

Review Article

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Vitamin D and smell impairment: a systematic literature review

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Abstract

Objective. Smell impairment affects 60–80 per cent of individuals aged over 80 years. This review aimed to identify any association between vitamin D deficiency and smell impairment, and determine the efficacy of vitamin D to treat smell impairment.

Methods. A literature search was conducted across four databases between the years 2000 and 2022. The literature screen was performed by two independent reviewers.

Results. Seven articles were included in this review. Four studies examined the association between vitamin D deficiency and smell impairment, with three studies identifying a significant relationship. Three studies investigated the use of vitamin D as treatment for smell impairment, which found complete resolution or significant symptom improvement after vitamin D deficiency was treated.

Conclusion. This review identified limited studies on this topic. As vitamin D supplementation is relatively cost-efficient, further large-scale studies should be carried out to investigate the efficacy of vitamin D for treating anosmia.

Introduction

Smell impairment ranges from a decreased sense of smell (hyposmia) to a complete loss of smell (anosmia). Smell impairment can also be qualitative, whereby patients have distorted perceptions of smell (parosmia), or olfactory hallucinations (phantosmia). A large cross-sectional study conducted in the USA in 2016 found an estimated prevalence of 13.5 per cent for smell impairment (spectrum of hyposmia to anosmia) in people aged 40 years or older.¹ This progressively worsens with age, with smell and taste impairment affecting more than 50 per cent of individuals aged over 65 years, and 60–80 per cent of individuals aged over 80 years old.² Anosmia has been associated with increased five-year mortality rates in older adults.³ In addition, studies have shown that smell impairment significantly affects quality of life with regard to eating habits and nutritional intake, leading to depression.^{4–6}

One of the recognised symptoms of coronavirus disease 2019 (Covid-19) is sudden-onset anosmia.⁷ Various theories of pathogenesis have been proposed for this, such as damage to olfactory sensory neurons or the olfactory centre in the brain, nasal obstruction, or inflammation-related olfactory epithelium dysfunction.⁸ Studies showed that Covid-19 patients have high recovery rates for smell impairment, with approximately 2 per cent having persisting symptoms after one year.^{9,10} Nonetheless, with the high incidence of Covid-19 globally (584 million cases as of August 2022), there are a significant number of individuals who may have persistent olfactory dysfunction, with an estimated 11.6 million people affected.¹¹ Many studies have investigated treatments for Covid-19-related anosmia, including olfactory training, intranasal and systemic corticosteroids, oral theophylline, vitamin A and omega 3 supplements, or sodium citrate, as summarised in the British Rhinological Society Consensus Guidelines published by Hopkins *et al.* in 2020.^{12,13} However, further evaluation is required before recommendations on their use can be made.¹³ It would therefore be useful to identify further potential treatments for smell impairment.

Vitamin D acts as a neurosteroid hormone involved in brain homeostasis.¹⁴ Studies have shown that it binds to vitamin D receptors, which are widely disseminated in the brain of rats, suggesting multiple functional properties of vitamin D in the central nervous system, including the olfactory system.^{15–17} Vitamin D has been shown to have neuroprotective and immunomodulating effects through several mechanisms, including the regulation of neurotrophins and stimulation of neurotrophic factors.^{18,19} A vitamin D deficiency has been shown to be associated with neurological dysfunction,¹⁸ with hypoacusis demonstrated in mice with defective vitamin D receptors.²⁰

This systematic study aimed to identify any association of vitamin D deficiency with smell impairment, and to review existing literature on the efficacy of vitamin D for the treatment of smell impairment.

Materials and methods

Literature search strategy

This review was carried out using structured methods recommended by Tawfik *et al.*²¹ The Population, Intervention, Comparison, Outcome ('PICO') tool was utilised to develop our literature search strategy.²²

A literature search was conducted across four databases: PubMed/Medline, Cochrane Database of Systematic Reviews, ScienceDirect and ProQuest. The following search strategy was used across all databases, for studies published between the years 2000 and 2022: '(vitamin D) AND (anosmia OR hyposmia OR olfactory function)'.

Inclusion and exclusion criteria

Studies investigating the use of vitamin D for the treatment of hyposmia or anosmia, and any association between vitamin D and smell impairment, were included. Studies that investigated other nasal symptoms, such as congestion, discharge or obstruction, were excluded. Abstracts, conference titles, books, letters to editors, and articles not written in English language were excluded. All articles were screened by two independent reviewers, and the results were compared.

