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PROGRAMA DE PÓS-GRADUAÇÃO EM NUTRIÇÃO, ATIVIDADE FÍSICA E PLASTICIDADE FENOTÍPICA – PPGNAFPF

DANIELLY ALVES MENDES BARBOSA

COVID-19: PREVALÊNCIA E IMPACTO DAS DISFUNÇÕES OLFATIVAS E GUSTATIVAS NA QUALIDADE DE VIDA E NOS HÁBITOS ALIMENTARES DE PROFISSIONAIS DE SAÚDE

VITÓRIA DE SANTO ANTÃO
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Dissertação apresentada ao programa de pós-graduação em nutrição, atividade física e plasticidade fenotípica da universidade federal de pernambuco, como requisito parcial à obtenção do título de mestre.

Área de concentração: Fatores Ambientais Moduladores da Plasticidade Fenotípica

Orientador(a): Dra. Kelli Nogueira Ferraz Pereira Althoff

Coorientador(a): Dra. Ana Lisa Do Vale Gomes

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BANCA EXAMINADORA

Dr.ª Alice Valença Araújo (Examinador interno)

Universidade Federal de Pernambuco

Dr. Caio Bezerra Souto Maior (Examinador externo)

Universidade Federal de Pernambuco

Dr.ª Renata Angeli (Examinador externo)

Universidade do Estado do Rio de Janeiro

RESUMO

Os sintomas mais mencionados pelos primeiros pacientes infectados pelo SARS-CoV-2 foram: febre, tosse, mialgia e dispinéia. Contudo, quando o vírus adentra outros continentes, outros sinais e sintomas passam a pertencer ao quadro de manisfestações clínicas da COVID-19; sintomas incomuns estava sendo cada vez mais relatado, sendo ele as alterações olfativas e gustativas. Muitos pacientes que tiveram COVID-19 desenvolveram sintomas persistentes, chamados de *Long* COVID, e um dos sintomas mais duradouros foi a perda do olfato e do paladar. Ter essas alterações, de forma persistente ou não, pode acarretar riscos à qualidade de vida e aos hábitos alimentares. Por isso, esse estudo objetiva avaliar a prevalência e o impacto das disfunções olfativas e gustativas na qualidade de vida e nos hábitos alimentares de profissionais de saúde da Zona da Mata de Pernambuco infectados ou não pelo SARS-CoV-2. Trata-se de uma pesquisa caso-controle realizada com 53 profissionais de saúde da linha de frente ao combate da COVID-19. Esses profissionais passaram previamente pelo Teste do ELISA e foram distribuidos em 3 grupos de acordo com o resultado do teste e da listagem sintomatológica: (1) IgA e/ou IgG negativo para SARS-CoV-2 (n=9); (2) IgA e/ou IgG positivo para SARS-CoV-2 com perda de olfato e/ou paladar (n=37); e (3) IgA e/ou IgG positivo para SARS-CoV-2 sem perda de olfato e/ou paladar (n=7). A coleta das informações foram feitas através de entrevista por ligação telefônica com auxílio de questionários validados. De acordo com o teste de Fisher não há associação entre fatores de risco/comorbidade com o diagnóstico para COVID-19. Quanto aos sinais/sintomas apenas mal-estar e perda de olfato e/ou paladar revelaram associação com a variável do resultado do teste para COVID-19. Do total de 53 participantes desse estudo, 39 indivíduos relataram o comprometimento do olfato e paladar, sendo 37 com diagnóstico positivo para o SARS-CoV-2 e 2 indivíduos com diagnóstico negativo para o SARS-CoV-2. Apenas 1 pessoa relatou o comprometimento isolado do paladar, todos os demais participantes mencionaram o comprometimento integrado tanto do olfato quanto do paladar. Dos 53 profissionais, 31 relataram ter sintomas com duração superior a 4 semanas, classificando-os com *Long* COVID. Entre os sintomas duradouros os mais citados foram: perda do olfato, perda do paladar e fraqueza/cansaço. Referente a análise do impacto dessas disfunções sobre a qualidade de vida os escores totais do sQOD-NS não diferiram entre os pacientes com perda de olfato e/ou paladar e aqueles sem essas disfunções. Em relação ao impacto das disfunções sobre os hábitos alimentares houve associação entre os grupos apenas quanto ao fato de “gostar da comida”, onde grande porcentagem dos indivíduos com resultado positivo e com perda de olfato e/ou paladar relataram que essas disfunções o fizeram gostar menos da comida. Diante disso, esse estudo revelou que existe uma alta prevalência das disfunções do olfato e/ou paladar, a curto e longo prazo, nos sujeitos com diagnóstico positivo para COVID-19 e que esses sintomas podem interferir nos hábitos alimentares reduzindo o prazer pela comida, bem como, fazer com que os indivíduos para compensar a perda desses sentidos optem por alimentos mais temperados e palatáveis.

Palavras-chave: COVID-19; SARS-CoV-2; anosmia; ageusia.

ABSTRACT

The symptoms most mentioned by the first patients infected with SARS-CoV-2 were: fever, cough, myalgia and dyspnea. However, when the virus enters other continents, other signs and symptoms become part of the clinical manifestations of COVID-19; an unusual symptom was being increasingly reported, namely the olfactory and gustatory alterations. Many patients who had COVID-19 developed persistent symptoms, called Long COVID, and one of the most enduring symptoms was a loss of smell and taste. Having these changes, whether persistent or not, can pose risks to quality of life and eating habits. Therefore, this study aims to evaluate the prevalence and impact of olfactory and gustatory dysfunctions on the quality of life and eating habits of health professionals in the Zona da Mata of Pernambuco infected or not by SARS-CoV-2. This is a case-control research carried out with 53 health professionals on the frontlines of the fight against COVID-19. These professionals had previously passed the ELISA test and were divided into 3 groups according to the test result and symptom list: (1) IgA and/or IgG positive for SARS-CoV-2 with loss of smell and/or taste (n=37); (2) IgA and/or IgG positive for SARS-CoV-2 without loss of smell and/or taste (n=7); and (3) SARS-CoV-2 negative IgA and/or IgG (n=9). The collection of information was carried out through a telephone interview with the aid of validated questionnaires. According to Fisher's test, there is no association between risk factors/comorbidity with the diagnosis for COVID-19. As for signs/symptoms, only malaise and loss of smell and/or taste revealed an association with the test result variable for COVID-19. Of the total of 53 participants in this study, 39 individuals reported impaired smell and taste, 37 of which were positive for SARS-CoV-2 and 2 individuals were negative for SARS-CoV-2. Only 1 person reported the isolated impairment of taste, all other participants mentioned the integrated impairment of both smell and taste. Of the 53 professionals, 31 reported having symptoms lasting longer than 4 weeks, classifying them as Long COVID. Among the lasting symptoms, the most cited were: loss of smell, loss of taste and weakness/tiredness. Regarding the analysis of the impact of these dysfunctions on quality of life, the total sQOD-NS scores did not differ between patients with loss of smell and/or taste and those without these dysfunctions. Regarding the impact of dysfunctions on eating habits, there was an association between the groups only regarding the fact of “liking food”, where a large percentage of individuals with a positive result and with loss of smell and/or taste reported that these dysfunctions made them like it. minus the food. Therefore, this study revealed that there is a high prevalence of short and long-term smell and/or taste disorders in subjects with a positive diagnosis for COVID-19 and that these symptoms can interfere with eating habits, reducing the pleasure of food, as well as making individuals, to compensate for the loss of these senses, opt for more seasoned and palatable foods.

Keywords: COVID-19; SARS-CoV-2; anosmia; ageusia.

LISTA DE ILUSTRAÇÕES

LISTA DE ABREVIATURAS

AAO HNS	Relatório de Anosmia da Academia Americana de Otorrinolaringologia - Cirurgia de Cabeça e Pescoço
AMP	adenosina 3,5-monofosfato
CDC	Centro de Controle e Prevenção de Doenças
CEP	Comitê de Ética em Pesquisa
COVID	*Coronavirus Disease 2019*
DNA	Ácido Desoxirribonucleico
ELISA	Enzyme Linked Immunosorbent Assay
IBGE	Instituto Brasileiro de Geografia e Estatística
IL-6	Interleucina 6
MERS-CoV	Síndrome respiratória do Oriente Médio
MS	Ministério da Saúde
NICE	Instituto Nacional de Excelência em Saúde e Assistência
OMS	Organização Mundial de Saúde
PACS	Síndrome Pós-COVID Aguda
PASC	Sequela Pós-Aguda da Síndrome SARS-CoV-2
RNA	Ácido Ribonucleico
SARS-CoV-2	coronavírus da síndrome respiratória aguda grave
SPSS	Statistical Package for the Social Sciences
SQOD-NS	Questionário de Transtornos Olfatórios – Declarações Negativas
TCLE	Termo de Consentimento Livre Esclarecido

SUMÁRIO

1 INTRODUÇÃO

O S*evere Acute Respiratory Syndrome Coronavirus 2* (SARS-CoV-2) teve seu primeiro registro em dezembro de 2019, na China, sendo associado a um quadro severo de síndrome respiratória aguda grave (TONG *et al.,* 2020). O alastramento desse vírus foi muito acelerado, alcançando um cenário de pandemia já no início de 2020 (TONG *et al.,* 2020). Dentre os países da América Latina, o Brasil foi o primeiro país a identificar um paciente infectado pelo vírus e com sintomas da síndrome respiratória aguda grave, em 25 de fevereiro de 2020, na cidade de São Paulo (BAGGIO J. *et al.,* 2021).

Os principais sintomas nos primeiros pacientes com *Coronavirus Disease 2019* (COVID-19) no continente asiático incluíam febre, tosse, mialgia e dispneia (JOTZ *et al.,* 2020). Contudo, a medida que o vírus se expandia para outras localidades e a quantidade de infectados se tornava maior, outros sintomas foram considerados dentro das manifestações clínicas da COVID-19. Sintomas incomuns se apresentaram em uma quantidade cada vez maior, as disfunções olfativas (anosmia) e gustativas (ageusia) tornaram-se conhecidas por todos (CATTANEO *et al*., 2022; VARGAS-GANDICA *et al.,* 2020; CORBELLINI *et al.,* 2020).

Um estudo que comparou indivíduos com diagnóstico de COVID-19 positivo e negativo, evidenciou que o grupo COVID-19 positivo apresentou alterações tanto do olfato quanto do paladar em aproximadamente 7 vezes mais em comparação ao grupo COVID-19 negativo (SAYIN *et al.,* 2020). Na Inglaterra foi evidenciado que dois terços dos profissionais de saúde relataram perda do olfato ou paladar, e destes, 73% continuaram trabalhando normalmente, mesmo com esses sintomas sendo um alto indicativo de infecção pelo SARS-CoV-2 (LECHIEN *et al.,* 2020).

