeur (chocolat, fraise, raisin, oignon, fumée, gaz naturel, cuir et savon). L'association entre l'olfaction et les paramètres d'AP a été évaluée à l'aide de corrélations et de régressions logistiques, rapportées ici sous forme de d'intervalles de confiance (IC) à 95 % et de rapport de cotes (RC). La valeur $p \leq 0,05$ était considérée comme statistiquement significative.

En analysant l'association entre les paramètres de l'AP et le score olfactif total, il a été montré une corrélation positive avec la durée, la fréquence de l'AP modérée et la fréquence de l'AP vigoureuse, ainsi que le volume total de l'AP (tous $p \leq 0,05$). La durée, (intervalles de 10 min/jour), une fréquence (jour/semaine) et un volume (METs*h/semaine) plus élevés d'AP modérée étaient associés à une plus grande capacité à détecter les odeurs de raisin [1,002< RCs <1,047, IC95 % (1,000 -1,082), p=0,007]. La fréquence des AP modérées était positivement associée à la capacité à identifier les odeurs de fumée [RC =1,074, IC 95% (1,019-1,131), p=0,008] et de cuir [RC =1,060, IC 95% (1,019-1,103), p= 0,004]. De plus, la fréquence des AP vigoureuses était positivement associée à la détection de l'odeur de raisin [RC = 1,002, IC 95 % (1,000-1,005), p = 0,028]. D'après ces résultats, les paramètres du PA sont liés à la capacité de détection de certaines odeurs, principalement pour l'AP modérée. Cependant, il faut considérer que l'effet constant de l'AP sur les chances de détecter correctement les odeurs est son meilleur de 7.4%. Par conséquent, ces résultats pourront être utilisés par d'autres chercheurs et kinésiologues pour explorer comment améliorer les troubles olfactifs à l'avenir. En ce sens, l'AP d'intensité modérée pourrait particulièrement être recommandée pour la prévention et le traitement des certains troubles olfactifs.

**Mots clés :** Activité physique, Durée, Fréquence, Intensité, Maladie, Odeur, Olfaction, Volume.

# Abstract

The olfactory system has a significant impact on the quality of life. A decrease in the sense of smell may influence individuals' physical and mental health, and physical activity (PA) might improve olfactory function. This thesis aimed to determine the association between PA and olfaction and whether the duration, frequency, and volume of moderate to vigorous PA could be related to the olfactory function in adults.

The data (n=3527) were extracted from the U.S. National Health and Nutrition Examination Survey (NHANES) 2013-2014. The study included participants who completed both self-reported PA questionnaire and smell tests (chocolate, strawberry, grape, onion, smoke, natural gas, leather, and soap). The association between olfaction and PA parameters was assessed using correlations and logistic regressions, reported here as Odds-Ratio (OR) and 95% confidence intervals (CI). P-value ≤0.05 was considered statistically significant.

In analyzing the association between PA parameters and total smell score showed a positive correlation with the duration, frequency of moderate and frequency of vigorous PA, as well as PA total volume (all p≤ 0.05). Higher duration (bouts of 10min/day), frequency (day/week), and volume (METs*h/week) of moderate PA was associated with a higher ability to detect the smells of grapes [1.002<ORs<1.047, CI95% (1.000-1.082), p=0.007]. The frequency of moderate PA was positively associated with the capacity to identify smoke [OR =1.074, CI 95% (1.019-1.131), p=0.008] and leather [OR =1.060, CI 95% (1.019-1.103), p=0.004] odors. Furthermore, the frequency of vigorous PA was positively associated with the detection of grape smell [OR =1.002, CI 95% (1.000-1.005), p=0.028]. As a result of these findings, PA parameters are associated with the ability to detect some odors, mostly moderate PA. However, it should be considered that the constant effect of PA on the chance of correctly detecting the smells is his best at 7.4%. Therefore, these results could be used by other researchers and kinesiologists to improve olfactory disorders in the future. Moderate-intensity PA could especially be recommended for the prevention and treatment of some olfactory disorders.

**Keywords**: Disease, Duration, Frequency, Intensity, Olfaction, Physical activity, Smell, Volume.

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# List of acronyms and abbreviations

PA: Physical Activity

NHANES: U.S. National Health and Nutrition Examination Survey

kg: Kilograms

METs: Metabolic Equivalents

COVID-19:  Coronavirus disease - 19

OR: Odds-Ratio

CI: Confidence Intervals

*To my parents, who taught me to be hardworking.*

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In closing, I would like to express my gratitude to my family, who have always supported me and taught me many things.

# Chapter 1 – [Introduction]

High quality of life is associated with a healthy olfactory system.(Auffarth 2013, Elkholi, Abdelwahab et al. 2021) (Smeets, Veldhuizen et al. 2009). Sense of smell influences both the taste and the enjoyment of food and drink (Smeets, Veldhuizen et al. 2009, Boesveldt and de Graaf 2017, Doty 2019). In addition to being vital for nutrition, social interactions, emotions, and memory formation, the smell is essential in protecting against environmental hazards (Boesveldt and de Graaf 2017). The elderly are more susceptible to olfactory impairment, gas poisoning, cooking accidents, and rotten food consumption as they age(Doty and Kamath 2014). Also, those who suffer from smell dysfunction have difficulties enjoying food and drinks, socializing, and forming intimate relationships (Smeets, Veldhuizen et al. 2009). As a result, smell loss or dysfunction significantly impacts our physical, mental, and emotional well-being, as well as safety (Doty and Kamath 2014, Doty 2019).

Over 200 000 physician visits are attributed to olfactory dysfunction in the United States every year, representing a considerable public health burden (Choi, Jang et al. 2021). A cross-sectional study in the United States showed that about half of the population between the ages of 65 and 80 has olfactory dysfunction. Over the age of 80, approximately three-quarters experience a loss of smell (Doty and Kamath 2014). A 2003 European study reports that over 82 million European citizens over the age of 15 suffer from olfactory dysfunction, and 1.5 million have completely lost their sense of smell (Mullol, Alobid et al. 2012, Mullol, Alobid et al. 2020). Also, in a cross-sectional population-based survey of 1387 adults from 20 to 80 years in Sweden, 19.1% were diagnosed with olfactory dysfunction (Brämerson, Johansson et al. 2004). Furthermore, in 1176 patients aged 5 to 86 years referred to an outpatient ear, nose, and throat clinic in Germany, slightly more than 20% were diagnosed with olfactory dysfunction (Landis, Konnerth et al. 2004). In addition greater degree of olfactory loss was observed during the recent COVID-19 pandemic than in previous years (Moein, Hashemian et al. 2020). A recent meta-analysis identified that 45% of COVID-19 patients had olfactory dysfunction (Kandemirli, Altundag et al. 2021). As a result, due to the relatively high prevalence of olfactory disorders in different countries, further studies are required regarding the etiologies and treatments for olfaction impairment.

Various methods have been studied to improve olfactory function and treat dysfunctions (DeVere 2017). Medications such as corticosteroids effectively help olfactory recovery (Shu, Lee et al. 2012), and antibiotics are commonly recommended in treating olfactory disorders, especially in patients with chronic rhinosinusitis (Ramakrishnan, Mace et al. 2017). There is also evidence that caroverine, used in tinnitus (ringing in the ears), helps treat patients with olfactory disorders. A study on 51 patients showed that caroverine treatment improves odor identification in anosmia patients (Quint, Temmel et al. 2002). Supplements can also be effective in enhancing olfactory disorders. For example, there is a theory that due to the role of free calcium in the nasal mucous layer in smell function, separating such free calcium and use as a supplement might strengthen the olfactory signal and enhance olfactory performance (Hummel, Whitcroft et al. 2017, Doty 2019). In addition, vitamin A has been suggested as a possible treatment for secondary olfactory reduction (Rawson and LaMantia 2007). Vitamin D can also be involved in the brain's proliferation and differentiation of olfactory neurons (Nair, Maseeh et al. 2012). Also, systematic exposure to odorants, called “olfactory training”, may be of benefit to some persons with hyposmia (reduced sense of smell) or anosmia (loss of sense of smell) (Patel, head et al. 2017, Sorokowska, Drechsler et al. 2017, Doty 2019). In addition to improving olfactory function, PA has also been proposed as a treatment or prevention method (Zhang, Li et al. 2020) for improving brain function or general health (Schubert, Cruickshanks et al. 2013).

To date, some studies suggested that exercise may positively affect olfactory function (Manestar, Tićac et al. 2013, Rosenfeldt, Dey et al. 2016). For example, exercising, such as Taiji (tai chi), dancing, or running, improves performance and odor identification (Schubert, Fischer et al. 2017, Zhang, Li et al. 2020). Another study found that older people who exercised three times a week had a lower risk of developing olfactory disorders (Schubert, Cruickshanks et al. 2013). Even so, the number of studies remains limited in this field on the association between PA and the detection of different odors. There is a necessity for a better understanding of how PA can help improve the functioning of the olfactory system and can be integrated into the treatment of olfactory diseases and disorders. Therefore, given the importance of the olfactory system for human health, the present thesis investigated in great detail the relationship between PA and the function of the olfactory system.

The present thesis is based on a secondary analysis of data collected from the 2013−2014 cohort of the U.S. National Health and Nutrition Examination Survey (NHANES), an organization whose mission has been to assess a health and nutrition status sample of the US population. The NHANES is a multidisciplinary health examination and a context designed explicitly for data collection with sensory testing (NHANES 2021). The general objective is to investigate the association between subcomponents of PA and human olfactory function.

The thesis is organized as follows. The second chapter provides an overview of the olfactory system and olfactory disorders, as well as how PA affects olfactory disorders, then focuses on the specific objectives of the thesis. Chapter 3 presents a scientific article about the associations between duration, frequency, intensity, and total volume of PA and olfaction. The general discussion and conclusion are presented in Chapters 4 and 5, respectively.

# Chapter 2 – [Literature review]

Chapter 2 presents the current knowledge about olfaction, including the potential influence of different parameters of PA, that is the duration, frequency, intensity, and volume of PA on olfactory function. The first part of this chapter presents a comprehensive, summary, and objective analysis of the olfactory mechanisms, types of olfactory disorders, and the effect of PA on olfactory disorders. In more detail, this section explains the olfactory system's mechanism it focuses on examining olfactory disorders and damage caused by age, gender, and diseases affecting the central nervous system, olfactory transmission, olfactory memory, and hallucinations, olfactory epithelium, the hormones affecting the olfactory function, and nerve damage affecting the olfactory function. Then, the effect of PA on some olfactory disorders is examined.

## 2.1 The olfactory function and olfactory impairments

The olfactory function is essential in humans due to its association with social life, health, and eating ability (Zhou, Lane et al. 2019). An impaired olfactory function can result in nutritional and safety risks, such as the inability to recognize gas leaks, smoke, and spoiled food (Desiato, Levy et al. 2021). Olfactory dysfunction is also associated with decreased quality of life (Schubert, Cruickshanks et al. 2015, Hummel, Whitcroft et al. 2017, Schubert, Fischer et al. 2017).