Data extraction

The data extraction process of the included articles was carried out by two authors (WWA and ETG). Extracted data included the year, country and design of each study, sample size, treatment regimen, follow-up period, olfactory test used, and findings. The extracted data were then compared and summarised in tables.

Results

Literature search results

The results of the literature search are shown in Fig. 1.

After abstract screening, 15 articles remained. Seventeen full-text articles were reviewed independently by two authors (WWA and ETG); these included 2 additional articles identified from the 15 articles. Nine articles were excluded as they were deemed irrelevant, and one article had no full text. Thus, a total of seven articles were ultimately included in this review.

Vitamin D deficiency and smell impairment association

Four studies that investigated the association between vitamin D deficiency and smell impairment^{23–26} were included, with details summarised in Table 1. Three studies found a significant relationship between vitamin D deficiency and smell impairment, and these three studies all utilised objective olfactory tests to evaluate the olfactory function of their study participants.^{23,25,26} Bigman's study revealed a significant relationship between vitamin D deficiency (serum 25-hydroxyvitamin D (25(OH)D) level of less than 20 ng/ml) and smell impairment ($p=0.038$).²³ It also found a greater prevalence of smell impairment with increased age ($p<0.001$) and with decreased vitamin D levels ($p<0.001$).²³ Shin and colleagues' study investigated 518 children (mean age, 11.45 years), and found vitamin D deficiency (serum 25(OH)D level of less than 20 ng/ml) to be

significantly associated with smell impairment, independent of aeroallergen sensitisation, nasal obstruction and the presence of allergic rhinitis ($p=0.009$).²⁶ Kim and colleagues' study investigated patients with Parkinson's disease, and found significant correlations between serum 25(OH)D levels and the sum olfactory identification score, in addition to an independent association between 25(OH)D levels and olfactory identification test scores after adjusting for other variables such as age, gender, body mass index (BMI) and disease duration.²⁵

Catton and Gardner's study investigated patients with Covid-19-induced smell loss; in their study, vitamin D did not significantly influence the smell loss recovery period, which was classified as rapid (28 days or fewer) or prolonged (more than 28 days), with a follow-up period of 120 days.²⁴ Their study used a patient survey to collect data on patients' olfactory function ($p=0.27$).²⁴

Vitamin D to treat smell impairment

We identified three articles that investigated the use of vitamin D as a treatment for smell impairment;^{27–29} their extracted data are shown in Table 2. These included a case report,²⁷ a case series²⁸ and a cohort study.²⁹

All the cases from the case report and case series (total patients $n=3$) demonstrated complete resolution of smell impairment after vitamin D deficiency was treated with vitamin D supplements.^{27,28} One of the patients had a relapse of smell impairment once she stopped taking vitamin D supplements and had low serum 25(OH)D levels on a repeat blood test.²⁸ Unfortunately, these two papers did not utilise any objective olfactory test, and the improvement in symptoms was based on a subjective evaluation as reported by patients themselves. The authors also did not investigate other confounding factors that may have resulted in symptom resolution.

The cohort study, by Baki *et al.*,²⁹ which comprised 182 patients and used the validated Connecticut Chemosensory Clinical Research Center olfactory test³⁰ as an outcome measure, revealed a significant difference in olfactory test scores between pre-replacement and post-replacement groups ($p<0.001$), implying improved olfactory function with vitamin D supplementation. The median value of serum 25(OH)D was 11.8 ng/ml in the pre-replacement group and 42.8 ng/ml in the post-replacement group, which also represented a significant difference ($p<0.001$).²⁹

The studies generally utilised Institute of Medicine criteria, defining vitamin D deficiency as a serum 25(OH)D level of less than 20 ng/ml, vitamin D insufficiency as a 25(OH)D level of 20–30 ng/ml and vitamin D sufficiency as a 25(OH)D level of more than 30 ng/ml.³¹

Discussion

Current treatments for smell impairment

There are multiple aetiologies for smell impairment, with the most common being post-infectious olfactory dysfunction, particularly virally mediated upper respiratory tract infections.³² Recent systematic reviews have found that olfactory function in patients with post-viral olfactory dysfunction improved with olfactory training.^{12,33,34} This is supported by previous studies which found olfactory training to be effective for olfactory dysfunction associated with a broad range of