Segundo o Centro de Controle e Prevenção de Doenças (CDC) (2020) embora os pacientes infectados pelo SARS-CoV-2 recuperem sua saúde normal, alguns podem apresentar sintomas que podem durar semanas ou meses mesmo após a recuperação da fase aguda da doença (ISLAM *et al.,* 2020). Coelho e colaboradores (2021), mencionam que em 322 pessoas estudadas, 67% relataram que as alterações do olfato e paladar duraram por um período de 6 meses ou mais. Ter a perda do olfato e paladar, e ainda mais como um sintoma persistente traz diversas consequências psicológicas e emocionais, que afetarão a qualidade de

vida dos pacientes (KANJANAUMPORN *et al.,* 2020). Indivíduos com déficit olfativo e gustativo sofrem alterações nos hábitos alimentares, apresentam problemas para cozinhar, tem diminuição do apetite, da higiene pessoal, dos relacionamentos sociais, desenvolvem problemas emocionais, como depressão, sentimento de insegurança e solidão, e pode ocasionar também a perda de peso e levar à desnutrição (KANJANAUMPORN *et al.,* 2020; KUBA *et al.,* 2018).

Como tantos aspectos que norteiam a urgente necessidade de investigações sobre o impacto da COVID-19 na população mundial, é relevante que se conheça o impacto da anosmia e ageusia em casos de COVID-19. Diante da importância do olfato e do paladar para a vida, esse projeto objetiva avaliar a prevalência e o impacto das disfunções olfativas e gustativas na qualidade de vida e nos hábitos alimentares de profissionais de saúde da Zona da Mata de Pernambuco infectados ou não pelo SARS-CoV-2.

2 REVISÃO DA LITERATURA

2.1 Trajetória do SARS-CoV-2

O vírus SARS-CoV-2 pertence à família *coronaviridae* e à subfamília *Coronavirinae*. É assim chamado pois desencadeia a Síndrome Respiratória Aguda Grave, assim como os vírus antecedentes a ele, o coronavírus da síndrome respiratória aguda grave (SARS-CoV) e o coronavírus da síndrome respiratória do Oriente Médio (MERS-CoV) (MACHHI *et al*., 2020; ZEPEDA *et al*., 2020).

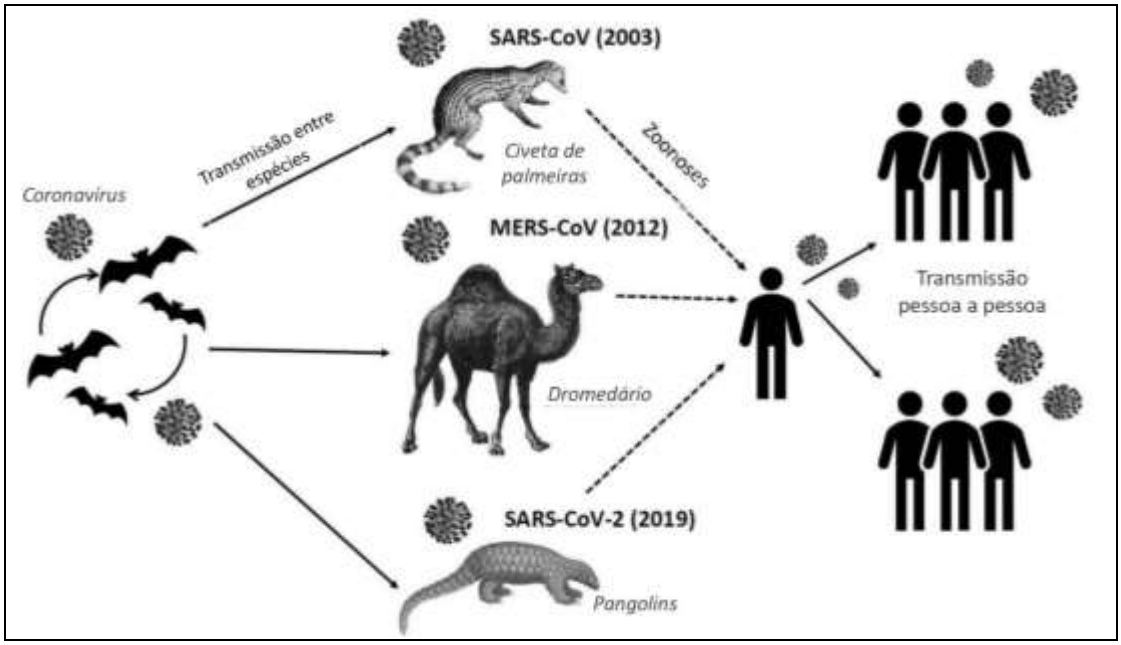
O vírus SARS-CoV foi descoberto na China, em Guangdong, no ano de 2003 (MACHHI *et al*., 2020). Esse vírus se disseminou para 29 países, principalmente na Ásia, até julho de 2003 quando foi controlado. Houve aproximadamente 8 mil casos e mais de 700 mortes, com letalidade de 9,6% (MACHHI *et al*., 2020; YESUDHAS *et al*., 2020). O MERS-CoV foi descoberto em 2012, sendo um vírus altamente patogênico com quase 2 mil pessoas infectadas e uma alta taxa de mortalidade de 36% (YESUDHAS *et al*., 2020). O MERS se espalhou para várias regiões, como a Arábia Saudita, Emirados Árabes Unidos e Coréia (MACHHI *et al*., 2020).

Já o SARS-CoV-2, vírus causador da COVID-19, foi registrado pela primeira vez em dezembro de 2019, na China, na cidade de Wuhan, sendo associado a um quadro com alto nível de letalidade (TONG *et al.,* 2020). A propagação desse vírus foi muito rápida, alcançando uma realidade de pandemia já no começo de 2020 (TONG, *et al.,* 2020). O Brasil foi o primeiro país da América Latina a registrar um paciente infectado com COVID-19; nos momentos atuais, segundo os dados da OMS, o Brasil registrou, até o início de dezembro de 2022, 35.452.099 casos confirmados e 690.409 mortes (WHO, 2022).

Essa família de vírus estão extensamente distribuidos no meio ambiente, infectando animais e seres humanos (ZEPEDA *et al*., 2020). São de origem zoonóticas tendo associação genômica aos coronavírus de morcegos; eles utilizam esses animais como reservatório e a partir deles são capazes de ultrapassar as barreiras entre as espécies infectando hospedeiros intermediários, e então, chegam aos humanos. O SARS-CoV utiliza o mamífero Civeta como intermediário; para MERS-CoV o hospedeiro intermediário é o Dromedário; e para o SARS-CoV-2, uma

das possíveis teorias apontam que, os pangolins, gatos e cães sejam seus hospedeiros intermediários (figura 1) (MACCHI *et al*., 2020; ZEPEDA *et al*., 2020).

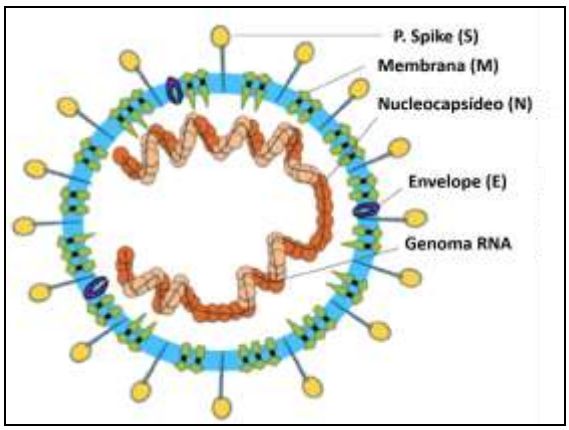
Figura 1 - Origem e transmissão do coronavírus SARS-CoV, MERS-CoV, e SARS-CoV-2



Fonte: Adaptado de Zepeda *et al.* (2020).

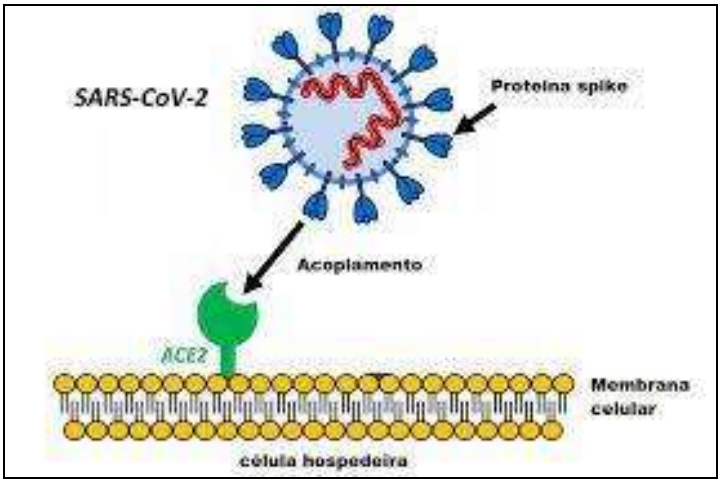
O SARS-CoV-2 é um víron esférico com espículas que se exteriorizam, constituindo proeminências similares a uma coroa solar, por isso é chamado de "*corona*", que em latim significa coroa. Apresenta um RNA de fita simples de polaridade positiva (5'-3') e possui 4 proteínas estruturais: 1. S (spike), 2. E (envelope), 3. M (membrana) e 4. N (nucleocapsídeo) (Figura 2) (MOHAMMADI *et al*., 2021; LIMA *et al.,* 2020). A infecção ocorre quando a proteína S (spike), formada por glicoproteínas, se liga à membrana da célula hospedeira a partir dos receptores celulares, que neste caso, são as enzimas conversora de angiotensina 2 (ACE2) (figura 3), ou seja, o vírus causador da COVID-19 faz uso da ACE2 para adentrar nas células. Vale ressaltar que a ACE2 é uma proteina de membrana tipo I com a função de facilitar a maturação da angiotensina, que irá levar a vasoconstrição. Essa enzima pode ser encontrada nos pulmões, coração, rins e intestino (LIMA *et al*., 2020).

Figura 2 - Estrutura viral do SARS-CoV-2



Fonte: Adaptado de Li *et al.* (2020).

Figura 3 - Acoplamento chave-fechadura da proteína viral



Fonte: Adaptado de The Federal (2020)[1].