The olfactory system is a part of human physiology that is responsible for the sense of smell. The human olfactory system's first part is the nose's outer part and the inner nasal cavity. The nose consists of two separate passages, from where the inhaled air is transported to the nasal mucosa through the respiratory cilia (Doty and Kamath 2014). Then, the odorant molecules in the blown air in the mucous membrane cover the olfactory epithelium and stimulate this part. The mucous membrane covering the olfactory epithelium is located in the upper and posterior part of the nasal cavity, which contains bipolar olfactory cells, known as olfactory receptor cells. The arrangement of bipolar olfactory cells is such that their dendrites are located in the olfactory epithelium, their axons are extended toward the olfactory bulb (Sankaran, Khot et al. 2012, DeVere 2017), and the surrounding axons are covered with the meningeal sheath and glial cells. Meningeal sheaths and glial cells prevent nerve damage by creating a membrane sheath around axons (Anderson 1969, Lakatos, Smith et al. 2003). Then, the olfactory cell synapses with the glomeruli of the outermost area of the olfactory bulb at the base of the brain, and the olfactory information is distributed to different brain parts, such as the nucleus accumbens and the anterior olfactory cortex (Doty 2009, Desiato, Levy et al. 2021). In the brain, the nucleus accumbens functions as an interface between motivation and odor response (Okun, Mann et al. 2007). The anterior olfactory cortex is for olfactory perception (Shepherd 2006). In some cases, it is possible to transmit olfactory information by extracellular diffusion or convection in compartments associated with olfactory nerve bundles, such as the olfactory subarachnoid space of the cerebrospinal fluid or into the olfactory bulb (Lochhead and Thorne 2012). The transport mechanism of the odorant from the nose to the brain is summarized in Figure 1 (Selvaraj, Gowthamarajan et al. 2018). Disorders in any part of the olfactory system can cause complete loss of smell (anosmia), incomplete loss of smell (partial anosmia, hyposmia, or microsomia), distortions (parosmia or dysosmia), or spontaneous sensations (phantosmia) (Doty 2009).

Epidemiological studies have shown that olfactory dysfunction is prevalent between 1.4 and 62.4% in a healthy population (Desiato, Levy et al. 2021). Olfactory disorders can be caused by physiological factors such as age and gender, as well as can be caused by damage to different parts of the olfactory system, malfunctioning hormones, or nerve damage. Also, these disorders can affect the central nervous system and impair olfactory memory (Hawkes and Doty 2018). The following section describes and reviews diseases and disorders with loss or reduction of smell as common symptoms.

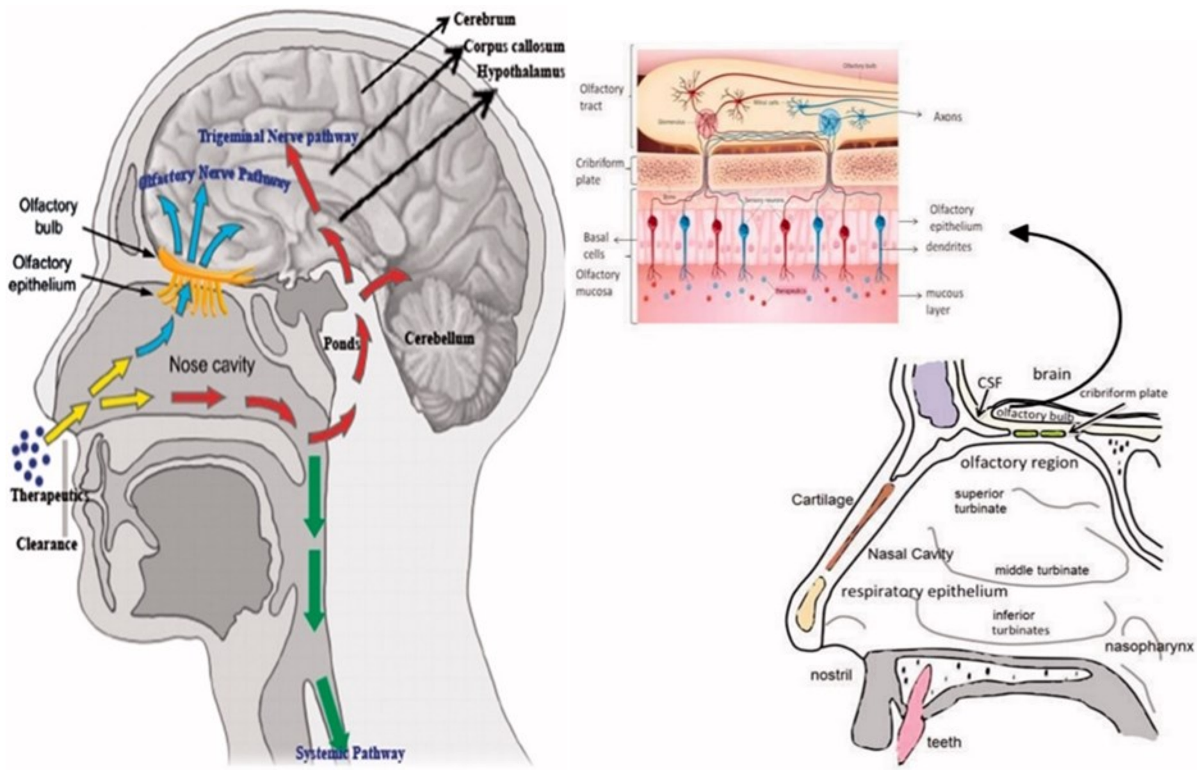


Figure 1. – (left) The transport mechanism of therapeutics from nose to brain and (right) the olfactory pathway after nasal administration (Selvaraj, Gowthamarajan et al. 2018) with permission.

### 2.1.1 Age affecting the olfactory function

Epidemiological studies have shown that olfactory performance worsens with age (Kondo, Kikuta et al. 2020), especially at 60 and above (Murphy, Schubert et al. 2002, Conley, Robinson et al. 2003, Richard, Taylor et al. 2010, Suzukawa, Kondo et al. 2011, Schubert, Cruickshanks et al. 2012, Kondo, Kikuta et al. 2020) In a human study and chemosensory assessments among 1,281 participants aged 40 years and older in the 2011-2014 NHANES protocol, it was found that olfactory impairment is prevalent among older adults [4.2 % (40–49 years), 12.7 % (60–69 years), and 39.4 % (80+ years)] (Hoffman, Rawal et al. 2016, Choi, Jang et al. 2021). Also, in a study on 2,234 people aged 60 to 90 in Stockholm, Sweden, who examined olfactory disorders through standard olfactory tests and self-assessment, a high prevalence of olfactory disorders was observed in both methods among the participants (Seubert, Laukka et al. 2017). This shows that with increasing age, there are changes in the olfactory nervous system that reduce the ability to smell. According to animal studies conducted in this field, it has been determined that the reduction in smell ability is affected by aging (Kondo, Kikuta et al. 2020). In this context, in the olfactory pathway, the blood circulation between the neurons of the olfactory bulb is reduced, and the activity in the olfactory cortex is reduced under olfactory stimulation (Richard, Taylor et al. 2010, Kondo, Kikuta et al. 2020). Also, increasing age causes a decrease in neuronal proliferation and the loss of mature olfactory neurons in the olfactory neuroepithelium in the nasal cavity (Conley, Robinson et al. 2003, Suzukawa, Kondo et al. 2011). Therefore, age can be associated with an increase in smell disorders.

### 2.1.2 Sex affecting the olfactory function

Olfactory disorders are associated with sex and most studies have shown that males have a higher risk of reduced ability to smell and detect odors (Kondo, Kikuta et al. 2020). According to Doty et al. (1984) who investigated the olfactory identification ability in 1955 persons ranging in age from 5 to 99 years using the Pennsylvania smell identification test, they found that women outperformed men at all ages (Doty, Shaman et al. 1984). Also, another study on older adults aged 60–90 years in Stockholm, Sweden, has demonstrated that the female gender is linked to a lower probability of olfactory disorder (Seubert, Laukka et al. 2017). NHANES 2011-2014 found that men are more likely than women to have olfactory dysfunction based on chemosensory assessments of 1,281 participants (Hoffman, Rawal et al. 2016). Moreover, a study on 12-15-year-old children with COVID-19 who suffered from anosmia and hyposomia found that boys displayed significantly higher disturbances than girls (Concheiro-Guisan, Fiel-Ozores et al. 2021). It is unclear why gender influences olfactory function, but social, hormonal, or genetic factors may be involved (Altundag, Tekeli et al. 2015). In this way, brain imaging findings of females suggested that discrimination of odor quality activates the same neural areas as working memory functions (Savic, Gulyas et al. 2000). So, it showed that women are superior in odor identification. In addition, it has been observed that women are highly sensitive during ovulation (Öberg, Larsson et al. 2002). Thus, the olfactory ability is related to sex, and research suggests women perform better than men.

### 2.1.3 Diseases affecting the olfactory epithelium and bulb

The olfactory epithelium and olfactory bulb, which contain olfactory receptor neurons inside the nasal cavity, play the most important role in olfactory function. The olfactory epithelium is involved in processing olfactory information, and the olfactory bulb is in the sense of smell (Choi and Goldstein 2018). Diseases and external factors can affect the olfactory function by disrupting the function of the epithelium and the olfactory bulb (Ruan, Zheng et al. 2012).

Decreased thyroxine in hypothyroidism can reduce the number of cells in olfactory bulbs, resulting in olfactory dysfunction (Baskoy, Ay et al. 2016, Aydin, Ramazanoglu et al. 2017). As well as, in type 2 diabetes, the decrease in insulin secretion alters the response to certain odors by about a quarter in the cells of the olfactory bulb (Gouveri, Katotomichelakis et al. 2014, Greenberg, Shaw et al. 2016).In Parkinson's disease, the decrease in the olfactory bulb volume causes anosmia in people (Oppo, Melis et al. 2020). During Kallmann syndrome, anosmia is caused by the lack of development of the olfactory bulb (Koenigkam-Santos, Santos et al. 2011, Ottaviano, Cantone et al. 2015, Shetty, Kapoor et al. 2015). Moreover, the olfactory bulb of Down syndrome patients follows a fast degeneration process. Therefore their olfactory threshold, identification, and discrimination are severely affected (Cecchini, Viviani et al. 2016). Also, defective olfaction in neuromyelitis Optica (Devic's disease) could be a consequence of damage to or atrophy of the olfactory cortex and bulb (Schmidt, Göktas et al. 2013). In kidney and adrenal diseases, the decrease in the glomerular filtration rate causes a decrease in extracellular peptide hormone receptor enzymes. So, the reduction of peptide hormones causes a reduction of amino acids and other essential nutrients for the continuous regeneration and renewal of cells, including the cells of the olfactory epithelium. As a result, the olfactory function is reduced (Raff, Lieu et al. 2008, Kuhn 2016, Hawkes and Doty 2018). In contrast, adrenal insufficiency (Addison's disease) increases olfactory sensitivity because, during the condition, there are decrements in the concentration of secreted steroids that can increase the olfactory threshold by affecting the olfactory nerve cells (Henkin and Bartter 1966, Han, Stiller-Stut et al. 2020).

In some cases, smell impairments are due to the closure or pressure on the olfactory epithelium and olfactory bulb. Tumors block airflow to the nasal olfactory receptor region and damage the olfactory epithelium and olfactory bulb by applying pressure (Daniels, Gottwald et al. 2001, Neto, Targino et al. 2011, Skrandies and Zschieschang 2015, Tajudeen, Adappa et al. 2016) and olfactory meningioma can start as a small lesion and damage the olfactory nerves by pressing on the bulb (Youssef, Sampath et al. 2016). Also, nasal polyps, which are soft, painless, and non-cancerous lumps on the lining of the nasal passages, and rhinitis allergens lead to nasal congestion. After that, they have chronic allergic sinus inflammation which increases the secretion from the glands of the nasal passages and causes the olfactory epithelium and olfactory bulb to close (Bhattacharyya and Gilani 2018). The coronavirus (COVID-19) is a neuroinvasive and neurotrophic virus that can affect the sensory, olfactory, and respiratory epithelium and then cause a decrease in the ability to smell in people with this virus (Brann, Tsukahara et al. 2020, Glezer, Bruni-Cardoso et al. 2020). As a result of these diseases and syndromes, the olfactory epithelium and bulbs are affected, reducing the ability to smell in patients.