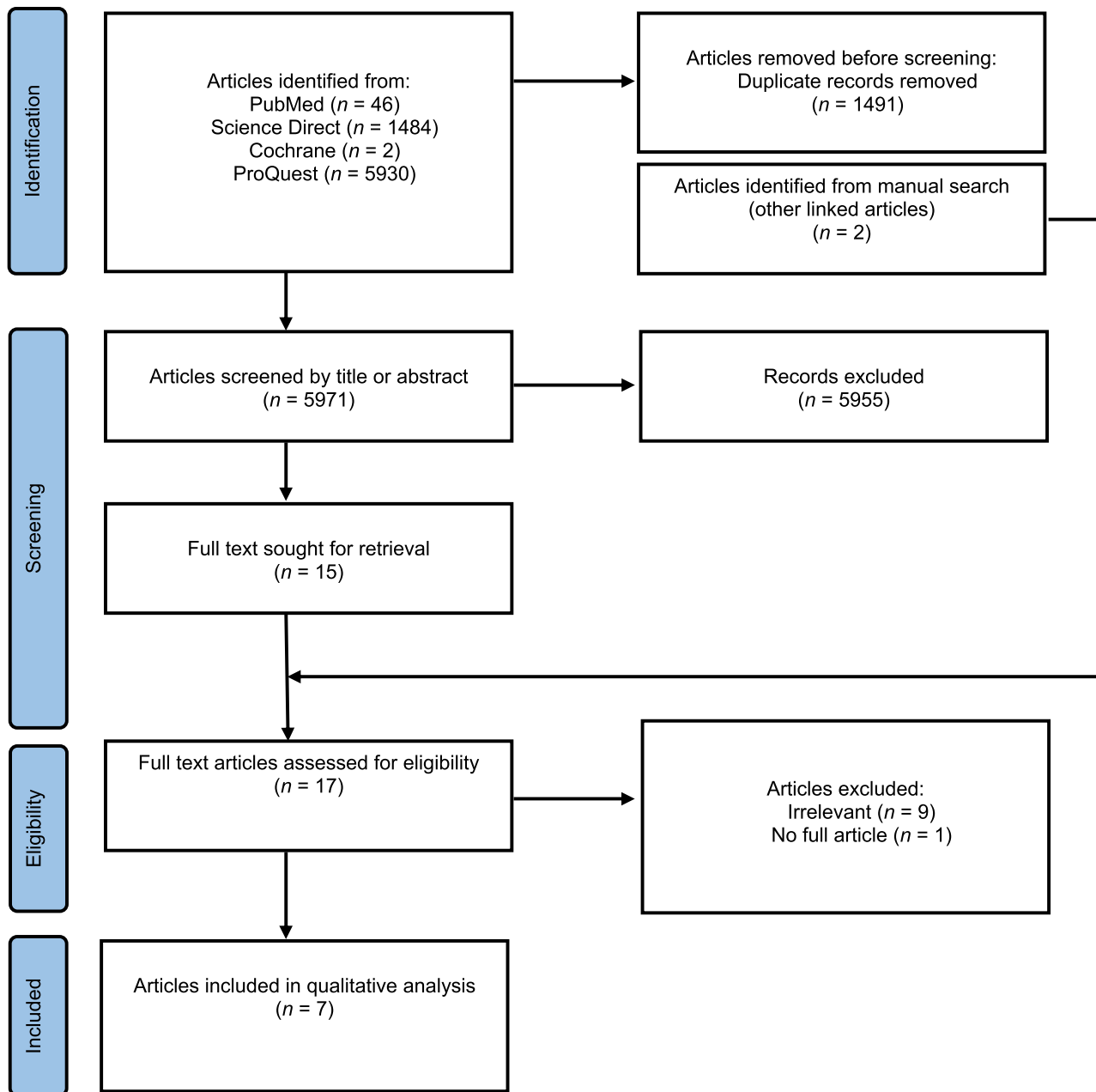


Figure 1. Preferred Reporting Items for Systematic reviews and Meta-Analyses ('PRISMA') flowchart, showing the article selection process for this review.

aetiologies,^{35,36} although some studies have shown it is less efficacious for post-traumatic olfactory dysfunction,³⁷ idiopathic olfactory dysfunction³⁸ and olfactory dysfunction related to Parkinson's disease.³⁹ Nonetheless, the studies included in systematic reviews often lack control groups or a double-blinded study design.⁴⁰

Apart from olfactory training, there have been suggestions that topical steroids, oral steroids, vitamin or zinc supplements, and sodium citrate, can be used to treat smell impairment.³² However, all of these treatments lack robust evidence, and there is a potential risk of harm with steroids.⁴¹

There are also reports of spontaneous resolution of symptoms, with certain factors being found to improve chances of this, such as younger age, being female, a higher olfactory function baseline, and not smoking.⁴²