Até chegar nas células humanas, a passagem do vírus de morcegos para hospedeiros intermediários favorece diversos ciclos de replicação e mutações (MACHHI *et al.,* 2020). Além disso, à medida que o vírus realiza a replicação ele também sofre alterações no seu RNA, devido a erros cometidos pela RNA polimerase dependente de RNA (RdRp), originando proteínas com conformidades diferentes da original (HARVEY *et al.,* 2021). As polimerases dos vírus de RNA tendem a executar mais erros do que as polimerases de vírus de DNA durante o processo de replicação. Logo, os coronavírus, assim como outros vírus de RNA,

[1] Disponível em: https://thefederal.com/the-eighth-column/coronavirus-is-not-man-made-only-rumours-are/

passam por frequentes mutações em seu genoma apresentando uma taxa média de substituição de ~ 3 × 10^{-4} substituições por local por ano (HARVEY *et al.,* 2021; SILVA *et al.,* 2021). Essa mudança pode alterar diversas características da funcionalidade do vírus, como: a patogenia; replicação; grau de infecção e disseminação; nível de transmissibilidade e/ou antigenicidade; bem como as características sintomatológicas (HARVEY *et al.,* 2021; SILVA *et al.,* 2021).

Nos primeiros casos de COVID-19 no continente Asiático, o quadro sintomatológico incluía febre, tosse, mialgia e dispneia (JOTZ *et al.,* 2020). Em contrapartida, quando o SARS-CoV-2 adentra a outros continentes, outros sinais e sintomas passam a ser considerados como manifestações clínicas da COVID-19 (VARGAS-GANDICA *et al.,* 2020). De acordo com Muschi (2022), durante o primeiro semestre de 2021, a variante Gamma foi considerada a linhagem SARS-CoV-2 predominante no Brasil; essa variante estava fortemente associada a um sintoma incomum, que estava sendo relatado numa quantidade cada vez mais predominante: alterações olfativas e gustativas (CORBELLINI *et al.,* 2020).

2.2 Olfato: importância e anatomofisiologia

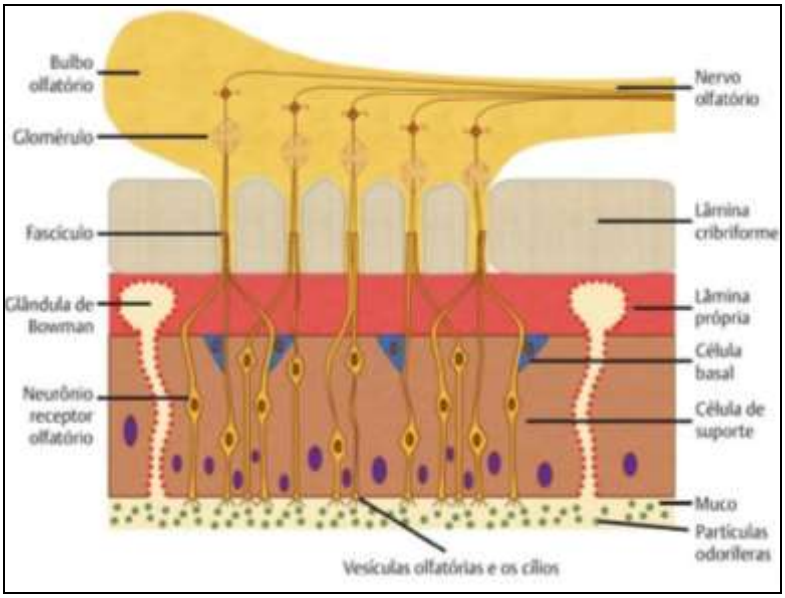
Do ponto de vista evolutivo o olfato é um dos sentidos mais antigos e que garantiu o desenvolvimento do homem. Este sentido é extremamente importante para manutenção e segurança da vida, pois funciona como alerta para situações de risco, como detecção de alimentos estragados e vazamento de gás e fumaça. O olfato também está associado à qualidade de vida, uma vez que, ele está ligado a emoções, memórias e recordações (ROMANO *et al.,* 2021). O olfato “é o sentido que tem acesso neurológico direto ao sistema límbico do cérebro – que guarda e intermedia as memórias” (BATEY, 2010, P117).

Quanto à anatofisiologia da olfação, um dos ossos que formam a cavidade nasal é o osso etmoide, este osso na região da base do crânio é chamado de lâmina cribriforme; assim denominado por possuir aberturas que favorecem a passagem das fibras nervosas olfativas que chegam a região superior da cavidade nasal, no epitélio olfativo, e se dirigem para o bulbo olfatório (ROMANO *et al.,* 2021).

Quando o ar é inalado ele se espalha por toda a mucosa nasal, mas uma

fração desse ar inalado, rico em partículas odoríferas, irá se dirigir para a porção mais superior da cavidade nasal, próximo a lâmina cribriforme. Nessa região as partículas odoríferas irão se ligar aos receptores olfatórios, ativando uma cascata intracelular que culminará com a síntese de AMP cíclico (AMPc). A elevação dos níveis de AMPc resulta no influxo de sódio e cálcio, seguido do potencial de ação do impulso neuronal. Então, os axônios direcionam a informação para o bulbo olfatório. Os feixes de fibras neurais saem do bulbo olfatório e seguem em direção ao córtex olfatório através do primeiro par de nervo craniano, o nervo olfatório (figura 4). Contudo, esse estímulo segue também em direção às áreas corticais olfatórias primárias. Acredita-se, que os estímulos após chegarem nessas áreas corticais primárias são enviados para o hipocampo, hipotálamo, cerebelo e córtex orbitofrontal. E são essas regiões que podem estar interligadas com a associação do olfato às emoções e memória. Logo, quando acontece o estímulo olfatório, várias áreas atuam na percepção do odor (ROMANO *et al.,* 2021; CALDAS *et al.,* 2011; HUMMEL *et al.,*2011).

Figura 4 - Representação esquemática da disposição das principais células do neuroepitélio olfatório.



Fonte: Romano *et al.* (2021).

2.3 Paladar: importância e anatomofisiologia

O paladar, assim como o olfato, é um sistema sensorial complexo dividido em sensações básicas de salgado, doce, azedo e amargo (MOURA *et al.,* 2015). Logo, o paladar atua na percepção do gosto dos alimentos, em conjunto com a olfação (ROMANO *et al.,* 2021; HUMMEL *et al.,*2011). Algumas situações adversas, como alteração no fluxo aéreo ocasionado por congestão nasal e que altere a influência do olfato sobre o sabor, pode resultar em disfunções do paladar. Essas disfunções são classificadas como ageusia - ausência do paladar; hipogeusia - diminuição da percepção do sabor; disgeusia- capacidade distorcida da percepção do paladar (MOURA *et al.,* 2015).

Uma alteração nesse sentido pode causar uma redução significativa na ingesta alimentar, podendo ocasionar distúrbios alimentares, que geralmente afeta o crescimento físico e desenvolvimento (MOURA *et al.,* 2015). Ademais, através da gustação é possível sentir prazer e também identificar situações de risco, como alimentos que podem prejudicar nosso organismo e exposição a produtos químicos nocivos (ROMANO *et al.,* 2021; HUMMEL *et al.,*2011).

Quanto à anatofisiologia da gustação, o sistema do paladar é formado por botões e papilas gustativas que estão localizadas ao longo da língua, no palato, na epiglote, na faringe e laringe. Os botões são formados por células neuroepiteliais, que apresentam alta capacidade regenerativa – tendo uma vida média de 8-22 dias (ROMANO *et al.,* 2021).

Cada receptor gustativo é específico para um sabor, seja doce, salgado, amargo, azedo e umami, contudo, na mesma papila pode existir mais de um tipo de receptor. Temos quatro papilas gustativas, mas apenas três estão associadas a detecção do sabor, que são as fungiformes, circunvaladas e foliáceas. Os nervos cranianos: facial, glossofaríngeo e vago, vão conduzir o estímulo para o núcleo do trato solitário, que irão estabelecer sinapses em direção ao tálamo e dele para o córtex gustativo (ROMANO *et al.,* 2021;HUMMEL *et al.,*2011).

2.4 Disfunções do olfato e paladar associadas à COVID-19

Muitas condições clínicas podem desencadear a perda de olfato e paladar; pacientes acometidos por doenças neurodegenerativas como Alzheimer, Parkinson ou que sofreram algum trauma craniano podem apresentar disfunções sensoriais. Assim como, indivíduos com problemas respiratórios como rinite, sinusite ou resfriado também podem desenvolver redução dos sentidos de olfação e gustação, contudo, geralmente estão associados a obstrução nasal, mas, a perda desses sentidos relacionados a COVID-19 ocorrem sem qualquer obstrução das vias nasais e o início desses sintomas são rápidos e não progessivos como em outras situações (FREITAS, 2019; BARROS *et al.,*2015; ESHRAGHI *et al.,* 2020).

Esse distúrbio quimiossensorial pode ser um importante indicador de infecção pelo SARS-CoV-2 (FREITAS, 2019). Em estudo comparativo entre indivíduos com diagnóstico positivo para COVID-19 em relação a indivíduos com diagnóstico negativo para COVID-19, descobriu que o grupo COVID-19 positivo apresentou comprometimento tanto do olfato quanto do paladar cerca de 7 vezes mais em comparação ao grupo COVID-19 negativo (SAYIN *et al.,* 2020). Inclusive, estudo realizado no Brasil com 183 pacientes testados, 145 tiveram diagnóstico positivo para COVID-19 e destes 126 apresentaram perda do olfato súbita e 19 desenvolveram redução do olfato aguda (KOSUGI *et al.,* 2020). Quantificar adequadamente a perda de olfato e paladar, e delimitar uma relação do tempo entre o contágio da doença e as alterações olfatórias e gustatórias são fatores importantes para auxiliar no diagnóstico precoce, evitando contágio e possíveis complicações (MULLOL *et al*, 2020). O rastreamento de sintomas de perda ou alterações olfativas e gustativas em pacientes não hospitalizados pode caracterizar uma estratégia de triagem clínica (VAIRA *et al*., 2020).

Segundo revisão sistemática acerca das alterações olfativas e gustativas associadas à COVID-19, foi possível identificar que as mulheres apresentavam maior percentual de alterações de olfato e/ou paladar em comparação com os homens; que nos países asiáticos a prevalência da disfunção do olfato e paladar foi menor em comparação com os continentes da América do Norte e Europa; e que os sintomas mais relatados em associação a perda do olfato e paladar foram: febre,

tosse, dor de cabeça, fadiga e sintomas gastrointestinais (SANTOS *et al*., 2021).