Entry of a foreign substance through the nasal passages or physical damage through a foreign agent can lead to disruption of the olfactory system (Hawkes and Doty 2018). For example, the inhalation of toxins, such as air pollutants, manganese, and mercury vapor, deposited in the olfactory mucosa is transmitted to the olfactory bulb, impairing olfactory function (Sulkowski, Rydzewski et al. 2000, Sunderman and Science 2001, Mascagni, Consonni et al. 2003, Flora and Sciences 2014, Ajmani, Suh et al. 2016). Cocaine abuse by inhalation also may damage the olfactory epithelium and cause a decrease in the sense of smell (Miccoli, Franco et al. 2014, Hawkes and Doty 2018). Chemotherapeutic medications can also produce volatiles that arises from lung air and damage replication of olfactory receptors by inhibiting mitosis. (Doty and Haxel 2005, Schiffman and surgery 2018). Furthermore, nerve damage at the base of the skull and hematoma due to frontal bleeding could cause disruption and increase damaged cells (Haxel, Grant et al. 2008). Then, the reduction or absence of nerve cells inside the skull causes problems transmitting olfactory information to the olfactory bulb. Also, the increase in damaged cells causes diffuse axonal damage and interrupts the transmission of olfactory information through axons in the olfactory tract (Johnson, Stewart et al. 2013, Ciofalo, De Vincentiis et al. 2018). Elevated intracranial pressure and the subarachnoid space surrounding the olfactory pathway can also compromise the olfactory nerve system since the meningeal sheath encloses the subarachnoid space and covers the olfactory bulb (Schmidt, Wiener et al. 2012, Kunte, Schmidt et al. 2013). As a result, inhalation of a foreign substance or an external factor can damage the olfactory epithelium and the olfactory bulb and affect the sense of smell.

The olfactory epithelium and olfactory bulb may be damaged not because of disease or an external factor but by inflammation or infection in this part of the olfactory system (Hawkes and Doty 2018). This is believed as an important factor leading to reduce smell function(Frasnelli 2021). In the upper respiratory system, bacteria can enter the nose, causing bacterial infections and possibly damaging the olfactory epithelium, leading to chronic and acute rhinitis (Hamilos and Immunology 2000, Morcom, Phillips et al. 2016). Additionally, in upper respiratory tract viral infections, the virus can disrupt the olfactory function by attacking the olfactory center (Desforges, Le Coupanec et al. 2014, Fasunla, Daniel et al. 2016) and the olfactory epithelium (Xydakis, Albers et al. 2021). Also, the Kartagener syndrome, a rare genetic olfactory disorder, is characterized by frequent sinus infections and immobilized olfactory cilia. Mucosal transmission is delayed, leading to chronic inflammation of the upper and lower respiratory tract and olfactory dysfunction (Sommer, Schäfer et al. 2011).

Other genetic disorders can also affect and disrupt the olfactory epithelial function. For example, in Bardet-Biedl Syndrome, the mutation of the BBS4 gene, which contributes to ciliary motility in the olfactory neuroepithelium, causes defective olfactory sensory neurons. Thus, ciliary motility is impaired, and olfactory function is reduced (Forsythe and Beales 2013).

The epithelium and bulb function can sometimes be affected by changes in hormone levels throughout life. Changes in the secretion of sex hormones during menopause and pregnancy also affect olfactory function (Pawluski, Brummelte et al. 2009). With menopause, estrogen reduction reduces olfactory acuity in women. Olfactory function decreases because the structure partition of the olfactory epithelium, bulb, cortex, and pathway are degraded (Singh, Agarwal et al. 2019). The reason is that estrogen affects neuronal plasticity and conduction time into the olfactory system (Doty, Tourbier et al. 2015). Finally, changes in circulating levels of hypophyseal and the hormone human chorionic gonadotropin in pregnancy cause misperceptions in odor perception, particularly odor hedonics (Ochsenbein-Kölble, Von Mering et al. 2007). Pregnant women usually experience these changes in their olfactory abilities in the first few months of pregnancy (Heinrichs 2002, Cameron 2014).

### 2.1.4 The central nervous system diseases affecting the olfactory function

The brain and spinal cord make up the central nervous system (Baillieul, Chacaroun et al. 2017). Several disorders and diseases in the central nervous system can affect the ability to smell (Wetter, Peavy et al. 2005, Ros, Alobid et al. 2012, van der Valk, Smans et al. 2016, Smith, Rogers et al. 2019). For example, narcolepsy with cataplexy, which is a sleep disorder and accounts for 0.02 to 0.18% of the world's population, disorders in the central nervous system cause olfactory disorders in patients. So that the neuropeptides of the hypothalamus and the central nervous system called hypocretin, which plays a role in the sleep-wake cycle and olfactory function, are lost and reduce the ability to smell (Bayard, Plazzi et al. 2010, Chen, Rosen et al. 2020). Also, Turner syndrome, which occurs in one out of 2500 girls (Silberbach, Roos-Hesselink et al. 2018), changes the structure of parts of the central nervous system, such as the hypothalamus, limbic and auditory system, leading to disturbances in sensory functions, including reduces olfactory function (Ros, Alobid et al. 2012, van der Valk, Smans et al. 2016, Smith, Rogers et al. 2019). Additionally, in autosomal dominant cerebral arteriopathy, a rare inherited small vascular disease, severe hypoxemia or anosmia appears in patients. This reduction in olfactory ability occurs due to white matter lesions, indicative of small vessel disease, in areas related to smell in the brain, such as the forehead, wall, and anterior (Vishnevetsky, Inca-Martinez et al. 2016, Panahi 2019). As well as Foster-Kennedy syndrome is usually associated with olfactory groove meningioma growth, resulting in unilateral olfactory loss and optic nerve atrophy (Koçak, Altundağ et al. 2020). Huntington's disease is an inherited condition that causes progressive destruction of nerve cells in the brain (Wanker, Ast et al. 2019) that affects approximately 4 to 10% of the world's population. This disease can also disrupt the olfactory function by disrupting parts of the olfactory system such as the dentate gyrus, which is part of the hippocampus, and reducing cortical neurons (Wetter, Peavy et al. 2005). The hippocampus is part of the central nervous system of mammals and is involved in their olfactory memory and olfactory function

(Buchanan, Tranel et al. 2003). Olfactory disorders have been observed in patients with Sjögren's syndrome (Rui, Hong et al. 2021, Xu, Geng et al. 2021). A malfunction of the immune system causes this syndrome, and its estimated prevalence is between 0.5 and 1% of the general population (Shen, Yang et al. 2015). This syndrome reduces olfactory function due to a decrease in neurogenesis in the hippocampus and amygdala and disruption of olfactory neuron proliferation (Rui, Hong et al. 2021, Xu, Geng et al. 2021). As a result, the disorders and loss of smell observed in patients with narcolepsy with cataplexy, turner syndrome, autosomal dominant cerebral arteriopathy, Huntington's disease, and Sjögren's syndrome are due to disruptions and changes in parts of the central nervous system.

In some cases, disorders in the central nervous system can cause increased olfactory stimulation. For example, in people with migraines, smell as a stimulus increases migraine attacks and the sense of smell in these people (Harriott and Schwedt 2014). This performance could be due to the activation of the amygdala, which is involved in the perceptual processing of olfactory stimuli transmitted from the olfactory bulb (Heinrichs 2002, Sjöstrand, Savic et al. 2010, Mainardi, Maggioni et al. 2017). Consequently, a disease can sometimes increase olfactory stimulation.

### 2.1.5 Diseases affecting the olfactory transmission

Occasionally, the reduction and disruption of enzymes and neurotransmitters in the olfactory system can disrupt the olfactory function. These enzymes and neurotransmitters generally transfer olfactory information to different parts of the olfactory system (Buck and Bargmann 2000)(Wilson, Fletcher et al. 2004). For example, in patients with pseudohypoparathyroidism, an inherited disease, the sense of smell is decreased due to reduced levels of adenylyl cyclase (Ishii, Fukuda et al. 2010, Shushan, Yakirevitch et al. 2019). This enzyme plays a vital role in odor transmission by preparing olfactory cilia that bind to odorants (Buck and Bargmann 2000). Also, there are several neurotransmitters in the olfactory nervous system, including acetylcholine, which is an important modulation of olfactory associative memory (Wilson, Fletcher et al. 2004). Under normal conditions, this system is rich in neurotransmitters, but in Alzheimer's, the number of acetylcholine decreases, which becomes one of the leading causes of memory impairment and other cognitive disorders, including olfactory dysfunction in these patients (Doty and Haxel 2005, Zou, Da Lu et al. 2016). As a result, reducing a series of enzymes and neurotransmitters can effectively mitigate olfactory ability.

### 2.1.6 Diseases affecting the olfactory memory and hallucinations

Psychological conditions and disorders in some parts of the olfactory system can lead to changes in olfactory memory and, subsequently, hallucinations in olfactory function (Chernigovskaya, Arshavsky et al. 2007). Among patients with schizophrenia, olfactory hallucinations occur due to disturbances between the nucleus accumbens and the anterior olfactory cortex, which is involved in olfactory function (Rolland, Amad et al. 2015). Disruption of the connection between the anterior cortex and the olfactory system in these patients can cause the incompatibility of olfactory information with visual information. Therefore, these patients have disorders detecting smells and experience olfactory hallucinations (Kiparizoska and Ikuta 2017). Schizophrenia also affects the hippocampus, essential for memory learning, causing cognitive and executive memory impairments. These patients not only experience olfactory hallucinations but also suffer from olfactory memory loss (Masaoka, Velakoulis et al. 2020). In addition, multiple chemical sensitivities syndrome, in which various symptoms occur with low-level chemical exposure, can lead to olfactory hallucinations (Hojo, Ishikawa et al. 2008). During this syndrome, the olfactory memory is disturbed and the frontal olfactory cortex activation during olfactory stimulation makes patients more sensitive to smells (Hillert, Musabasic et al. 2007, Azuma, Uchiyama et al. 2013). As a result, some diseases and syndromes affect olfactory memory and cause olfactory impairments, improvements, and hallucinations.

## 2.2 The olfactory dysfunction and the role of physical activity

Some studies have been conducted on the evaluation, methods of diagnosis, and treatment of olfactory disorders (Cho 2014, DeVere 2017, Hawkes and Doty 2018). However, appropriate assessment techniques to determine such causes are limited. A thorough head and neck examination are recommended for patients with suspected olfactory decline. Another method consists of a psychological assessment that includes odor threshold or odor detection tests, which are comprehensive sensory chemistry tests (Hummel, Whitcroft et al. 2017, Hawkes and Doty 2018). Studies have shown that different treatment methods can improve smell disorders

(Hummel, Whitcroft et al. 2017). For example, the use of topical and oral corticosteroids is one of the effective treatments for improving smell (Shu, Lee et al. 2012). Some olfactory disorders may be treated by removing parts of the olfactory system, such as the olfactory bulbs and olfactory mucosa, and performing rhinoplasty (Kohli, Naik et al. 2016, Morrissey, Pratap et al. 2016). Regular exposure to odor substances, known as olfactory training, is also effective in treating olfactory disorders (Sorokowska, Drechsler et al. 2017).