The most recent British Rhinological Society consensus guidelines recommend olfactory training for patients with Covid-19-related anosmia persistent for

more than two weeks, with oral steroids, topical steroids and omega 3 supplements considered on an individual basis.¹²

Possible mechanisms of vitamin D improving olfactory function

This review has identified three studies that show a significant association between vitamin D deficiency and smell impairment,^{23,25,26} alongside three studies which revealed that correcting vitamin D deficiency can lead to significant improvements in smell impairment.²⁷⁻²⁹ There has not been a proven explanation for this relationship between vitamin D and olfactory function, although several possible mechanisms have been proposed.

As mentioned, vitamin D is known to have a neuroprotective effect.^{18,19} With the discovery that rat olfactory systems contain widespread vitamin D receptors, vitamin D could be

Table 1. Summary of four articles investigating vitamin D deficiency and smell impairment

Authors	Year	Country	Study design	Sample size (n), population	Olfactory test used	Findings
Bigman ²³	2020	USA	Cross-sectional survey	2216	NHANES Pocket Smell Test	Significant relationship between vitamin D deficiency & smell impairment ($p = 0.038$)
Catton & Gardner ²⁴	2022	UK	Cross-sectional survey	235, Covid-19-induced smell loss	Patient survey	No significant difference in vitamin D between rapid (<28 days) & prolonged (>28 days) recovery groups ($p = 0.27$)
Shin <i>et al.</i> ²⁶	2021	Korea	Cross-sectional study	518, paediatric population	Burghart Sniffin' Sticks kit	Vitamin D deficiency significantly associated with smell dysfunction, independent of aeroallergen sensitisation, nasal obstruction & presence of allergic rhinitis ($p = 0.009$)
Kim <i>et al.</i> ²⁵	2018	Korea	Cross-sectional survey	39, PD patients	Korean Sniffin' Sticks II test	Serum 25(OH)D level significantly correlated with sum olfactory identification test score ($p < 0.01$)

NHANES = National Health and Nutrition Examination Survey; Covid-19 = coronavirus disease 2019; PD = Parkinson's disease; 25(OH)D = 25-hydroxyvitamin D

neuroprotective against degenerative processes in the olfactory system.¹⁷ This is especially relevant for patients with Parkinson's disease related olfactory dysfunction, or idiopathic olfactory dysfunction which is more prevalent in older age groups.

One of the four cardinal symptoms of chronic rhinosinusitis is the reduction or loss of sense of smell. Low-grade chronic inflammation may lead to smell impairment, either through conductive or sensorineural mechanisms.⁴³ Apart from neuroprotective effects, vitamin D has also been shown to have anti-inflammatory effects, by suppressing the release of pro-inflammatory cytokines such as interleukin (IL)-2, IL-6 and IL-12, and tumour necrosis factor alpha, the levels of which have been proven to be directly related to coronavirus outcome.^{19,44} Vitamin D exerts important regulatory functions on both innate and adaptive immunity, by inducing the differentiation of macrophages and exerting direct antibacterial and antiviral actions.¹⁹ These anti-inflammatory effects of vitamin D may provide a possible explanation as to how it can improve olfactory function.

Vitamin D deficiency

Vitamin D deficiency, defined as a serum 25(OH)D level of less than 30 ng/ml, is estimated to have a worldwide prevalence of 1 billion people.⁴⁵ A national survey in 2017 by Public Health England revealed the prevalence rate to be about 24.0 per cent in men and 21.7 per cent in women aged 19–64 years, in the UK.⁴⁶ Vitamin D deficiency was found to be more prevalent in winter and spring, in the northern part of the UK, and amongst non-white ethnic groups.⁴⁷

Studies in our review demonstrated an association between vitamin D deficiency and smell impairment,^{23–26} therefore, patients presenting with smell impairment may have unidentified vitamin D deficiency, which is not routinely screened for. It may be prudent to measure the serum 25(OH)D levels in patients presenting with smell impairment, as treatment with vitamin D supplements can be easily achieved.