Os profissionais da saúde estando em contato direto com os pacientes infectados e pacientes em situações de saúde fragilizada, constituem um público com alto risco de adquirir e também de transmitir o novo coronavírus (TEIXEIRA *et al.,* 2020). De acordo com a OMS e o MS, dentre os países que compõem as Américas, 570 mil profissionais de saúde se infectaram pelo novo coronavírus, destes, 307 mil são do Brasil (TEIXEIRA *et al.,* 2020). Em Pernambuco, mais de 18 mil profissionais de saúde foram infectados e 194 evoluíram para óbito (BENITO *et al.,* 2020).

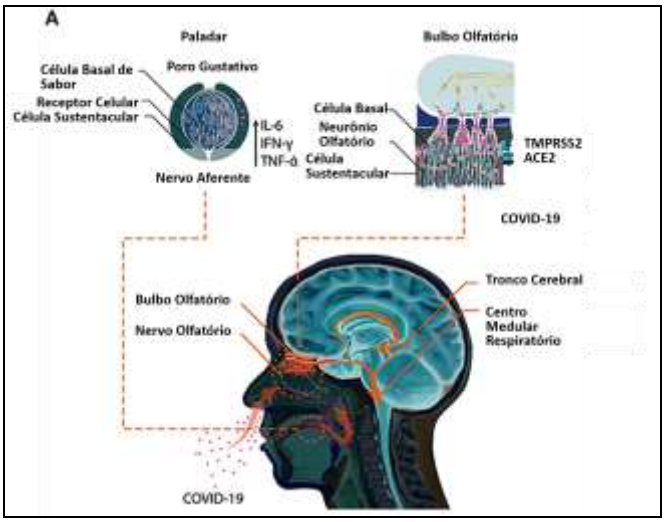
A vigilância do Centro de Controle e Prevenção de Doenças (CDC), nos Estados Unidos, revelou uma prevalência de 16% de perda do olfato ou paladar entre mais de 9.000 profissionais de saúde com COVID-19 (KEMPKER *et al.,* 2021). No entanto, estudo desenvolvido na Inglaterra evidenciou que apesar de dois terços dos profissionais de saúde relatarem perda do olfato ou paladar, 73% continuaram trabalhando normalmente, mesmo com esses sintomas sendo um alto indicativo de infecção pelo SARS-CoV-2 (LECHIEN *et al.,* 2020).

Em relação aos mecanismos patogênicos tem-se a hipótese que as disfunções no sentido do paladar podem estar associadas a danos na enzima conversora de angiotensina 2 (ACE2) (VAIRA *et al.,* 2020) – identificada como receptor celular do vírus SARS-CoV-2 (ZHOU *et al.,* 2020), principalmente no bulbo olfatório (VAIRA *et al*., 2020). Esses receptores são altamente expressos na mucosa oral e nas células epiteliais da língua e são associadas à percepção do paladar (XU *et al.,* 2020). Em relação às alterações no sentido do olfato pesquisas apontam que esta alteração pode ser desencadeada por danos nas células que sustentam os neurônios da olfação, logo o dano na célula de suporte que fica ao redor do neurônio acaba inibindo a sua funcionalidade (BRANN *et al.*, 2020).

Um outro estudo detectou uma relação inversamente proporcional das alterações de olfato e paladar com os níveis de Interleucinas 6 (IL-6), à medida que ocorria o retorno das funções do olfato e paladar ocorria a redução dos níveis de IL-6 (CAZZOLA *et al.,* 2020). Esta associação pode estar ligada ao fato da IL-6 apresentar níveis periféricos nos receptores celulares infectados pelo SARS-CoV-2 (CAZZOLA *et al.,* 2020), e também pelo fato das citocinas pró-inflamatórias como

TNF-α, IFN-γ e IL-6 serem capazes de reduzir a vida útil das células das papilas gustativas, o que pode levar a disgeusia (ESHRAGHI *et al.,* 2020) (figura 5).

Figura 5 – Representação esquemática de mecanismos potenciais da disfunção do olfato e paladar ocasionada pela infecção do SARS-CoV-2



Fonte: Adaptado de Eshraghi *et al.* (2020).

2.5 Impacto das disfunção do olfato e paladar e da pandemia da COVID-19 sobre os hábitos alimentares e qualidade de vida

Como abordado anteriormente, o olfato e paladar são sentidos cruciais à vida. Alterações nesses sentidos também podem resultar em alterações dos hábitos alimentares e interferência na qualidade de vida. Ocasionando disfunções alimentares, perda de apetite, mudança de peso, redução do prazer pela comida, diminuição do engajamento e relacionamento social e dificuldade em detectar situações de perigo como vazamento de gás, fumaça e alimentos estragados (WATSON *et al*., 2021; OLIVEIRA *et al.,* 2013).

Segundo o estudo de Gois *et al.* (2020), que avaliaram o impacto e a prevalência da disgeusia e hiposmia/anosmia na ingestão alimentar de pacientes diagnosticados com COVID-19, evidenciaram que 50,4% relataram mudanças nos hábitos alimentares, sendo que 50,9% reduziram a ingestão alimentar e 11% aumentaram a ingestão alimentar.

Já em relação à interferência desses sintomas sobre a qualidade de vida, com

base no estudo de Coelho *et al.* (2021), que avaliou a qualidade de vida e os déficits de segurança pessoal dos distúrbios do olfato e paladar experimentados por 322 indivíduos infectados pelo SARS-CoV-2, foi identificado que, 87% relataram redução do prazer pela comida, 43% mencionaram depressão e 45% relataram incapacidade de detectar cheiro de fumaça.

No entanto, deve-se compreender também o impacto que a própria pandemia da COVID-19 ocasionou sobre os hábitos alimentares e a qualidade de vida, uma vez que, para conter o alastramento do vírus foram adotadas as medidas de *lock down,* e o fato de ficar confinado em casa por um longo período tende a resultar em estresse, que pode causar alterações nos hábitos alimentares e interferir na qualidade de vida.

O cenário de quarentena esteve associado a uma dieta pobre em frutas e vegetais frescos e rica em alimentos embalados e de alta durabilidade (DEMOLINER *et al.,* 2020). Segundo Malta *et al.* (2020), no período de isolamento os brasileiros realizaram menos atividades física, gastavam muito tempo diante das telas (tv, computador, celular), reduziram o consumo de alimentos saudáveis e intensificaram o uso de ultraprocessados. Com o pico da pandemia, sair de casa se tornou perigoso, então, muitos para evitar idas ao supermercado optaram por estocar alimentos embalados e com tempo de validade maiores (DEMOLINER *et al.,* 2020). Com base no estudo de Dalmolin *et al.* (2021), que avaliaram os hábitos alimentares e de higiene, de 165 pessoas, no período de isolamento social durante a pandemia da COVID-19 no Brasil, foi possível observar que a maioria absoluta dos participantes consumiram produtos de alto valor energético.

2.6 Sintomas persistentes da COVID-19

O Instituto Nacional de Excelência em Saúde e Assistência do Reino Unido (NICE) classificou as fases sintomáticas da COVID-19, em: “COVID-19 aguda” quando os sinais e sintomas duram até 4 semanas após o início da doença; “COVID-19 sintomático contínuo” para 4 a 12 semanas após o início dos sintomas; "Síndrome pós-COVID-19" quando sinais e sintomas são desenvolvidos durante ou depois de uma infecção duradoura da COVID-19, continuando por mais de 12

semanas - neste caso os sintomas não são explicados por um diagnóstico alternativo, podendo ser relacionados à COVID-19. A *long* COVID é o termo que inclui “COVID-19 sintomático contínuo” e a "Síndrome pós-COVID-19" (RAJ *et al*., 2021).

Segundo o CDC (2020) embora alguns pacientes infectados pelo SARS-CoV-2 recuperem sua saúde normal, em pouco tempo, alguns podem apresentar sintomas que podem durar semanas ou meses mesmo após a recuperação da doença. O American Autonomic Society denominou esses sintomas contínuos em "síndrome pós-COVID aguda" (PACS), "sequela pós-aguda da síndrome SARS-CoV-2" (PASC), caracterizando pacientes que ficam com uma série de sintomas contínuos, mesmo após terem tido diagnóstico de melhora da fase aguda da doença (RAJ *et al*., 2021). Casos de sintomas duradouros da COVID-19, o chamado *Long COVID*, estão cada vez mais recorrentes (SUDRE *et al*., 2021). A Organização Mundial da Saúde (OMS) define este cenário como uma variedade de sintomas que afetam a vida cotidiana, como é o caso da fadiga, falta de ar e disfunção cognitiva, que ocorrem após história de infecção provável ou confirmada por SARS-CoV-2 e não podem ser explicados por um diagnóstico alternativo (SUBRAMANIAN *et al.,* 2022).

Dados do Reino Unido, Estados Unidos e Suécia evidenciaram que de 4.182 indivíduos que mencionaram teste positivo para o SARS-CoV-2, um total de 558 (13,3%) participantes relataram sintomas que duraram mais de 28 dias, onde 189 (4,5%) entrevistados relataram a persistência de sintomas por mais de 8 semanas e 95 (2,3%) chegaram a relatar a duração dos sintomas por mais de 12 semanas (SUDRE *et al*., 2021). Na China, de um estudo com 1.733 pacientes que foram hospitalizados com COVID-19, três quartos deles tiveram pelo menos um sintoma em curso de 6 meses mesmo após a recuperação da fase aguda, sendo os sintomas mais persistentes e recorrentes: fadiga ou fraqueza muscular 63%, dispneia 26%, dificuldade para dormir 26%, ansiedade ou depressão 23%, transtorno do olfato 11% e dor nas articulações 9% (HUANG *et al*., 2021).

Em um estudo de coorte retrospectivo selecionou 486.149 adultos com infecção confirmada por SARS-CoV-2 através de um banco de dados de cuidados primários do Reino Unido, a fim de determinar os sintomas associados à infecção

confirmada por SARS-CoV-2 além de 12 semanas e identificaram que os sintomas com os maiores aHRs foram: anosmia, queda de cabelo, espirros, dificuldade de ejaculação e libido reduzida (SUBRAMANIAN *et al*., 2022).

Uma pesquisa on-line nacional com 322 indivíduos positivos para COVID-19, 67% relatou que as disfunções do olfato e paladar persistiram por um período igual ou superior a 6 meses (COELHO *et al.,* 2021). Apresentar perda do olfato e paladar, e ainda mais como um sintoma persistente traz inúmeras consequências psicológicas e emocionais, que afetará a qualidade de vida dos pacientes (KANJANAUMPORN *et al.,* 2020).