PA is another treatment of interest. It has been shown that PA prevents (Yau, Gil-Mohapel et al. 2014), treats (Speelman, Van De Warrenburg et al. 2011, Zhang, Li et al. 2020), and improves the complications (Hoffman, Rawal et al. 2016) caused by smell disorders. Suk-yu Yau et al. (2014) found that PA plays a strongly enhancing role in hippocampal neurogenesis in adults as a potential preventive strategy to reduce cognitive decline. Also, a study on patients with Parkinson's, that showed PA as a treatment may lead to an improvement in the quality of life in these people (Speelman, Van De Warrenburg et al. 2011). Moreover, a review of chemosensory evaluations in the 2014-2011 protocol showed that PA reduced the complications caused by olfactory disorders (Hoffman, Rawal et al. 2016). Zhang, Li et al. (2020) found that in 57 people who did sports such as tai chi (n=20), dance (n=14), walking (n=11), or running (n=12), the odor detection threshold score was significantly higher after one year of PA. This may be explained by an increased volume and blood volume of the hippocampus, which is an integral part of the olfactory system, following exercise (Zhang, Li et al. 2020). Also, some studies showed that exercise frequency could improve the olfactory threshold and odor detection in the elderly with Alzheimer's disease (Djordjevic, Jones-Gotman et al. 2008).

There is little information regarding the mechanism by which PA and smell are associated. The probable mechanism is that olfactory disorders are associated with cognitive impairments, and exercise can improve brain function and general health by affecting olfactory brain regions. So, exercise can increase growth factors, cognitive function, and neurogenesis of olfactory cells (Schubert, Cruickshanks et al. 2013). Additionally, exercise has been shown to reduce inflammation and improve cardiovascular health, which may also improve cognition and olfactory function (Hamer, Sabia et al. 2012). The relationship between PA and olfactory function might also be partly explained by the fact that olfactory function and hippocampal volume are closely related (Growdon, Schultz et al. 2015). So PA would increase the size of the hippocampus, thus improving olfactory function (Pereira, Huddleston et al. 2007). In addition, a study found that swimming increased nerve growth factor and synapse levels in the olfactory bulb, improving olfactory perception (Chae, Jung et al. 2014). Therefore, PA could be used as a treatment or prevention for olfactory disorders, which are discussed below.

### 2.2.1 Physical activity's impact via olfactory epithelium and bulb

PA may reduce the effects of diseases on this part of the olfactory system by improving immunity and respiratory capacity. For example, regular PA has a neuro-inflammatory impact on the nervous system during upper respiratory tract infections and can increase resistance to oxidative damage (Scharhag, Meyer et al. 2005). Accordingly, in a study of 547 adults between 20 and 70 years of age who performed regular moderate PA (3.0 - 5.9 METs) for 12 months, a 20% reduction in the risk of upper respiratory tract infections was observed (Matthews, Ockene et al. 2002). Also, an animal study has shown that moderate exercise on a treadmill for 20 - 30 minutes at a speed of 8-12 m/min for three days significantly reduced mortality of influenza infection in mice compared to long-term exercise for 2.5 hours at a speed of 8 - 12 m/min for three days (Lowder, Padgett et al. 2005). Moreover studies on COVID-19 patients have shown that an active lifestyle can enhance immunity and respiratory capacity (Woods, Hutchinson et al. 2020). In this regard, animal studies have shown that moderate PA can influence the immune system and improve morbidity and mortality from COVID-19 (Zhu 2020). Also, studies have predicted that endurance exercisers-trained individuals who develop COVID-19 have better respiratory capacity than normal patients due to adaptive changes in the mitochondria of diaphragm cells during endurance exercise (Woods, Hutchinson et al. 2020). An active lifestyle can also play an essential role in regulating hormones and thus can improve the smell. For example, PA decreases insulin demands by reducing insulin resistance in patients with diabetes (Bainbridge, Byrd-Clark et al. 2018) and can help preserve the ability to smell considering that insulin resistance contributes to smell impairments (Simunkova, Jovanovic et al. 2016). Furthermore, regular PA can increase glomerular filtration, and kidney function can be improved. Consequently, amino acids and other nutrients necessary for the continuous regeneration of olfactory epithelial cells are provided in larger quantities, thereby improving olfactory function in kidney and adrenal patients (Kramer and Wells 1996, Lima, Campos et al. 2018).

Additionally, injuries caused by an external factor on the olfactory epithelium and olfactory bulb may be healed through PA. Following traumatic brain injury, exercise, precisely aerobic exercise, increases levels of endogenous neurotrophic factor or nerve growth factor and strengthens the brain's adaptive processes. Also, PA facilitates the development of existing associations by increasing the proliferation of cholinergic neurons (Ang, Wong et al. 2003, Archer 2012, Bos, De Boever et al. 2014). In one animal study, 15 days of PA using Rota-rod training, a static motor task to assess balance and coordination aspects of motor function, and treadmill exercise improved ischemic stroke-induced brain damage in adult male rats (Seo, Kim et al. 2010). There is a possibility that exercise-induced mechanisms, including changes in the size, shape, and structure of motor neurons, glial activation, and altered gene expression levels of anti-apoptotic proteins, contribute to improved olfactory function (McCrate and Kaspar 2008). Anti-apoptotic genes can give the cell a state resistant to apoptosis or cell death, thus preventing the destruction of nerve cells (Susuki 2010). Also, a study on patients with amyotrophic lateral sclerosis showed that PA could be associated with the improvement of olfactory disorders in these people. This study collected and evaluated information about exercise history, leisure activities, and PA. The results showed an inverse correlation between amyotrophic lateral sclerosis and the duration of PA (Pupillo, Messina et al. 2014). Therefore, it is thus possible that aerobic exercise can be beneficial in preventing and improving the sense of smell and healing the effects of nerve damage.

In contrast, animal studies have shown that long-term daily wheel-running exercise for 10 months can reduce the number of mature olfactory sensory neurons and negatively affect cell dynamics in the olfactory epithelium (Tuerdi, Kikuta et al. 2018). Also, PA does not affect neurogenesis and enrichment of the olfactory bulb of mice (Brown, Cooper-Kuhn et al. 2003). A study on 15 healthy adults showed that controlled aerobic physical exercise for two exercise tests could activate the vasoconstriction of the nasal mucosa, which reduces blood flow to the olfactory epithelium (Marioni, Ottaviano et al. 2010). Hence, PA may negatively affect the epithelium and olfactory bulb, based on the studies conducted.

### 2.2.2 The effect of PA on olfactory function via the central nervous system

Studies have shown that PA has a regenerative effect on the hippocampus and may affect olfactory function by increasing the size of the hippocampus(Glachet and El Haj 2020, Han, Stiller-Stut et al. 2020, Zhang, Li et al. 2020). Also, performing PA promotes the continuous growth of new neurons in the dentate gyrus of the hippocampus (Kempermann, Kuhn et al. 1997, Johnston and Amaral 2004, Kee, Teixeira et al. 2007, Glachet and El Haj 2020, Han, Stiller-Stut et al. 2020). For example, the study on rats showed that PA increased neurogenesis in the dentate gyrus of the hippocampus (Van Praag, Kempermann et al. 1999, Laviola, Hannan et al. 2008).

### 2.2.3 Physical activity's impact on olfactory transmission

Studies have not explicitly examined the effects of PA on olfactory transmitters. Nevertheless, animal studies suggest that PA can enhance motor skill learning by changing neurotransmitters (Marmeleira 2013). Following these changes, PA can induce neurons to change their transmitter identity in response to stimuli by altering gene expression, typically leading to behavioral changes in animals (Süudhof 2008, Li and Spitzer 2020). Therefore, the results of this study can be used to investigate effective neurotransmitters in the olfactory system in the future. In contrast, strenuous activities such as running, cycling, and swimming, reduce acetylcholine levels, a neurotransmitter enhancing olfaction (Jäger, Purpura et al. 2007, Penry, Manore et al. 2008). As a result, more studies need to be conducted to determine the association between olfactory transmitters and PA for patients and healthy individuals.

### 2.2.4 Potential impact of physical activity on olfactory memory and hallucinations

There has been no study specifically examining the effect of PA on olfactory hallucinations up to now. Despite this, exercise can increase the volume of the hippocampus through the stimulation of blood flow and neurogenesis, modifying synaptic plasticity and enhancing memory (Girdler, Confino et al. 2019). In human studies, aerobic exercise increases the volume of the hippocampus by 2% (Erickson, Voss et al. 2011). In animal studies, one week of exercise improves learning and memory, along with the expression of hippocampal molecules associated with energy management (Gomez-Pinilla, Vaynman et al. 2008). In addition, it has been observed that acute aerobic exercise is associated with improved working memory. Li et al. (2014) investigated the effects of an acute aerobic exercise session on memory-evoked brain activity and working performance in 15 young female participants who underwent functional magnetic resonance imaging while engaging in a working memory task. The results showed that acute aerobic exercise benefits working memory. As a result, acute aerobic exercise may affect olfactory memory and subsequently improve olfactory illusions; whether one can maintain scent memory by adopting an active lifestyle remains to be investigated.

### 2.2.5 Caution towards the practice of PA

The practice of PA can have negative effects, so a person's physical condition should be evaluated as safe and effective before doing PA (Miles 2007). For example, aerobic exercise can exacerbate migraine symptoms (Irby, Bond et al. 2016). PA increases the pressure inside the blood vessels compared to the outside, which may increase the regional blood flow of the brain and further increase the olfactory stimulation (Spierings, Ranke et al. 2001, Varkey, Hagen et al. 2008). For instance, a study showed that PA, as a migraine trigger, increases the frequency of headaches in people with migraine, and because of this, people avoid PA. (Varkey, Hagen et al. 2008). Also, prolonged endurance exercise (>3 hours) reduces the function of neutrophils, suppresses the immune system, and puts a person at risk for upper respiratory tract infection (Bermon 2007). Therefore, this has the opposite effect on improving the function of the olfactory system because inflammatory responses cause the loss of olfactory sensory neurons (Imamura and Hasegawa-Ishii 2016).

## 2.3 Conclusion

The olfactory system plays a vital role in human life. Some diseases and external factors can affect and disrupt the olfactory system. One of the ways to prevent and treat olfactory disorders caused by diseases and external factors is PA, but studies in this field are minimal. PA can be suggested according to the effect of the disease on different parts of the olfactory system, and some points should be considered when recommending PA. In this regard, considering PA parameters, recognizing disease symptoms, and the individual's ability to initiate PA in time to prevent side effects and improve olfactory function is essential. Although most studies do not include PA parameters, paying more attention to specific PA parameters (PA duration, frequency, intensity, and volume) to improve olfactory function is imperative.