With vitamin D being shown to be important for preventing osteoporosis, cardiovascular diseases, type 1 diabetes, autoimmune diseases and some cancers,⁴⁸ the recommendation from Public Health England to take vitamin D supplements

Table 2. Summary of three articles investigating vitamin D as treatment for smell impairment

Authors	Year	Country	Study design	Sample size (n)	Vitamin D treatment regimen	FU period	Olfactory test used	Findings
Ibrahim & Elnimeiri ²⁷	2020	Sudan	Case report	1	50 000 IU weekly for 8 wks	6 mths	n/a	Complete symptom resolution after serum 25(OH)D normalised
Kruse & Cambron ²⁸	2011	USA	Case series	1	10 000 IU a day	8 mths	n/a	Complete symptom resolution after serum 25(OH)D normalised
				1	50 000 IU weekly for 8 wks	8 wks	n/a	Symptom improvement after serum 25(OH)D normalised
Baki <i>et al.</i> ²⁹	2021	Turkey	Non-blinded, non-placebo-controlled trial	182	50 000 IU weekly for 8 wks	12 wks	CCCRC olfactory test	Significant difference in olfactory test scores between pre- & post-replacement groups ($p < 0.001$), with normalised serum 25(OH) levels post replacement

FU = follow-up; wks = weeks; mths = months; n/a = not applicable; 25(OH)D = 25-hydroxyvitamin D; CCCRC = Connecticut Chemosensory Clinical Research Center

between winter and spring may well be sound advice.⁴⁹ Studies have shown that patients who take vitamin D supplements have a lower risk of developing vitamin D deficiency.^{46,47} Interestingly, certain studies have shown that diseases such as inflammatory bowel disease which affect nutrient absorption are associated with smell impairment.^{50,51} These patients may well be vitamin D deficient, and it would be beneficial to measure their serum 25(OH)D levels and provide vitamin D supplements as necessary.

Studies on vitamin D as treatment for smell impairment

In conducting this literature review, it was apparent there were no robust, large-scale, blinded, placebo-controlled trials investigating the use of vitamin D to treat smell impairment. Of three studies included in this review, two were case reports,^{27,28} which were level 5 in terms of hierarchy of evidence. Additionally, they did not use any objective olfactory test to measure olfactory function, instead relying on the subjective improvement reported by the patients themselves. Baki and colleagues' study utilised an objective measuring tool for olfactory function and ensured the serum 25(OH)D levels were taken with a standardised method; however, this study was not blinded, and there was no placebo-controlled group to determine whether vitamin D was the causative factor leading to improvements in olfactory function scores.²⁹

Studies on vitamin D deficiency and smell impairment association

Bigman's cross-sectional study involved a robust statistical analysis, employing multivariate analyses, and adjusting covariates to form ideal weighted logistic regression models, to investigate the relationships between the outcomes and each covariate studied.²³ It also included a large population group, standardised the method of measuring serum 25(OH)D levels, and measured olfactory function using the validated Pocket Smell Test.⁵² They also ensured their study sample had appropriate exclusion criteria.

Catton and Gardner's study did not investigate the association between vitamin D deficiency and smell impairment; rather, it examined whether there was a significant difference in vitamin D between groups that experienced either rapid (28 days or fewer) or prolonged (more than 28 days) recovery of Covid-19-induced smell loss, for which they found none.²⁴ Their study utilised statistical methods that only included binary variables, and were not able to adjust for confounding factors. Additionally, they relied on self-reports of olfactory function, with patients rating the severity of smell loss on an 11-point scale (with possible responses ranging from 0 to 10), making the data less reliable.

Shin and colleagues adjusted for confounding factors in their statistical analysis, and determined that low serum 25(OH)D levels were significantly associated with low olfactory threshold scores, independent of age, sex, secondary smoking, BMI score, nasal obstruction, aeroallergen sensitisation and nasal obstruction.²⁶ By using the Sniffin' Sticks test, the authors were able to obtain objective measurements for olfactory impairment. One limitation, however, was that their study only included children. Kim and colleagues also adjusted for other variables when performing their statistical analysis; however, their study had a small sample size, lacked a control group, and focused on patients with Parkinson's disease.²⁵

Overall, the studies included were cross-sectional surveys, which increases the risk of selection bias and/or recall bias.^{23,24,26} Studies with a large sample size, and which include comparison with a control group, will be able to increase the validity of the association identified by these studies.

Conclusion

This review identified limited studies showing the efficacy of using vitamin D to treat smell impairment, alongside the association of vitamin D deficiency and smell impairment. Nonetheless, as vitamin D supplementation is relatively low-cost, can be easily measured and has other proven benefits when the deficit is corrected, the authors would recommend its use. Further large-scale studies, including randomised, controlled trials, should be carried out to investigate the efficacy of using vitamin D for the treatment of anosmia, for the benefit of patients suffering from smell impairment.

Competing interests. None declared.

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