Acredita-se, que esses sinais e sintomas de longo prazo dependem da extensão e gravidade da infeção viral, dos órgãos afetados e da "tempestade de citocinas" durante a fase aguda da COVID-19 (ISLAM *et al.,* 2020). É necessário a cooperação de várias linhas de estudos para verificar o comportamento destes sintomas a longo prazo, e aprender a melhor forma de tratar estes pacientes (RAJ *et al.,* 2021).

Sendo assim, o cenário pandêmico atual é acompanhado de preocupações e incertezas; aqueles que foram atingidos pelas implicações decorrentes da pandemia necessitam ser acompanhados a longo prazo (FERREIRA *et al*., 2021), pois, a persistência dos sintomas e as sequelas, sendo elas físicas ou psicológicas, ligadas aos anseios trazidos pela restrição social podem acarretar um impacto considerável sobre a qualidade de vida (JACOBS *et al.,* 2020). Ademais, os sentidos do olfato e paladar são sentidos cruciais à qualidade de vida e a sua preservação, atuando na identificação de odores e sabores que ofertam riscos à saúde (COSTA *et al.,* 2020).

3 HIPÓTESE

As disfunções olfativas e gustativas, a curto e longo prazo, afetam a qualidade de vida e os hábitos alimentares de profissionais de saúde da zona da Mata de Pernambuco infectados pelo SARS-CoV-2.

4 OBJETIVOS

4.1 Geral

Avaliar a prevalência, persistência, e o impacto das disfunções olfativas e gustativas na qualidade de vida e nos hábitos alimentares de profissionais de saúde da zona da Mata de Pernambuco infectados ou não pelo SARS-CoV-2.

4.2 Específicos

Nos profissionais de saúde da Zona da Mata de Pernambuco infectados ou não pelo SARS-CoV-2:

1. Identificar os sintomas persistentes, por mais do que 4 semanas, da COVID-19.
2. Investigar o tipo de disfunção de olfato e paladar, bem como o grau de alteração, o tempo para início e duração;
3. Avaliar a ocorrência de sintomas e comorbidades associados às alterações olfativas e gustativas;
4. Avaliar o impacto das disfunções na qualidade de vida e nos hábitos alimentares.

5 MATERIAIS E MÉTODOS

5.1 Desenho da Pesquisa (tipo de estudo)

Trata-se de um estudo do tipo caso-controle.

5.2 Local da pesquisa:

O presente estudo foi realizado na cidade de Vitória de Santo Antão, localizada na zona da Mata Sul do estado de Pernambuco, onde a densidade demográfica é de 348,80 hab/km^2 e o município possui 139.583 habitantes (IBGE, 2020).

5.3 Procedimento metodológico

Inicialmente foi feito o levantamento dos profissionais que participaram da pesquisa “Diagnóstico sorológico ANTI-SARS-CoV-2 ELISA (IgA, IgM e IgG) e perfil de citocinas em profissionais de saúde”, que consistia em realizar diagnóstico sorológico semiquantitativo a partir da pesquisa de IgA e IgG em soro de profissionais de saúde do município de Vitória de Santo Antão suspeitos da síndrome respiratória aguda grave por coronavírus 2 (SARS-CoV-2). A partir dessa pesquisa já foram produzidos e publicados outros artigos baseados nas informações trazidas por essa pesquisa (LINS *et al*., 2022; MAIOR *et al*., 2022).

Em seguida, esses participantes receberam individualmente por aplicativo de mensagem ou ligação uma carta convite para participar dessa pesquisa. Após entender o objetivo, a metodologia do estudo e relatar interesse em ser um participante, era enviado o TCLE em PDF para análise e consentimento virtual através de áudio declarando o nome completo e que aceitava participar da pesquisa. Quando dado o consentimento virtual, o participante da pesquisa era orientado a guardar em seus arquivos uma cópia do documento eletrônico – TCLE.

Só depois da anuência do TCLE o indivíduo era incluido no estudo, e realocado em um grupo a depender do resultado do exame e histórico sintomatológico; em: (1) grupo controle com IgA e/ou IgG negativo para o SARS-CoV-2 ou (2) grupo com IgA e/ou IgG positivo para o SARS-CoV-2 com perda de olfato e/ou paladar ou (3) grupo com IgA e/ou IgG positivo para o SARS-CoV-2 sem perda de olfato e/ou paladar (estes resultados dos títulos de imunoglobulinas contra

o SARS-CoV-2 está disponível no banco de dados do biorrepositório que temos acesso). O participante respondeu os questionários através de entrevista por ligação telefônica, que não era gravada, mas suas respostas foram registradas na folha dos questionários que estava com o entrevistador/pesquisador. Salientamos que ele não era obrigado a responder as perguntas e poderia recusar participar da pesquisa em qualquer momento.

5.4 Amostra de Participantes

Este estudo, caso-controle, foi realizado com uma amostra de 53 profissionais atuantes na linha de frente ao combate da COVID-19 ligados ao serviço de saúde do município de Vitória de Santo Antão, Pernambuco, no periodo de junho de 2020 e maio de 2021.. Estes profissionais já haviam se submetidos ao teste diagnóstico sorológico ANTI-SARS-CoV-2 ELISA (IgA e IgG); e a partir do resultado e do histórico sintomatológico eles foram divididos entre os três grupos.

5.5 Critérios de Inclusão e Exclusão

- Critérios de inclusão**:**

1. Ter 18 anos ou mais;
2. Ser profissional de saúde, da linha de frente ao combate da COVID-19, que tenha realizado previamente o exame de sorologia pela equipe da pesquisa “Diagnóstico sorológico ANTI-SARS-CoV-2 ELISA (IgA, IgM e IgG);
3. Ter acesso ao whatsapp e celular para ligação.

- Critérios de exclusão:

1. Tenha história de desordens de olfato e/ou paladar antes do diagnóstico da COVID-19, como: trauma de face, cirurgia de nariz, rinosinusite alérgica ou crônica, Alzheimer, Parkinson ou alterações salivares.
2. Participantes que receberam ou recebem tratamento por quimioterapia e radioterapia.

5.6 Avaliação da prevalência e das características sintomatológicas

O primeiro questionário foi o da Ferramenta de Relatório de Anosmia da Academia Americana de Otorrinolaringologia - Cirurgia de Cabeça e Pescoço (AAO-

HNS) - Anosmia Reporting Tool (Anexo A) (SAYIN *et al*., 2020). O questionário foi adaptado de acordo com o grupo que foi aplicado: o grupo IgA e/ou IgG positivo para SARS- CoV-2 ou o grupo controle IgA e/ou IgG negativo para SARS-CoV-2; a fim de estabelecer a importância das alterações do olfato e paladar nos casos SARS-CoV-2 positivo ao conduzir uma análise comparativa com indivíduos SARS-CoV-2 negativo.

O questionário possui 17 perguntas, relacionadas a: idade; sexo; fator de risco; comorbidades; sintomas da COVID-19; origem e estado atual da infecção; se recebeu tratamento; se desenvolveu alterações no olfato e/ou paladar; classificação do comprometimento do olfato em: anosmia, hiposmia e parosmia e do paladar em: ageusia, hipogeusia e disgeusia. Caso fosse relatado a hiposmia e/ou a hipogeusia, os indivíduos teriam que avaliar a diminuição relativa do paladar e do cheiro em uma escala analógica (VAS) de 10 pontos; quais disfunções foram notadas antes ou após o diagnóstico; presença de outros sintomas antes de desenvolver a perda do olfato e/ou paladar e quais foram; condição do paciente se melhorou ou piorou após as disfunções do olfato e paladar; e se a alteração no olfato e/ou paladar já havia sido resolvida até o momento da entrevista. Para o grupo IgA e/ou IgG negativo para SARS-CoV-2, com o objetivo de manter a consistência e a comparabilidade dos achados, as questões direcionadas a COVID-19 foram removidas do questionário para esse grupo (Anexo B).

5.7 Avaliação do impacto das disfunções de olfato e/ou paladar sobre a qualidade de vida

A avaliação do impacto das disfunções olfativas e gustativas sobre a qualidade de vida foi feita através do questionário sQOD-NS (Anexo C) (LECHIEN *et al*., 2020). Este questionário contém 7 perguntas voltadas para a disfunção do olfato. No entanto, para esse estudo o questionário sofreu uma adaptação, na qual foi acrescentado também a disfunção do paladar a cada questionamento. O questionário tem como função avaliar se as alterações no olfato e paladar: (1) o fizeram se isolar da sociedade; (2) se teve impacto negativo nas atividades sociais diárias; (3) o deixaram mais irritável; (4) o fizeram se alimentar menos; (5) provocou perda de apetite; (6) o fizeram fazer mais esforço para relaxar; (7) o fizeram ter medo de nunca ser capaz de se acostumar com essas alterações. Cada item

poderia ser classificado em uma escala de 0-3, onde 3 reflete melhor qualidade de vida. A pontuação total varia de 0 (impacto severo na qualidade de vida) a 21 (nenhum impacto na qualidade de vida).

Para o grupo IgA/IgG positivo para o SARS-CoV-2 sem perda de olfato e paladar tais perguntas foram direcionadas ao diagnóstico positivo para COVID-19. Assim, ao invés de avaliar o impacto da perda de olfato e paladar sobre a qualidade de vida (Anexo D); neste caso, o questionário avaliava o efeito do diagnóstico positivo para a COVID-19 sobre a qualidade de vida. Neste caso o questionário avaliava se o diagnóstico positivo para COVID-19: (1) o fizeram se isolar da sociedade (2) teve impacto negativo nas atividades sociais diárias; (3) o deixaram mais irritável; (4) o fizeram se alimentar menos; (5) provocou perda do apetite; (6) o fizeram fazer mais esforço para relaxar; (7) o fizeram ter medo de nunca ser capaz de se acostumar com os problemas acarretados pela COVID-19. Cada item poderia ser classificado em uma escala de 0-3, onde 3 reflete melhor qualidade de vida. A pontuação total varia de 0 (impacto severo na qualidade de vida) a 21 (nenhum impacto na qualidade de vida).