Table 1 - Summary of olfactory function and role of physical activity

| Category of impairment | Mechanism | Structure affected | Example of a cause of olfactory dysfunction | Role of physical activity in olfactory function (references) |
|---|---|---|---|---|
| Olfactory epithelium and olfactory bulbs | Atrophy and direct injury | Olfactory cortex, olfactory bulb, limbic system, olfactory mucosa, olfactory epithelium, olfactory receptors | Neuromyelitis Optica (Devic's Disease), inhalation of toxins, cocaine abuse, Chemotherapeutic medications, Down syndrome, Bardet–Biedl Syndrome | None/unknown |
| | Damage by number and volume reduction | Brain, dentate gyrus, hippocampus, and olfactory bulb | Hypothyroidism, Parkinson's disease, Kallman Syndrome | None/unknown |
| | Damage by inflammation and infection | Olfactory receptor, olfactory epithelium, olfactory nerve, Kartagener syndrome | Upper respiratory system bacterial and viral infections, COVID-19, Kartagener syndrome | - (Bermon 2007, Imamura and Hasegawa-Ishii 2016) |
| | | | | + (Matthews, Ockene et al. 2002, Lowder, Padgett et al. 2005, Scharhag, Meyer et al. 2005, Powers, Bomkamp et al. |

| Category of impairment | Mechanism | Structure affected | Example of a cause of olfactory dysfunction | Role of physical activity in olfactory function (references) |
|---|---|---|---|---|
| | | | | 2020, Woods, Hutchinson et al. 2020) |
| | Damage by pressure | Olfactory epithelium, olfactory bulbs, the nasal olfactory receptor, orbitofrontal area, nasal airway glands, the subarachnoid space, the base of the skull and hematoma due to frontal bleeding | Tumors, allergic rhinitis, nasal polyps, elevated intracranial pressure, blowback or the front of the head, olfactory groove meningioma, amyotrophic lateral sclerosis | + (Ang, Wong et al. 2003, McCrate and Kaspar 2008, Seo, Kim et al. 2010, Archer 2012, Bos, De Boever et al. 2014, Pupillo, Messina et al. 2014) |
| | Decreased hormone secretion and Precursor reduction | Olfactory bulbs, epithelium, cortex, and pathway | Type 2 diabetes, Kidney disease, Addison's disease, menopause | + (Kramer and Wells 1996, Simunkova, Jovanovic et al. 2016, Bainbridge, Byrd-Clark et al. 2018, Lima, Campos et al. 2018) |
| | Increased hormone secretion | Hypophyseal | Pregnancy | None/unknown |

| Category of impairment | Mechanism | Structure affected | Example of a cause of olfactory dysfunction | Role of physical activity in olfactory function (references) |
|---|---|---|---|---|
| Central nervous system | Neuronal loss and necrosis | Hypothalamus | Narcolepsy, cataplexy | None/unknown |
| | | Entorhinal cortex, thalamus, parahippocampal gyrus, and caudate nucleus | Huntington's disease | + (Pang, Stam et al. 2006) |
| | | The forehead, wall, and anterior of the brain, olfactory groove meningiomas, optic nerves, | Cerebral autosomal dominant arteriopathy, Foster-Kennedy syndrome | None/unknown |
| | Decrease in neurogenesis | Hippocampus and amygdala | Sjögren's syndrome | None/unknown |
| | Change structures | Hypothalamus, the limbic or auditory system | Turner syndrome | None/unknown |
| | Stimulation of neurons | Left temporal pole, the frontal and temporoparietal regions | Migraine | - (Spierings, Ranke et al. 2001, Varkey, Hagen et al. 2008) |
| Olfactory transmission | Decrease of an enzyme | Decrease of adenyl cyclase | Pseudohypoparathyroidism | None/unknown |
| | Changes in a neurotransmitter | Changes in the neurotransmitter of acetylcholine | Alzheimer's Disease | + (Belarbi, Burnouf et al. 2011, Law, Rol et al. 2018) |

| Category of impairment | Mechanism | Structure affected | Example of a cause of olfactory dysfunction | Role of physical activity in olfactory function (references) |
|---|---|---|---|---|
| Olfactory memory and hallucination | A disturbance between the anterior olfactory cortex and the nucleus accumbens | The anterior olfactory cortex and the nucleus accumbens | Schizophrenia | + )Gomez-Pinilla, Vaynman et al. 2008, Erickson, Voss et al. 2011( |
| | Disturbance of the olfactory memory and the anterior olfactory cortex | The anterior olfactory cortex | Multiple chemical sensitivity syndrome | |

A positive sign (+): a positive effect on olfactory function, Negative sign (-): a negative effect on olfactory function

## 2.4 Physical activity parameters

According to the definition provided by the World Health Organization, PA is any bodily movement produced by skeletal muscles and requires energy (Dasso 2019). Various parameters are used to evaluate and prescribe PA. There are four main parameters of PA: duration, frequency, intensity, and volume. These parameters measure a person's activity level over a period of time, such as a week, a month, or a year (Piercy, Troiano et al. 2018). Since these four PA parameters are widely used in literature (Kowalski, Rhodes et al. 2012, Vanhees, Geladas et al. 2012) and are the specific objectives of this thesis, this section of the literature review briefly defines them. How each PA parameter is evaluated in the present study is also explained.

### 2.4.1 Physical activity duration

The duration of PA is the total time of an activity session or PA program (Vanhees, De Sutter et al. 2012). The duration of PA in present studies is considered if performed at least 10 minutes continuously during work on a typical day at moderate or vigorous-intensity work (Center for Disease Control and Prevention 2020). Ultimately, the duration of PA refers to the length of time during which it occurs (Piercy, Troiano et al. 2018).

### 2.4.2 Physical activity frequency

Frequency refers to the number of times a particular activity is performed within a given period of time (Powell, Paluch et al. 2011). The frequency of PA is usually expressed as the number of activity sessions per day, week, or month (Vanhees, De Sutter et al. 2012).

In our study, the number of days corresponding to moderate or vigorous PA in a typical week was analyzed (Center for Disease Control and Prevention 2020).

### 2.4.3 Physical activity intensity

PA intensity is the amount of energy spent when doing PA and refers to how PA affects heart rate and breathing. Exercise specialists classify PA into light, moderate and vigorous intensities and measure it in metabolic equivalents (METs). A MET is equal to 3.5 ml of oxygen per kilogram of body weight per minute (Jetté, Sidney et al. 1990). The MET measures a person's active metabolic rate to their resting rate.

In the present study, 4.0 METs were considered for moderate work-related activities and 8.0 METs for vigorous work-related activities (Center for Disease Control and Prevention 2020).

### 2.4.4 Physical activity volume

Volume refers to the total amount of PA performed in a specified period of time, and the volume of PA is expressed in energy expenditure like METs*minute/week (Powell, Paluch et al. 2011).

The present study assessed PA volume using METs per hour during a typical week and the PA volume was reported as METs*h/week. Accordingly, PA volume can be described as the total frequency, intensity, and duration over a period (Piercy, Troiano et al. 2018).

## 2.5 The research problems

Humans rely on their sense of smell for vital functions, eating, and communication (Boesveldt, Parma et al. 2021). According to our review, some diseases related to the nervous system, genetic, hormonal, infectious, psychological, or physical factors can affect the olfactory system and impair olfactory function. Olfactory complications caused by diseases may be improved or not by PA, which can affect the olfactory system.

Recent studies show that PA can improve olfactory function (Schubert, Cruickshanks et al. 2013, Chae, Jung et al. 2014). For example, in a study of 38 Parkinson's patients that examined the effect of aerobic exercise on olfactory function, the exercise group found no evidence of worsening olfactory function compared to the no-exercise group where a decrease was measured (Zhang, Li et al. 2020). Further, exercising significantly improved olfactory scores compared to those who did not exercise (Rosenfeldt, Dey et al. 2016). Furthermore, Schubert et al. (2013) found that regular exercise reduced the risk of developing olfactory dysfunction over ten years. The studies mentioned above did not separately examine the effects of exercise parameters on the olfactory system (Schubert, Cruickshanks et al. 2013).

Previous studies that analyzed NHANES data did not investigate the relationship between PA components (duration, frequency, intensity, volume) and olfaction. For example, Rasmussen, V. F., et al. (2018) investigated the prevalence of olfactory disorders in adults with diabetes and did not consider PA (Rasmussen, Vestergaard et al. 2018). Another study analyzed self-reported chemosensory changes (NHANES) in 2011-2012 and focused solely on participants who reported doing at least 10 continuous minutes of vigorous- or moderate-intensity activity ≥3 days a week and found that PA has a strong protective effect on people who did the eight-item NHANES pocket test ($P<0.001$) (Rawal, Hoffman et al. 2016). Therefore, this article aims to assess PA parameters using NHANES 2013-2014 data.

# Chapter 3 – [The association between duration, frequency, intensity, and volume of physical activity and olfaction]

Chapter 3 assessed the relationship between PA parameters and olfactory function. The chapter follows the structure of a journal paper but has not yet been submitted. This study is a secondary analysis of NHANES 2013-2014 data that examines the association between the volume, duration, and frequency of moderate to vigorous PA and sense of smell. The paper entitled "The association between duration, frequency, intensity, and volume of PA and olfaction" was co-authored by: Khoosheh Namiranian, Alexandre-Charles Gauthier, Jo-Anne Gilbert, and Marie-Eve Mathieu. All authors are affiliated to the École de Kinésiologie et des Sciences de l'Activité Physique, Université de Montréal.

## 3.1 Author's contribution

We present each author's contribution according to CRediT (Contributor Roles Taxonomy).

Khoosheh Namiranian: Writing - Original Draft preparation, Visualization, Methodology, Data Curation, and Investigation.

Alexandre-Charles Gauthier: Writing - Review & Editing preparation

Jo-Anne Gilbert: Validation of statistical analysis and writing review

Marie-Eve Mathieu: Project administration, Supervision, and Conceptualization

In more detail, my contribution was:

I began the initial preparation by focusing on the NHANES data. According to the statistical data available on the NHANES information site, I selected the study population as people who had done tests on PA and sense of smell simultaneously in 2013-2014. At this stage, with the guidance of Prof Marie-Eve Mathieu, who is responsible for research activities, we formulated and developed the general goals and objectives of the research. Then I analyzed the data with the software SPSS 27.0 (SPSS Inc., USA) with the support of Prof Marie-Eve Mathieu, Prof Jo-Anne Gilbert, Prof Mickael Begon, as well as Miguel Chagnon and Justine Zehr, computer scientist statisticians. I wrote the first draft of the article and sent it to Prof Marie-Eve Mathieu, Prof Jo-Anne Gilbert, and Alexandre-Charles Gauthier for critical review, editing and validation, interpretation, and revision.

## 3.2 Abstract

**Introduction:** The olfactory system has a significant impact on the quality of life. A decrease in the sense of smell may influence individuals' physical and mental health and physical activity (PA) might improve olfactory function. This study aimed to determine the association between PA and olfaction and whether the duration, frequency, and volume of moderate to vigorous PA could be related to the olfactory function in adults.

**Methods:** NHANES 2013-2014 data was used in this study, and the participants were people aged ≥40 years (n=3527). The study included participants who completed both self-reported PA questionnaire and smell tests (chocolate, strawberry, grape, onion, smoke, natural gas, leather, and soap). Participants were considered active if they continuously practiced moderate to vigorous PA for at least 10 minutes during a typical week. The association between olfaction and PA was assessed using correlations and logistic regressions, reported here as Odds-ratio (OR) and 95% confidence intervals (CI). P-value ≤0.05 was considered statistically significant.

**Results:** PA parameters and total smell score showed a positive correlation with the duration, frequency of moderate and frequency of vigorous PA, also PA total volume (all p≤ 0.05). The duration (10min/day), frequency (day/week), and volume (METs*h/week) of moderate PA was associated with the chance of correctly detecting the smell of grapes [1.002<ORs<1.047, CI95% (1.000-1.082), p=0.007]. The frequency of moderate PA was positively associated with the capacity to identify smoke [OR =1.074, CI 95% (1.019-1.131), p=0.008] and leather [OR =1.060, CI 95% (1.019-1.103), p=0.004] odors. Furthermore, the frequency of vigorous PA was positively associated with the detection of grape smell [OR =1.002, CI 95% (1.000-1.005), p=0.028].

**Conclusion:** We found that PA parameters could be related to the detecting capacity of some smells but the constant effect of PA on the chance of correctly detecting the smells is below 7.4%. Therefore, that should be regarded in some future studies. Also, the duration, frequency, and volume of moderate PA were related to improved detection of all three groups of the nutrient, warning, and common household odors. So, researchers and kinesiologists can consider moderate-intensity PA as a recommendation for the prevention and treatment of some olfactory disorders.

**Keywords:** Duration, Frequency, Intensity, Olfaction, Physical activity, Smell, Volume.

## 3.3 Introduction

An accurate olfactory system increases the quality of life (Auffarth 2013). Olfaction is essential for vital functions such as warning and protection from environmental hazards such as gas leak detection, eating behavior, and social communication (Stevenson 2010). For example, not feeling the smell of food impairs taste perception and can affect appetite and malnutrition (Boesveldt and de Graaf 2017). Thus, it is not surprising that smell loss or dysfunction negatively impacts physical and mental well-being, safety, appetite, and nutritional profile (Doty and Kamath 2014, Doty 2019). Such impairments were manifested in the recent COVID-19 pandemic (Martínez-de-Quel, Suárez-Iglesias et al. 2021). An olfactory loss was present in 45% of patients, so the loss of smell was regarded as the most significant symptom (Moein, Hashemian et al. 2020, Kandemirli, Altundag et al. 2021). However, new variants of covid-19 show that this symptom is less common, and the findings have prompted some doctors to call for a review of the official COVID-19 symptom list (Mahase 2021).

Various factors can affect olfactory function such as hunger and satiety, and changes in body weight, age, and gender (DeVere 2017, Rolls 2019). Hunger and satiety have been shown to alter sensitivity to olfactory stimuli and the impaired olfactory sensitivity could somehow interfere with mechanisms that signal satiation (Stafford and Welbeck 2011). Individuals with obesity are more likely to present olfactory dysfunctions and increasing body mass index is associated with a decrease in olfactory sensitivity (Skrandies and Zschieschang 2015). Moreover, olfactory function decreases with age (Kondo, Kikuta et al. 2020). Moreover, in clinical studies that have identified olfactory disorders in patients with neurological and mental disorders as well as healthy, it was observed that females have better olfactory performance than males (Huisman, Uylings et al. 2008, Ryo, Takeuchi et al. 2017).

Research has recommended various interventions for improving olfactory function and treating dysfunctions (DeVere 2017) such as regular PA (Manestar, Tićac et al. 2013, Rosenfeldt, Dey et al. 2016, Zhang, Li et al. 2020). For example, Taiji (tai chi), dancing, or running could improve odor function and identification (Schubert, Fischer et al. 2017, Zhang, Li et al. 2020). According to another study, older people who exercised three times a week had a lower risk of developing olfactory disorders than those who exercised once a week or did not exercise(Schubert, Cruickshanks et al. 2013). Although little is known about the mechanism by which PA and smell are connected, exercise might improve brain function and general health. As exercise improves the functioning of the olfactory regions of the brain via increased growth factors, cognitive function, and neurogenesis of olfactory cells due to the association of olfactory disorders with cognitive impairment (Schubert, Cruickshanks et al. 2013).

Therefore, there is a necessity for a better understanding of how PA can help improve the functioning of the olfactory system and the treatment of olfactory diseases and disorders. In this way, the chemosensory component has been investigated in the US National Health and Nutrition Examination Survey (NHANES). This organization evaluated the health and nutritional status of the US population and showed that a minimal level of moderate to vigorous PA reduced the risk of olfactory dysfunction (Hoffman et al. 2016). However, the distinction of specific PA parameters was not addressed. The present study thus aimed to investigate the association of duration, frequency, intensity, and volume) of PA with the olfactory function.

## 3.4 Materials and Methods

### 3.4.1 Study design and population

The NHANES is a multidisciplinary health examination that aims to assess the health and nutrition status of a representative sample of the US population. This program began in the early 1960s. The protocol of NHANES is described in detail elsewhere (NHANES 2021). The NHANES agreement has been approved by the National Center for Health Statistics Research Ethics Committee, and all adult participants provided written informed consent. Sampling was performed using a multi-stage classification method. The assessments were completed at the participant's home by a health technician using a computer-assisted personal interview system. In this study, we performed a secondary analysis of NHANES data from the 2013-2014 cycle years. The current study included 3,527 adults aged 40 years or older who completed the smell test and answered the self-report questionnaire PA.

### 3.4.2 Smell test

The eight-item NHANES pocket test (PST™, Sensonics, Inc., Haddon Heights, NJ) was used in this study. This odor detection test consisted of four related nutrient odors (chocolate, strawberry, grapes, and onions), two warning odors (smoke and natural gas), and two common household odors (leather and soap) (Hoffman, Rawal et al. 2016). The test is fully described in Hoffman, Rawal et al. (2016). Self-reported olfactory is such that if three or more smells were incorrect (which resulted in a score of 0 to 5 out of a total score of 8), it is considered an olfactory disorder. This study considered results with a score of 0 to 5 as a 0 (olfactory disorder) and results with a score of 6 to 8 as a 1 (Center for Disease Control and Prevention 2020). Also, based on the number of correct identifications of odors, the total smell score of the eight-item NHANES pocket test was between 0 and 8.

### 3.4.3 Physical activity questionnaire

In the NHANES study, PA data were collected using the self-report questionnaire (n=6648). The questionnaire was chosen over accelerometer data given that more people participated in this method and this method allows the analysis of PA parameters in great detail.

The self-report questionnaire was based on the PA Global Questionnaire (Center for Disease Control and Prevention 2020) and included questions related to daily activities, leisure activities, and sedentary activities. For respondents, the questions were asked before the physical examination, at home, using the computer-assisted Personal Interview system (Center for Disease Control and Prevention 2020). In the NHANES study, work that causes small increases in breathing or heart rate, such as brisk walking or carrying light loads for at least 10 minutes, is defined as moderate-intensity activity. Also, works that increase heart rate or respiration rate - such as carrying or lifting heavy loads, digging, or building work – continuously for at least 10 minutes during the week were considered as vigorous PA (Control, Prevention et al. 2013, Hoffman, Rawal et al. 2016). PA period during a typical day was considered to calculate PA parameters. The PA duration was defined in bouts of 10 minutes. The frequency of PA was determined by the number of PA sessions in a typical week (day/week). Also, the volume of PA was calculated by metabolic equivalent (METs*h/week). METs in the NHANES study were considered for moderate work-related activity 4.0 METs and vigorous work-related activity 8.0 METs (Center for Disease Control and Prevention 2020). For presentation purposes of total volume in logistic regressions, the total volume was divided by 100.

### 3.4.4 Statistical analysis

The statistical analyses were performed using SPSS 27.0 (SPSS Inc., USA). All data are presented as mean ± standard deviation. Associations between olfaction and PA parameters were estimated using Pearson correlation coefficient tests and logistic regressions. In logistic regression, age and sex were considered covariates since they are associated with both olfactory function and PA. The odds ratio represents the constant effect of PA on the probability of eight-item NHANES pocket smell test detection to evaluate the effect of PA parameters on the chance of detecting odors correctly. A p-value ≤ 0.05 was considered statistically significant.

## 3.5 Results

A total of 3527 participants (47.6% men; age from 40 to 80) with body mass index 29.38 ± 6.90 kg/m2 from NHANES 2013-2014 responded to the PA questionnaire and performed the smell test (Table 2).

Table 2 - Characteristics of the participants selected from the NHANES 2013-2014

| | **Mean ± SD** | **n** |
|---|---|---|
| Age | 59.03 ± 12.05 | 3527 |
| sex (MALE) | | 1680 |
| Body mass index (kg/m$^2$) | 29.38 ± 6.90 | 3486 |
| Duration of PA-moderate intensity (bouts of 10min/days) | 4.06 ± 9.60 | 3517 |
| Frequency of PA moderate intensity (days/week) | 1.20 ± 2.15 | 3521 |
| Total PA moderate intensity (METs*h/week) | 12.38 ± 33.35 | 3517 |
| Duration of PA-vigorous intensity (10min/ days) | 11.02 ± 40.47 | 3522 |
| Frequency of PA-vigorous intensity (days/week) | 0.60 ± 1.58 | 3526 |
| Total PA vigorous intensity (METs*h/week) | 14.69 ± 53.97 | 3522 |
| PA total volume (METs*h/week) | 27.09 ± 72.94 | 3517 |
| Total smell | 6.61 ± 1.42 | 3519 |
| Chocolate | 0.82 ± 0.38 | 3527 |
| Strawberry | 0.79 ± 0.40 | 3525 |
| Grape | 0.62 ± 0.48 | 3519 |
| Onion | 0.94 ± 0.23 | 3519 |
| Gas | 0.86 ± 0.34 | 3523 |
| Smoke | 0.86 ± 0.34 | 3519 |
| Leather | 0.76 ± 0.42 | 3520 |
| Soap | 0.92 ± 0.26 | 3520 |

Table 3 shows Pearson correlation coefficients computed to assess the linear relationship between PA parameters and smell score. The smell score showed a small but positive correlation with duration, frequency, and volume of moderate PA as well as with PA total volume (r=0.047, p=0.006). Also, the smell score correlated with the frequency of vigorous PA (p≤0.05).

Table 3 - Correlations (r) between total smell score and physical activity parameters

| *Duration (10min/days)* | | | *Frequency (days/week)* | | | *Volume (METs/week)* | | |
|---|---|---|---|---|---|---|---|---|
| n | r | P-value | n | r | P-value | n | r | P-value |
| **Moderate physical activity** | | | | | | | | |
| 3509 | 0.050 | **0.003** | 3513 | 0.076 | **<0.001** | 3509 | 0.051 | **0.002** |
| **Vigorous physical activity** | | | | | | | | |
| 3514 | 0.032 | 0.060 | 3518 | 0.049 | **0.004** | 3514 | 0.032 | 0.060 |

Bold represents significant p-value

Table 4 presents the results of the logistic regressions for PA total volume with individual smells. All eight olfactory detections had no relationship with PA total volume (p>0.05).

Table 4 - The effect of physical activity total volume on the chance of correctly detecting the odors' ability (total score)

| Odor | n | Odds-Ratio | 95% Confidence Interval | P-value |
|---|---|---|---|---|
| Chocolate | 3517 | 0.958 | [0.850-1.079] | 0.476 |
| Strawberry | 3515 | 0.979 | [0.887-1.120] | 0.959 |
| Grape | 3509 | 1.068 | [0.966-1.181] | 0.198 |
| Onion | 3509 | 1.056 | [0.830-1.345] | 0.655 |
| Gas | 3509 | 1.122 | [0.943-1.334] | 0.193 |
| Smoke | 3513 | 1.066 | [0.912-1.247] | 0.421 |
| Leather | 3510 | 1.108 | [0.979-1.255] | 0.105 |
| Soap | 3510 | 0.953 | [0.797-1.140] | 0.596 |

Odds-Ratio is for raising 100 units of PA total volume
Bold represents significant p-value

Table 5 shows logistic regressions to assess specific PA parameters with individual smells. The duration of moderate PA (bouts of 10 min/day) showed a small association with the chance of correctly detecting the smell of grapes [OR =1.010, CI 95% (1.002-1.017), p=0.015]. The frequency of moderate PA (day/week) showed small associations with the detection of the smell of grape [OR =1.047, CI 95% (1.013-1.082), p=0.007] smoke [OR =1.074, CI 95% (1.019-1.131) p=0.008], and leather [OR =1.060, CI 95% (1.019-1.103), p=0.004]. Also, for vigorous PA, the frequency (day/week) was related to grape detection [OR =1.051, CI 95% (1.004-1.101), p=0.034]. The volume of moderate PA (METs*h/week) was associated with correctly recognizing the smell of grapes [OR =1.002, CI 95% (1.000-1.005), p=0.028].