5.8 Avaliação do impacto das disfunções de olfato e/ou paladar sobre os hábitos alimentares

A avaliação do impacto das disfunções de olfato e/ou paladar sobre os hábitos alimentares foi realizada usando um questionário validado (Questões de aceitabilidade de comportamento alimentar) (Anexo E) (MATTES *et al.,* 1990), composto por 6 questões objetivas. A 1ª questionava como tinha sido o apetite desde o início das disfunções no olfato e/ou paladar, o entrevistado poderia relatar dentre as alternativas: a) Não tenho problemas de gosto e cheiro, b) Melhor, c) Não alterado, d) Pior. Na 2ª deveria dizer o quanto tinha gostado da comida desde o início das disfunções: a) Não tenho problema no olfato e paladar, b) Mais, c) O mesmo, d) Menos; Da 3ª até a 6ª deveria mencionar entre: a) Não tenho problema de gosto e cheiro, b) Não ou c) Sim, para se as disfunções no olfato e/ou paladar: afetaram a maneira como se alimenta; alteraram a quantidade de sal, açúcar ou especiarias; começou a não gostar ou evitar certos alimentos; sente um forte desejo ou anseio por certos alimentos. Se o entrevistado relatasse a opção “sim”, deveria descrever a mudança e/ou especificar o alimento.

Para o grupo IgA/IgG positivo para o SARS-CoV-2 sem perda de olfato e paladar tais perguntas foram direcionadas ao diagnóstico positivo para COVID-19, ao invés da perda de olfato e paladar (Anexo F). Então, a 1ª questionava como tinha sido o apetite desde o diagnóstico positivo para COVID-19, o entrevistado poderia relatar dentre as alternativas: a) Melhor, b) Não alterado, c) Pior. Na 2ª deveria dizer o quanto tinha gostado da comida desde o diagnóstico positivo para COVID-19: a) Mais, b) O mesmo, c) Menos; Da 3ª até a 6ª deveria mencionar: a) Não ou b) Sim, para se diagnóstico positivo para COVID-19: afetou a maneira como se alimenta; o fez alterar a quantidade de sal, açúcar ou especiarias; se começou a não gostar ou evitar certos alimentos; se sentiu um forte desejo ou anseio por certos alimentos. Se o entrevistado relatasse a opção "sim", deveria descrever a mudança e/ou especificar o alimento.

5.9 Sintomas persistentes da COVID-19 (*Long COVID*)

A investigação do *Long COVID* e os sintomas persistentes no período pós COVID foi realizada com auxílio do questionário da OMS (Anexo G) (AYOUBKHANI *et al.,* 2021) composto por 2 questões objetivas. A 1ª questionava se o entrevistado se considerava com "*Long COVID*", se ainda está sentindo sintomas ou se teve sintomas que duraram 4 semanas após ter tido COVID pela primeira vez e que eles não são explicados por outro motivo - o indivíduo deveria relatar: a) Sim ou b)Não; se relatasse sim ele deveria informar se esta situação do *Long COVID* reduziu sua capacidade de realizar atividades diárias em comparação com o tempo antes de ter COVID-19, em: a) Sim, muito, b)Sim, pouco, c)De jeito nenhum. Na 2ª questão o entrevistado deveria informar qual sintoma persistiu ou persiste no período pós COVID, deve responder sim ou não para cada um dos sintomas, sendo eles: febre, cansaço, diarreia, perda do paladar, perda do olfato, falta de ar, vertigem, dificuldade em dormir, dor de cabeça, náusea/vômito, perda de apetite, dor de garganta, dor no peito, ansiedade, perda de memória ou confusão, dor muscular, dor abdominal, tosse, palpitações, baixo humor e dificuldade de concentração.

5.10 Análise dos dados

Os dados foram descritos por meio da frequência absoluta (n) e relativa (%). Para testar a normalidade dos dados foi utilizado o teste de Kolmogorov-Smirnov.

Um teste t de Student independente foi realizado para comparar grupos de variáveis de distribuição normal. Para os dados que não apresentaram distribuição normal foram utilizados testes não paramétricos. O teste $\chi 2$ de Pearson e o teste exato de Fisher foram usados para comparação de dados qualitativos. O nível de significância estatística adotado foi de $P \leq 0,05$. As análises estatísticas foram realizadas utilizando o programa Statistical Package for the Social Sciences (SPSS) na versão 20.0.

5.11 Aspectos éticos

O estudo foi submetido e aprovado pelo Comitê de Ética em Pesquisa do Centro Acadêmico de Vitória da Universidade Federal de Pernambuco (CEP/CAV/UFPE) (Anexo H), sob **Número do Parecer:** 4.744.490. Respeitando os pressupostos da Resolução CNS Nº 441, de 12 de maio de 2011 sobre biorrepositórios, 510/16 do Conselho Nacional de Saúde e a nova Carta Circular nº 1/2021-CONEP/SECNS/MS, que trata de pesquisas realizadas em ambiente virtual. Os participantes foram esclarecidos sobre o objetivo e metodologia do estudo e convidados a assinar o Termo de Consentimento Livre e Esclarecido – TCLE.

6 RESULTADOS

Os resultados e a discussão estão apresentados no formato de artigo submetido à revista: International Journal of Otorhinolaryngology and Head and Neck Surgery (FI:3.497); com o título: *“Olfaction and taste disorders in covid-19: prevalence, long-term persistence and impact on quality of life and eating habits of health professionals”.*

6.1 Artigo Original

TITLE PAGE

Type of Article: Original article

Olfaction and taste disorders in covid-19: prevalence, long-term persistence and impact on quality of life and eating habits of health professionals

AUTORES: Danielly A. M. Barbosa[a,d], Ewerton H. da Conceição[a], Renata E. A. Santo[a,c], Felipe C. de Barros[e], Isis D. Lins[e,g], Caio S. Maior[f,g], Ana L. V. Gomes[a,d], Kelli N. Ferraz-Pereira[b,c*]

AFILIAÇÃO:
a Federal University of Pernambuco, Academic Center of Vitória, 55608-680, Vitória de Santo Antão, PE, Brazil.
b Department of Speech Therapy, Federal University of Pernambuco, Campus Recife, 50670-901, Recife, PE, Brazil.
c Graduate Program in Nutrition, Federal University of Pernambuco, 50670-901, Recife, PE, Brazil.
d Graduate Program in Nutrition, Physical Activity and Phenotypic Plasticity, Federal University of Pernambuco, 55608-680, Vitória de Santo Antão, PE, Brazil.
e CEERMA - Center for Risk Analysis, Reliability and Environmental Modeling, Universidade Federal de Pernambuco, Brazil
f Technology Center, Federal University of Pernambuco, Brazil
g Department of Production Engineering, Federal University of Pernambuco, Brazil

***Correspondence to:** Kelli Nogueira Ferraz-Pereira, Speech therapy Department, Federal University of Pernambuco. Av. Prof. Moraes Rego, 1235 – Cidade Universitária, Recife – PE, 50670-901, Brazil. E-mail: kelli.pereira@ufpe.br.

ABSTRACT

Background: The objective was to assess the prevalence, long-term persistence and impact of olfactory and taste disorders on the quality of life and food habits of professionals of health within the context of COVID-19.
Methods: The study was carried out with 53 professionals, who were divided into 3 groups: (1)IgA and/or IgG positive for SARS-CoV-2 with loss of smell and/or taste (n=37); (2)IgA and/or IgG positive for SARS-CoV-2 without loss of smell and/or taste (n=7); and (3)IgA and/or IgG negative for SARS-CoV-2 (n=9). The collection of information was made using questionnaires by telephone contact.
Results: Symptoms of malaise and loss of smell and/or taste revealed an association with COVID-19 test results. Of the 53 participants, 39 reported impaired smell and taste, 37 with a positive diagnosis and 2 with a negative diagnosis. Of the 53 professionals, 31 had Long COVID; the longest-lasting symptoms were: loss of smell and taste. Regarding the impact on quality of life, the scores did not differ between patients with and without loss of smell and/or taste. In relationship to impact on food habits, there was an association between the groups in terms of "liking food", because the group that had olfaction and taste disturbances mentioned liking food less.
Conclusions: The study showed that there is a high prevalence of olfactory and/or taste alterations, both in the short and the long term, in individuals who tested positive for COVID-19. And these dysfunctions can lead to changes in eating habits, reducing the enjoyment of food.

Key words: COVID-19, SARS-CoV-2, Anosmia, Ageusia.

INTRODUCTION

The first registered case of SARS-CoV-2, the virus responsible for COVID-19, was registered in December 2019, in China. It spread rapidly, attaining pandemic status in the first months of 2020.[1] In Latin America, Brazil was the first country to register an infected SARS-CoV-2 patient, in February 2020.[2]

The first patients affected by COVID-19 were those from the Asian continent, reporting symptoms such as fever, cough, myalgia and dyspnea.[3] When the virus appeared on other continents, Europe, in particular, other signs and symptoms were manifested during COVID-19 infection.[4] One particular symptom was increasingly reported: olfactory and gustatory alterations.[5] This same scenario was observed in Brazil. In a study carried out with 183 patients, Brazilians, 145 had the new coronavirus; of these 126 presented sudden anosmia and 19 developed acute hyposmia.[6]

Many individuals have reported olfactory and gustatory dysfunctions resulting from COVID-19 as persistent symptoms. Acconding Coelho et al. (2021), of the 321 people studied, 67% reported changes in smell and taste lasting 6 months or more.[7] According to the Centers for Disease Control and Prevention (CDC) (2020) although patients infected with SARS-CoV-2 recover their normal health within 4 weeks, some may experience symptoms that can last for weeks or months even after recovery from the acute phase of the disease.[8,9]

Loss of smell and taste, and even further their persistence, causes psychological consequences, affecting the quality of life of patients. Smell and taste are linked to emotions, memories and recollections.[10] These senses are also extremely important for the maintenance and safety of life, as they serve as an alert for risky situations.[11,12]

Individuals with olfactory and gustatory deficits may suffer from alterations in eating

habits, problems when cooking, a decrease in appetite, problems with personal hygiene, and difficulties with social relationships. These individuals develop emotional problems, such as depression, feelings of insecurity and loneliness, and can lead to a loss in weight and malnutrition.[10,13]

However, despite the importance of the senses of smell and taste for the quality of life, this has not yet been well defined in terms of olfactory and gustatory functions concerning the food habits of persons afflicted with COVID-19. The object of this study, then, was to evaluate the prevalence, persistence, duration and impact of olfactory and gustatory dysfunctions on the quality of life and food habits of health professionals in the interior of the State of Pernambuco, Brazil.

METHODS

Population

This case-control study was carried out with an initial sample of 54 individuals. Of these, one was excluded for reporting sinusitis and loss of smell and taste prior to the COVID-19 pandemic. Inclusion criteria were: 18 years of age or older; professional in health services on the front line of combating COVID-19; previous serological history; mobile and whatsapp access. Exclusion criteria were: a history of olfactory and /or taste disorders before the diagnosis of COVID-19 (such as facial trauma, nose surgery allergic or chronic rhinosinusitis, Alzheimer, Parkinson's or salivary gland changes); previous or current treatment by chemotherapy or radiotherapy.

The final sample consisted of 53 professionals health linked to the health service in the city of Vitória de Santo Antão-PE. The selection of participants was made from a database generated by the project "ANTI-SARS-CoV-2 ELISA serological diagnosis (IgA, IgM and IgG) and cytokine profile in health professionals", and identified according to the inclusion and exclusion criteria, considering the result of the serology exam, performed between June 2020 and May 2021. SerumCovid is the database with information about the participants whose description was published by our group in Lins *et al* (2022).[14] Then, based on the results and the symptomatic histories, the participants were divided into three groups: (1)IgA and/or IgG positive for SARS-CoV-2 with loss of smell and taste (n=37); (2)IgA and/or IgG positive for SARS-CoV-2 without loss in smell and taste (n=7); and (3)IgA and/or IgG negative for SARS-CoV-2 (n=9).

The study was approved by the Committee on Research Ethics of the Academic Center of Vitória of the Federal University of Pernambuco (CEP/CAV/UFPE), under Number CAAE 45588621.9.0000.9430. The study was in accordance with Resolution CNS No. 441, on 12 May 2011 about biorepositories and 510/16 of the National Health Council.

Methodological Procedure

The participants received an individual invitation to participate in this research by message or phone call. After being apprised of the objective, the methodology of the study and reporting interest in being a participant, the TCLE was sent in PDF for analysis and virtual consent through audio declaring their full name and interest in participating in the research. After consent, the individual was included in the study and assigned to a group depending on the examination results and symptomatic history.

The participant answered the questionnaires in this study through a telephone interview, which was not recorded; their answers were registered on the questionnaire sheet. The interviews took place from June-November/2021.

Evaluation of prevalence and of symptomatological features

To assess the prevalence and symptomatological characteristics, the (AAO-HNS) anosmia reporting tool was used.[15] With questions related to age; sex; risk factors/comorbidities; signs/symptoms related to COVID-19; drug treatment for symptoms of COVID-19; when anosmia or dysgeusia was first noticed; the stage of the infection at the time the change in smell and/or taste was observed; further changes at the smell and/or taste; type of smell disorder and of taste; degree of infection at the time the alteration of smell/taste was observed; whether the patient was hospitalized or outpatient; whether the alteration of smell/taste was noticed before or after receiving a diagnosis for COVID-19; the presence of other symptoms before developing loss of smell and/or taste and what they were; and if the patient's clinical condition improved or worsened after the onset of disorders.

In order to maintain consistency and comparability of findings, the questions directed at COVID-19 were removed for the IgA and/or IgG negative SARS-CoV-2 group.

Persistence of COVID-19 (Long COVID)

The investigation of Long COVID was performed with the WHO questionnaire[16] consisting of two objective questions. The first asks if any symptom lasted longer than 4 weeks after having been diagnosed with COVID-19 for the first time and that these symptoms cannot be explained for any other reason. Thus, the individual should report: a)Yes or b)No. In the second question, the respondent was asked to report which symptoms persisted: fever, tiredness, diarrhea, loss of taste, loss of taste of smell, shortness of breath, dizziness, difficulty sleeping, headache, nausea/vomiting, loss of appetite, sore throat, chest pain, anxiety memory loss or confusion, muscle pain, abdominal pain, cough, palpitations, low mood, and difficulty concentrating.

Assessment of the impact of olfaction and/or taste dysfunctions on quality of life

The assessment of the impact of olfactory and taste dysfunctions on quality of life was done using the sQOD-NS questionnaire.[17] However, for this study, the questionnaire was adapted by adding taste dysfunction to each question. The questionnaire was designed to assess whether the changes in smell and taste: (1)made the respondent feel isolated from society; (2)had a negative impact on the daily social activities; (3)made the respondent more irritable; (4)caused the respondent to eat less; (5)caused the respondent to lose his or her appetite; (6)made the person have to make more effort to relax; (7)made the respondent afraid that he or she would never be able to get used to these changes. Each item could be rated on a scale of 0-3, where 3 reflected better quality of life. The total score ranges from 0(severe impact on quality of life) to 21(no impact on quality of life).

For the IgA/IgG group positive for SARS-CoV-2 without loss of smell and taste such questions were directed at the positive diagnosis for COVID-19. Thus, instead of assessing the impact of the loss of smell and taste on quality of life, in this case, the questionnaire assessed the effect of the positive diagnosis for COVID-19 on quality of life. Thus, the questionnaire assessed whether the positive diagnosis for COVID-19: (1)made the respondent isolate himself or herself from society; (2)had a negative impact on daily social activities; (3)made the respondent more irritable; (4)made the respondent eat less; (5)caused the respondent to lose his or her appetite; (6)made the respondent have to make more effort to relax; (7)made the respondent afraid that he or she would never be able to get used to the problems brought on by COVID-19. Following the same scoring criteria, where the total

score ranges from 0-21.

Evaluation of impact of dysfunctions in smell and/or taste on quality of life

The evaluation of the impact of olfaction and/or taste disturbances on their eating habits was performed using a questionnaire Food Behavior Acceptability Questions[18], composed of 6 objective questions. The first asked how the respondent's appetite had been since the onset of the olfaction and/or taste disturbances: a)I have no problems with taste and smell, b)better, c)not changed, d)worse. The second question was about how much the respondent liked food since the onset of the disturbances: a)No problems with smell and taste; b)most; c)the same; d)less. From the third to the sixth questions, respondents were to choose: a)I have no problems with my sense of smell and taste, b)no; or c)yes, concerning the following: whether smell and/or taste had affected the way of eating; If there had been any changes in the amount of salt, sugar or spices used; if the respondent had started to dislike or avoid certain foods; if the respondent felt a strong desire for certain foods. If the respondent used the "yes" option to any of these, he/she was asked to describe the change and/or specify the food.

For the SARS-CoV-2 IgA/IgG positive group without loss of smell and/or taste, as well as in the previous questionnaire, these questions were directed at the positive diagnosis for COVID-19, rather than loss of smell and taste.

Data analysis

Data was described by mean, both absolute (n) and relative (%) frequencies. For the test on normality, the Kolmogorov-Smirnov test was used. The independent student's t-test was used to compare variable normal distribution among groups. As the data did not present normal distribution, the Mann-Whitney test without parameters was used. Pearson's $\chi 2$ test and Fisher's exact test were used for qualitative comparison. The statistical significance adopted was $P \leq 0.05$. In the analysis, the SPSS program, version 20.0 was used. GraphPad Prism version 9.4.1 was used for construction of the figures.

RESULTS

Evaluation of prevalence and symptomatic characteristics

Of the 53 participants, 47 were female and 6 were male. Of the 47 females, 33 had tested positive for SARS-CoV-2 and suffered loss of smell and/or taste, 5 also tested positive but had not suffered loss of smell and/or taste. The remaining 9, tested negative. Of the 6 male respondents, 4 were in the group that had tested positive and suffered loss of smell and/or taste. The other 2 had also tested positive, but had suffered no loss in smell and/or taste; none of the men in this study fell into the group that tested negative. Fisher's exact test showed no association between sex and the diagnosis for COVID ($P>0.05$) (**Table 1**).

Table 1 - Evaluation of prevalence and symptomatic characteristics.

Sex, n(%)					
Sex		**IgA and/or IgG positive for SARS-Cov-2 with loss of smell and/or taste (n = 37)**	**IgA and/or IgG positive for SARS-Cov-2 without loss of smell and taste (n = 7)**	**IgA and/or IgG negative for SARS-Cov-2 (n=9)**	**Value P**
Feminine		33 (89.2%)	5 (71.4%)	9 (100%)	0.161
Masculine		4 (10.8%)	2 (28.6%)	0 (0,0%)	
Risk factors / comorbidities, n.(%)					
Has risk factors/comorbidities		**IgA and/or IgG positive for SARS-Cov-2 with loss of smell and/or taste (n = 37)**	**IgA and/or IgG positive for SARS-Cov-2 without loss of smell and taste (n = 7)**	**IgA and/or IgG negative for SARS-Cov-2 (n=9)**	**Value P**
Yes		15 (40.5%)	2 (28.6%)	4 (44.5%)	0.829
No		22 (59.5%)	5 (71.4%)	5 (55.5%)	
Risk factors / comorbidities		**IgA and/or IgG positive for SARS-Cov-2 with loss of smell and/or taste (n = 15)**	**IgA and/or IgG positive for SARS-Cov-2 without loss of smell and taste (n = 2)**	**IgA and/or IgG negative for SARS-Cov-2 (n=4)**	**Value P**
Smoke	Yes	1 (6.7%)	0 (0.0%)	0 (0.0%)	1.000
	No	14 (93.3%)	2 (100%)	4 (100%)	
sinusitis/ allergy	Yes	7 (46.7%)	1 (50%)	1 (25%)	0.796
	No	8 (53.3%)	1 (50%)	3 (75%)	
Chronic respiratory disease/asthma	Yes	1 (6.7%)	1(50%)	0 (0.0%)	0.214
	No	14 (93.3%)	1 (50%)	4 (100%)	
Heart disease	Yes	3 (20%)	0(0.0%)	2 (50%)	0.405
	No	12 (80%)	2 (100%)	2 (50%)	
Other	Yes	8(53.3%)	0 (0.0%)	2 (50%)	0.522
	No	7 (46.7%)	2 (100%)	2 (50%)	
Signs and Symptoms, n.(%)					
		IgA and/or IgG positive for SARS-Cov-2 (n=44)		**IgA and/or IgG negative for SARS-Cov-2 (n=9)**	**Value P**
Yes		43 (97.7%)		7 (77.8%)	0.071
No		1 (2.3%)		2 (22.2%)	
Signals and symptons		**IgA and/or IgG positive for SARS-Cov-2 (n=43)**		**IgA and/or IgG negative for SARS-Cov-2 (n=7)**	**Value P**
Fever	Yes	28 (65.2%)		2 (28.6%)	0.100
	No	15 (34.8%)		5 (71.4%)	
Chills	Yes	26 (60.4%)		3 (42.9%)	0.434
	No	17 (39.6%)		4 (57.1%)	
Malaise	Yes	27 (62.8%)		1 (14.3%)	0.034*
	No	16 (37.2%)		6 (85.7%)	
Cough	Yes	21 (48.8%)		2 (28.6%)	0.430
	No	22 (51.2%)		5 (71.4%)	
Headache	Yes	37 (86.1%)		7 (100%)	0.576
	No	6 (13.9%)		0 (0.0%)	
Nasal congestion	Yes	17 (39.5%)		3 (42.9%)	1.000
	No	26 (60.5%)		4 (57.1%)	
Rhinorrhea	Yes	6 (13.9%)		1 (14.3%)	1.000