Table 5 - Relation between participants' ability to correctly identify specific odors and moderate and vigorous physical activity parameters

| | | Chocolate | | Strawberry | | Grape | | Onion | | Gas | | Smoke | | Leather | | Soap | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | n | OR [95% CI] | n | OR [95% CI] | n | OR [95% CI] | n | OR [95% CI] | n | OR [95% CI] | n | OR [95% CI] | n | OR [95% CI] | n | OR [95% CI] |
| **Moderate Physical activity** | *Duration (10min/days)* | 3517 | 0.999 [0.990-1.009] | 3515 | 0.997 [0.989-1.006] | 3509 | **1.010 [1.002-1.017]** | 3509 | 1.009 [0.989-1.028] | 3509 | 1.002 [0.991-1.014] | 3513 | 1.004 [0.993-1.016] | 3510 | 1.008 [0.993-1.016] | 3510 | 1.003 [0.999-1.018] |
| | *Frequency (days/week)* | 3521 | 1.014 [0.972-1.057] | 3519 | 0.992 [0.954-1.032] | 3513 | **1.047 [1.013-1.082]** | 3513 | 1.057 [0.976-1.145] | 3513 | 1.001 [0.954-1.051] | 3517 | **1.074 [1.019-1.131]** | 3514 | **1.060 [1.019-1.103]** | 3514 | 1.031 [0.967-1.099] |
| | *Volume (METs/week)* | 3517 | 1.000 [0.997-1.002] | 3515 | 0.999 [0.997-1.002] | 3509 | **1.002 [1.000-1.005]** | 3509 | 1.004 [0.997-1.010] | 3509 | 1.000 [0.997-1.004] | 3513 | 1.002 [0.999-1.006] | 3510 | 1.002 [0.999-1.005] | 3510 | 1.000 [0.996-1.004] |
| **Vigorous physical activity** | *Duration (10min/days)* | 3522 | 0.999 [0.997-1.001] | 3520 | 1.000 [0.998-1.002] | 3514 | 1.000 [0.999-1.002] | 3514 | 1.000 [0.996-1.004] | 3514 | 1.003 [0.999-1.006] | 3518 | 1.000 [0.998-1.003] | 3515 | 1.001 [0.999-1.004] | 3515 | 0.999 [0.996-1.002] |
| | *Frequency (days/week)* | 3526 | 0.985 [0.932-1.042] | 3524 | 0.984 [0.934-1.038] | 3518 | **1.051 [1.004-1.101]** | 3518 | 1.027 [0.922-1.142] | 3518 | 1.052 [0.976-1.134] | 3522 | 1.059 [0.985-1.139] | 3519 | 1.041 [985-1.099] | 3519 | 0.962 [0.887-1.045] |
| | *Volume (METs/week)* | 3522 | 0.999 [0.998-1.001] | 3520 | 1.000 [0.999-1.002] | 3514 | 1.000 [0.999-1.002] | 3514 | 1.000 [0.997-1.003] | 3514 | 1.002 [1.000-1.005] | 3518 | 1.000 [0.999-1.003] | 3515 | 1.000 [0.998-1.003] | 3515 | 1.000 [0.998-1.002] |

OR: Odds-Ratio
CI: Confidence Interval
Bold represents significant p-value

## 3.6 Discussion

The present study aimed to investigate the association of the frequency, duration, and volume of both moderate and vigorous intensities of PA in detecting eight odors related to nutrition, warning, and common household group smells. We found that moderate PA was associated with better detection of all three groups, mainly for moderate PA frequency. Also, the frequency of vigorous PA was associated with the chance of correctly detecting the nutrient smell. However, it should be emphasized that the constant effect of PA on the chance of correctly detecting the eight-item NHANES pocket smell test is his best at 7.4%. Additionally, the total smell score correlated with the duration, frequency, volume of moderate PA, and PA total volume. As well, the total smell score correlated with the frequency of vigorous PA ($p \leq 0.05$). Since Pearson's correlation coefficient was low ($0.049 < r < 0.076$), the influence of PA parameters on the chance of correctly detecting odors is present but rather small.

The total smell score was correlated to moderate PA parameters and PA total volume. Accordingly, the previous studies had findings consistent with the present study. For example, US NHANES findings in the 2011-2012 evaluations showed results similar to ours. The participants in this study were 1281 adults over 40 years of age who answered the PA self-report questionnaire and completed the eight-item NHANES Pocket Test. The results showed the prevalence of smell impairment who did PA was 8.9%. For those who did not PA, it was 20.1%. So, participation in PA (reporting doing at least ten continuous minutes of vigorous- or moderate-intensity activity ≥3 days a week) has a protective effect on the prevalence of smell impairment($P<0.001$) (Hoffman, Rawal et al. 2016). These results align with some studies that showed that exercise improves olfactory function in odor detection (Manestar, Tićac et al. 2013, Rosenfeldt AB, Dey T et al. 2016). Using an experimental design, Rosenfeld investigated the effect of 60 minutes of aerobic exercise three times a week for eight weeks on olfactory function in 38 patients with idiopathic Parkinson's disease (Rosenfeldt, Dey et al. 2016). The results of their study showed that the smell test scores of the group that did aerobic exercises were higher than the group that did not exercise. The authors suggest that aerobic exercise may regulate physiological processes or cognitive processes that control olfaction by altering neurophysiological pathways or neurotransmitter function

(Rosenfeldt, Dey et al. 2016). Also, some studies show that exercise may facilitate olfactory neuroplasticity (Schubert, Cruickshanks et al. 2013, Chae, Jung et al. 2014).

Furthermore, Schubert et al. (2011) found a link between regular exercise and reduced risk of olfactory dysfunction in older adults. The study showed that people who exercised regularly had a lower risk of developing olfactory disorders. Also, another study that examined the olfactory function of people over 70 years old for five years observed that regular exercise might positively affect olfactory function in older adults (Schubert, Cruickshanks et al. 2011). Also, a study by Zhang et al. (2020) was conducted to determine the effect of various types of physical exercise on olfaction decline in 99 healthy community-dwelling older adults using cognitive and olfaction tests. Their study shows that olfaction was better among participants who exercised, especially in Taiji (tai chi), dancing, or running (Zhang, Li et al. 2020). Although the mentioned studies had findings consistent with the present study, none have investigated the relationship of PA parameters on different smells separately. Also, most of their study population were patients, while the present study focuses on participants from the general population.

In the present study, moderate PA duration had a significant relationship, explaining as up to 5% of the association, with the chance of detecting smells correctly related to the nutrition odor group in a healthy adult. This finding is aligned with other studies. Sollai et al. (2021) showed a positive correlation between olfactory scores and the number of hours devoted to PA per week ($r > 0.32$, $p \leq 0.014$). This study investigated the reduction of age-related olfactory function in 122 older adults in Sardinia, Italy. The result of the study suggested that an active lifestyle in terms of PA and the increased duration of time spent on PA was associated with olfactory function and, therefore, the quality of life in the elderly (Sollai and Crnjar 2021).

Moreover, an increased moderate PA frequency has been associated with an increase of up to 7,4% in detection. In this regard, a study that investigated the effect of regular aerobic exercises on the olfactory rehabilitation of asthmatic patients with chronic rhinosinusitis obtained similar results. This study showed that an aerobic and breathing exercise program for 12 weeks (60 minutes a day, three days a week) improved the olfactory function ($p=0.002$), especially in smelling the odor of gas in these people compared to the control group (Zarneshan and Research 2020).

Also, another study examined the prevalence and potential risk factors for smell dysfunction in 3519 participants in NHANES 2013–2014. The results showed that the prevalence of smell disorder was associated with PA intensity (METs/week) [OR=1.61, CL 95% (1.27-2.05), P< 0.001] (Liu, Zong et al. 2016).

In our study, moderate PA volume was associated with correctly detecting nutrition odors, but the constant effect of PA on odor detection is small (0.2%). In this regard, a study that examined the relationship between PA volume (MET*hours/week) and features of Parkinson's disease, including hyposmia, from 1986 to 2014 showed no association between reduced risk of hyposmia and PA in baseline [OR=1.01, CI 95%(0.80-1.18), P=0.52] and cumulative average [OR=1.02, CI 95%(0.79-1.27), P=0.96] (P≤0.05) (Hughes, Gao et al. 2019).

As the results of the current study and previous studies show, moderate PA was associated with better recognition of odors. Fact, performing strenuous activities can negatively affect olfactory function by reducing the level of acetylcholine considering that, acetylcholine is an olfactory-enhancing neurotransmitter (Jäger, Purpura et al. 2007, Penry, Manore et al. 2008).

The current study has some strengths, including its large sample size and objective assessment of smell with the eight-item NHANES pocket test that includes various odors categorized as nutrition, warning, and common household odors. Furthermore, we used the PA questionnaire that allows PA parameters to be analyzed distinctively. Covariates that affect both PA and olfactory function, i.e., sex and age, were considered. Although our study assessed the smell of a wide range of 40 to 80 years old adults, it may be interesting to investigate in the future separate the age groups and assess the middle-aged and elderly groups separately. Older adults may have pathological changes in the central olfactory processing area due to age or cognitive disorders related to olfactory function (Schubert, Fischer et al. 2017), affecting odor smell scales. As this is the first study to explore the possible association between specific PA parameters and smell detection, simple analyses have been conducted and results could underline false positive results. That should be regarded in some future studies.

## 3.7 Conclusion

Based on the current analysis of NHANES data, the total smell score correlated with PA total volume and the parameters of mainly moderate intensity. At moderate intensity, the frequency was more often associated to smell detection in all three odor categories: nutrition, warning, and common household odors. Also, the frequency of vigorous PA was associated with nutrition group odors. Since moderate PA parameters influenced the greater chance of correctly detecting odors during the NHANES pocket test, moderate PA can be a special consideration when recommending PA.

According to our knowledge, the study is the first that investigates the relationship between PA parameters and separate odors recognition in a large-scale approach.

## 3.8 Acknowledgment

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# Chapter 4 – [Discussion]

The olfactory system influences human nutrition, emotions, and social relationships (Auffarth 2013, Elkholi, Abdelwahab et al. 2021). When it is disturbed or reduced in function, olfactory disorders occur (Churnin, Qazi et al. 2019). In the case of olfactory disorders, people risk environmental hazards such as food poisoning and cooking accidents, as well as a reduction in quality of life (Auffarth 2013, Boesveldt and de Graaf 2017, Elkholi, Abdelwahab et al. 2021). This study aimed to understand better whether there is a relationship between PA parameters and the olfactory system. This discussion begins with a summary of the main findings. Then, the literature related to the specific PA parameters and their relationship with olfactory is discussed. Finally, the strengths and limitations of the research are presented along with perspectives.

## 4.1 The relationship between physical activity parameters and olfaction

The results of our study showed that the total smell scores small correlated with the duration (r= 0.050), frequency (r= 0.076), volume (r= 0.051) of moderate PA, and PA total volume (r= 0.032). The total smell score is also minimally correlated with the frequency of vigorous PA (r=0.032). Despite the low Pearson correlation coefficient values, PA parameters are associated with an increased chance of correctly detecting odors. In this regard, previous studies reported that supervised PA can improve the olfactory system (Schubert, Cruickshanks et al. 2013, Chae, Jung et al. 2014). . For example, a survey of 38 patients with idiopathic Parkinson's has shown that eight weeks of aerobic exercise in the form of 3 sessions of 60 minutes can affect the olfactory function of the participants. Physiological processes that control olfaction may be modulated by aerobic exercise due to changes in neurophysiological pathways or neurotransmitter function (Rosenfeldt, Dey et al. 2016). In addition, Schubert et al. (2013) investigated the relationship between exercise and the incidence of olfactory disorders in 1611 participants aged 53 to 97 years who were examined and followed up for 10 years (1998-2010). The results showed that people who exercised regularly were less at risk of developing olfactory disorders (Schubert, Cruickshanks et al. 2013). Similarly, a Chinese study conducted on 99 healthy 62.2-year-olds examined the effects of PA on reducing odor in the elderly and found similar results. According to the results, those who exercised scored higher on the smell test. This study required all participants to complete questionnaires, cognitive tests, and olfactory tests. The results showed running, tai chi, and dancing were all associated with better performance than walking or not exercising (Zhang, Li et al. 2020). The results obtained in the present study are consistent with previous studies showing that PA improves olfactory function. However, there is a difference in that the present study is a cross-sectional approach and investigated the relationship between specific PA parameters and odor.

In the following parts of this section, studies that examine the relationship between the volume, duration, frequency, and intensity of PA and the function of the olfactory system will be highlighted.

### 4.1.1 The duration of physical activity and olfaction

According to the findings of this study, the duration (bouts of 10min/day) of moderate PA was related to detecting the smell of grapes [OR =1.010, CI 95% (1.002-1.017), p=0.015] relevant to the nutrition odor group in healthy adults.

An earlier study found similar results regarding the effect of PA duration on olfactory performance. This study examines the effect of the duration of PA (hours/week) and the olfactory function of the elderly. The survey of 122 elderly volunteers in Sardinia (Italy) showed a positive correlation between each older adult's olfactory scores obtained during the olfactory tests and the number of hours devoted to PA per week. Better olfactory function in active older adults can be due to the effect of exercise on synaptic structure and increasing synaptic efficiency. Then it affects the areas where olfactory memory is located (Sollai and Crnjar 2021).

It is believed that PA facilitates cognitive performance such as smell identification by increasing cerebral blood flow and that aerobic exercise influences components of cardiovascular fitness(Rogers, Meyer et al. 1990, Angevaren M, Vanhees L et al. 2007). Contrary to the present study, in a survey of 1927 healthy men and women aged 45-70 in the Netherlands who were examined from 1995 to 2000, no significant relationship was observed between the duration of PA (hours/week) and different cognitive domains. Cognitive performance was measured in terms of processing speed, memory performance, and cognitive flexibility (Angevaren M, Vanhees L et al. 2007). Since smell identification is related to memory, language, and organizational performance (Westervelt, Ruffolo et al. 2005), it can be speculated that the duration of PA does not affect smell performance. This is due to the large statistical population, as the reported data showed that more PA is associated with a small and significant benefit on cognitive decline. Still, this association disappeared after accounting for cognitively stimulating activities (Angevaren M, Vanhees L et al. 2007). As a result, it is recommended that future studies in this field be carried out with greater precision.

### 4.1.2 The frequency of physical activity and olfaction

An increased frequency (days/week) of moderate PA was most associated with detecting smells of grapes from nutrients, smoke from the warning, and leather from common household odors groups [(1.047 < ORs < 1.060), (See Table 5 in Chapter 3 for associated confidence intervals and p values). Also, the frequency of vigorous PA had a positive effect on the chance of detecting the smell of grapes related to the nutrient odor group [OR =1.051, CI 95% (1.004-1.101), p=0.034]. Westervelt, Ruffolo et al. (2005) examined the effects of regular aerobic exercise with nasal breathing on the olfactory function of 35 asthmatic patients (34.7±7.5 years) with chronic rhinosinusitis. The participants had 12 weeks of aerobic and breathing exercises for 60 minutes a day, three days per week, and their performance and olfactory acuity were measured (Westervelt, Ruffolo et al. 2005). The results of this research showed that the olfactory function improved after 12 weeks of training, and the intensity of the sense of smell of gas increased significantly. It can be affected by exercise, nasal volume, and upper respiratory tract infections, and it can facilitate neuroplasticity in the olfactory system. So, an increase in the frequency of PA may effectively improve the function of the olfactory system.

### 4.1.3 The intensity of physical activity and olfaction

Exercise intensity indicates how much metabolic energy is expended during exercise, and intensity determines the health benefits you will receive from training (Jackson, Morrow Jr et al. 2004). This study examined PA parameters in moderate and vigorous intensity categories. As shown in the previous sections, both moderate and vigorous intensities can improve smell test accuracy, especially moderate intensities.

An overview of US NHANES findings in the 2011-2012 evaluations showed results like our study. The risk of olfactory dysfunction was lower among 1,281 participants over 40 years who reported more than three days of moderate to vigorous PA per week (performed for at least 10 minutes). Accordingly, for participants who answered the self-report questionnaire PA and did the eight-item NHANES pocket test, the measured smell dysfunction was 8.9%, and for those who did not, it was 20.1% (P<0.001) (Hoffman, Rawal et al. 2016). It is possible that exercise intensity, such as high-intensity exercise and endurance exercise, increases growth factors (Wahl, Jansen et al. 2014) As well as, a study estimating prevalence and investigating potential risk factors for smell dysfunction in 3519 participants found similar results (NHANES 2013-2014). According to the results, the prevalence of olfactory dysfunction was significantly correlated with PA intensity (METs/week), with those having smell impairments having lower levels of PA intensity [OR=1.61, CI 95% (1.27-2.05), P< 0.001]. (Liu, Zong et al. 2016). According to Liu, Zong et al. (2016) study, the reason for these results may be the improvement of the cardiovascular system, which leads to more cerebral blood flow and oxygen flow and improves cognitive function (Wang, Eslinger et al. 2010).

Another study evaluated the relationship between Parkinson's disease risk factors and abnormal smell using the 40-item University of Pennsylvania Odor Identification Test and the effect of vigorous PA on 173 people. According to the results, no relationship was found between the history of vigorous PA and the University of Pennsylvania's smell recognition test scores for people who have participated in vigorous exercise for a lifetime. The obtained results are somewhat close to the results of the present study. According to the results of the present study, only the frequency (day/week) of vigorous PA was related to detecting grapes and the constant effects of PA on the chance of correctly detecting grapes were minor. Because some studies have shown that vigorous activities such as running, cycling, and swimming decrease the level of acetylcholine, an olfactory-enhancing neurotransmitter (Jäger, Purpura et al. 2007, Penry, Manore et al. 2008), it can be explained the absence of improvement in olfactory function.

### 4.1.4 The volume of physical activity and olfaction

The present study found that an increase in moderate PA volume (METs*h/week) increased the chance of the ability to recognize grape [OR =1.002, CI 95% (1.000-1.005), p=0.028] related to the nutrition odor group.

The result of our study showed that the constant effect of moderate PA volume on odor detection is small. In this regard, a study examined the relationship between the volume of PA (METs*h/week) and features of Parkinson's disease, including hyposmia from 1986 to 2014. In this research, hyposmia was measured using a brief olfactory identification test. Also, PA total volume was calculated by summing MET*hours/week across vigorous and moderate PAs reported by the participant in baseline and cumulative average PA($P \leq 0.05$). The result demonstrated that neither baseline PA [OR=1.01, CI 95%(0.80-1.18), P=0.52] nor cumulative average PA [OR=1.02, CI 95%(0.79-1.27), P=0.96] showed an association between hyposmia and PA volume in vigorous and moderate intensity (Hughes, Gao et al. 2019).

## 4.2 Implications for kinesiologists

Our findings indicate that PA parameters (duration, frequency, and volume), especially moderate PA, were associated with an enhanced ability for adults to detect odors. As moderate PA is associated with detecting grape and leather odors, performing different forms of PA for at least 10 minutes continuously during work or leisure time, such as brisk walking or carrying loads, according to this study's definition, can potentially assist people with smell problems. Also, performing PAs at moderate intensity can be effective. To recommend doing such moderate activities, one should consider PA parameters such as frequency and duration because all three factors have been associated with smell detection. However, while the effect of PA on the chance of correctly detecting odors is significant, it remains below 7.4%.

Furthermore, the vigorous PA was also related to the detection of smells. Gas odors, which are associated with environmental hazards and belong to the category of warning odors (Boesveldt and de Graaf 2017), are related to vigorous PA. According to the definition of vigorous PA in this study, (i.e. various forms of PA for at least 10 minutes continuously while working with or without pay, and housework in a typical week significantly increases breathing and heart rate, such as construction work (Loprinzi and Beets 2014, Vidot, Bispo et al. 2017)), such modality could be effective in improving adults' sense of smell.

The participants in this study were aged 40 years and more, so the age of people should be considered when prescribing the type of PA. Most adults, especially older adults, prefer moderate-intensity PA to vigorous PA (Stewart, Mills et al. 2001, Reitlo, Sandbakk et al. 2018). According to the Canadian Society for Exercise Physiology guidelines, moderate to vigorous aerobic PA for at least 150 minutes per week is recommended for people aged 18 to 64 and over 65 (CSEP 2021).

## 4.3 Strengthsngth and limitations

Several intervention-based studies have been conducted that investigate the effect of PA as a prevention or treatment of olfactory disorders caused by diseases or biological or environmental conditions. Still, very few studies have reported PA parameters and their association with olfactory function in healthy people. As such, one of the main strengths of our study is that the population was composed of healthy adults, in contrast to previous studies that focused more on patients. According to our knowledge, the study presented in this thesis is the first study that examines the association between PA parameters, including the frequency, duration, and volume of PA and olfactory function and its effect on the probability of detecting odors related to nutrition, warning, and common household odors. The current study is a secondary analysis of the 2013-2014 NHANES study because this organization, part of the US Public Health Surveillance, studies a large population yearly and has examined olfactory function since 2011. As a result, it provides a unique opportunity to investigate the relationship between olfactory function and PA.

There are some limitations to consider when interpreting the results of the present study. First, the assessment of PA parameters using NHANES interview data and self-report questionnaires involves bias and recall bias, thus increasing the risk of over-or under-reporting PA. Moreover, respondents' perceptions of PA intensity vary, and it can be difficult for respondents to identify and quantify PA periods. Second, the present study only considered age and sex as factors that affect both PA and olfactory function. It cannot be excluded that other confounding factors might be of interest. As this is the first study to explore the possible association between specific PA parameters and smell detection, simple analyses have been conducted and results could underline false positive results. Finally, it should be considered that the significance of this test is influenced by the sample size. Due to this study's large sample size, the correlation may be false because of its low significance.

## 4.4 Perspectives

Future studies on interventions aimed at improving the performance of the olfactory system should continue to monitor PA parameters such as frequency, duration, and volume of PA. Some studies have found a correlation between PA and smell, especially in the elderly (Zhang, Li et al. 2020). Still, no association was found between the sensation of different smells and variables such as frequency, duration, or volume. Therefore, to verify the existence of this relationship, different samples should be compared with PA parameters of varying intensities.

In future studies, it is suggested to examine intervening factors, such as physical condition, mental condition, and health, to have a better understanding of potential results.

# Chapter 5 – [Conclusion]

PA is emerging as one of the ways to prevent and treat olfactory disorders and can be related to improving the performance of the olfactory system. So, in this thesis, we investigated the association between PA parameters and olfactory performance. The relationship between the PA parameters (duration, frequency, and volume) in detecting smell in healthy people over 40 years of age was investigated the results of the present study showed that higher duration, frequency, and volume of moderate PA was associated with a higher ability to detect smells such as grapes from nutrition groups, smoke from the warning groups, and leather from common household smells. Also, a higher frequency of vigorous PA was related to detecting grapes from nutrition groups. Therefore, PA parameters, mainly frequency of moderate PA, are associated with odor detection capacity in all three categories of odors. However, the constant effect of PA on the chance of correct eight-item NHANES pocket smell test detection is rather small (below 7.4%). According to our knowledge, the study is the first that investigates the association between duration, frequency, and volume of PA on the recognition of different odors and the performance of the participants' olfactory system in a large-scale approach that NHANES implemented in 2014-2013.

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