	No	37 (86.1%)	6 (85.7%)	
Gastrointestinal discomfort	Yes	18 (41.9%)	2 (28.6%)	0.687
	No	25 (58.1%)	5 (71.4%)	
Loss of smell and/or taste	Yes	37 (86.1%)	2 (28.6%)	0.004*
	No	6 (13.9%)	5 (71.4%)	

SARS-CoV-2 IgA and/or IgG positive individuals

COVID-19 - Positive Individuals	**IgA and/or IgG positive for SARS-Cov-2 with loss of smell and/or taste (n = 37)**	**IgA and/or IgG positive for SARS-Cov-2 without loss of smell and/or taste (n = 7)**
Has the patient received specific drug treatment for the symptoms of COVID-19?		
Yes	23 (62.2%)	4 (57.1%)
No	14 (37.8%)	3 (42.9%)
When was anosmia or dysgeusia first noticed by the patient?		
Before diagnosis	36 (97.3%)	n/a
After diagnosis	1 (2.7%)	n/a
No smell/taste impairment	n/a	7 (100%)
What was the condition of the COVID-19 infection at the time the change in smell and/or taste was observed?		
Patient / hospitalized	1 (2.7%)	n/a
Ambulatory	36 (97.3%)	n/a

Comparison between categorical variables: Pearson's $\chi 2$ test and Fisher's exact test.
* = $p<0.05$

Of the 37 professionals who formed part of the SARS-CoV-2 positive IgA and/or IgG groups with loss of smell and/or taste, 15(40.5%) reported having some risk factor or comorbidity; of the 7 individuals in the IgA and/or IgG positive SARS-CoV-2 group without loss of smell and/or taste, 2(28.6%) persons presented some risk factor and/or comorbidity; and as for the 9 participants in the SARS-CoV-2 IgA and/or IgG negative groups, 4(44.5%) presented some risk factor or comorbidity. No association between positive diagnosis for COVID-19 and the occurrence of loss in smell and/or taste was observed with the presence of comorbidities ($P > 0.05$) **(Table 1).**

Of the 44 who tested positive for COVID-19, 43(97.7%) reported experiencing symptoms characteristic of the disease. And, of the 9 individuals in the COVID-19 negative group, only 7(77.8%) reported. The symptoms "malaise" and "loss of smell and/or taste" were positively associated with the result for COVID-19 ($P<0.05$), where, of the 43 professionals in the positive group who reported feeling some symptoms, 62.8% reported malaise. On the other hand, of the 7 individuals in the negative group who reported feeling some symptom characteristic of COVID-19, only 13.3% reported malaise (p-value=0.034). As for the loss of smell and/or taste, of the 43 individuals in the positive group who reported some symptomatology for COVID-19, 86.0% mentioned alterations in smell and/or taste; while in the negative group, only 28.6% mentioned alterations in smell and/or taste (p-value=0.004) (**Table 1**).

Of the 37 who had suffered a loss of smell and/or taste, 36(97.3%) noticed this loss for the first time before being diagnosed with COVID-19; while only 1(2.7%) noticed the dysfunctions after the diagnosis, revealing that these symptoms are one of the first to show up in a SARS-CoV-2 infection (**Table 1**).

Of the total 53 participants in this study, 39 reported impairment of smell and/or taste, with 37 diagnosed positive for SARS-CoV-2 and 2 diagnosed negative. Of the participants

diagnosed positive, only 1 reported isolated taste impairment, all other participants (n=36) mentioned integrated impairment of both smell and taste.

Of the 37 persons in the IgA and/or IgG group positive for SARS-CoV-2 with loss of smell and/or taste, 32(86.5%) defined their dysfunction of smell as anosmia, and 4(10.8%) as hyposmia (**Table 2**). Of the 9 people in the IgA and/or IgG negative SARS-CoV-2 group, 2 professionals reported olfaction disturbance. As for the definition of the alteration, 1(11.1%) defined it as anosmia, 1(11.1%) as hyposmia (**Table 2**). The data revealed that most patients suffered an absolute loss of smell and only a minority reported a reduction in smell. Fisher's test showed an association between the variable anosmia (p=0.000) with the positive diagnosis of COVID-19 (**Table 2**).

Of the 37 persons in the IgA and/or IgG group positive for SARS-CoV-2 with loss of smell and/or taste, 29(78.4%) defined their taste dysfunction as ageusia, and 8(21.6%) as hypogeusia (**Table 2**). Of the 9 people in the IgA and/or IgG negative SARS-CoV-2 group, 2 professionals reported taste dysfunction. As for the definition of the alteration, 1(11.1%) defined it as ageusia, 1(11.1%) as hypogeusia (**Table 2**). Fisher's test showed an association between the variables ageusia with the positive diagnosis of COVID-19 (p=0.000) (**Table 2**).

It is worth noting that of the 32 individuals who reported anosmia, 28 of these also reported ageusia. Of the 4 participants who mentioned hyposmia, the same 4 also reported hypogeusia.

It is interesting to note that the disturbances in smell and taste was reported as the only or first symptom during SARS-CoV-2 infection among the 13(35.1%) of the participants who tested positive and reported this symptom (**Table 2**).

Table 2: The classification of smell and taste impairment, and the presence of other symptoms before developing the loss of smell and/or taste, and what they were.

Characteristic		**IgA and/or IgG positive for SARS-CoV-2 with loss of smell and/or taste (n = 37)**	**IgA and/or IgG negative for SARS-Cov-2 (n = 9)**	**Value P**
Classification of smell impairment, N.(%)				
Anosmia	Yes	32 (86.5%)	1 (11,1%)	0.000*
	No	5 (13.5%)	8 (88,9%)	
Hyposmia	Yes	4 (10.8%)	1 (11.1%)	1.000
	No	33 (89.2%)	8 (88.9%)	
Parosmia	Yes	0 (0.0%)	0 (0.0%)	-
	No	37 (100%)	9 (100%)	
Classification of taste impairment, N.(%)				
Ageusia	Yes	29 (78.4%)	1 (11.1%)	0.000*
	No	8 (21.6%)	8 (88.9%)	
Hypogeusia	Yes	8 (21.6%)	1 (11.1%)	0.664
	No	29 (78.4%)	8 (88.9%)	
Dysgeusia	Yes	0 (0.0%)	0 (0.0%)	-
	No	37 (100%)	9 (100%)	
Any other symptoms prior to the development of loss of smell and/or taste? N. (%)		**IgA and/or IgG positive for SARS-Cov-2 with loss of smell and/or taste (n = 37)**	**IgA and/or IgG negative for SARS-Cov-2 (n = 2)**	
Yes		24 (64.9%)	2 (22.2%)	0.544
No		13 (35.1%)	0 (0.0%)	
What symptoms did the patient have prior to the development of loss of smell and/or taste? N. (%)		**IgA and/or IgG positive for SARS-Cov-2 with loss of smell and/or taste (n = 37)**	**IgA and/or IgG negative for SARS-Cov-2 (n = 2)**	**Value P**
Fever	Yes	18 (48.6%)	1 (50.0%)	1.000
	No	19 (51.4%)	1 (50.0%)	
Chills	Yes	14 (37.8%)	0 (0.0%)	0.528
	No	23 (62.2%)	2 (100%)	
Malaise	Yes	13 (35.1%)	0 (0.0%)	0.544
	No	24 (64.9%)	2 (100%)	
Cough	Yes	13 (35.1%)	0 (0.0%)	0.439

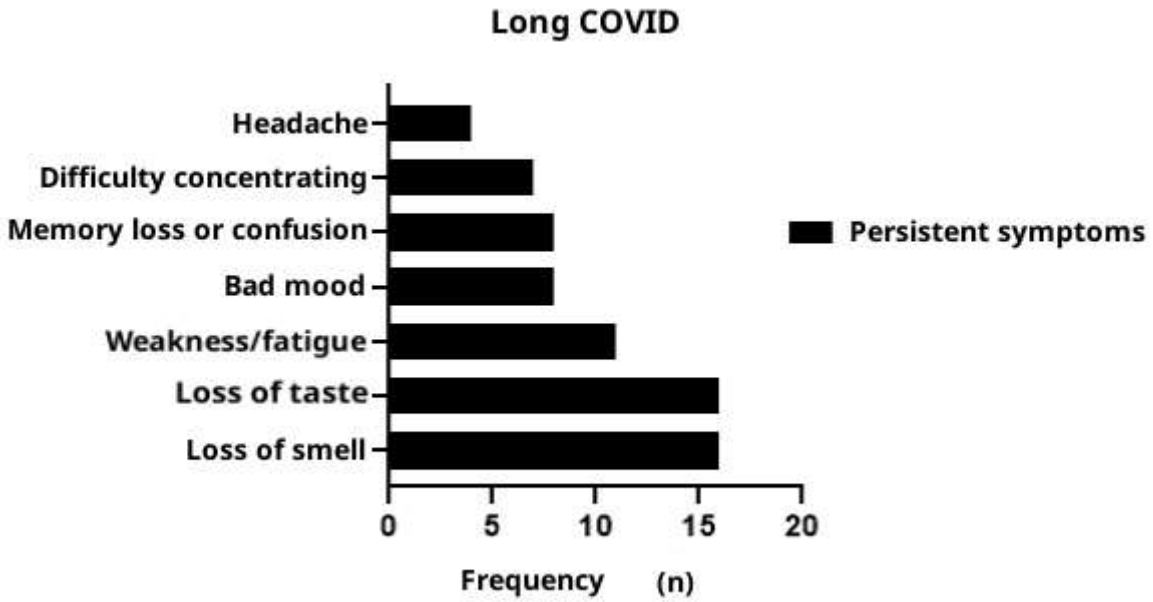
	No	24 (64.9%)	2 (100%)	
Headache	Yes	21 (56.8%)	1 (50.0%)	1.000
	No	16 (43.2%)	1 (50.0%)	
Nasal congestion	Yes	9 (24.3%)	1 (50.0%)	0.452
	No	28 (75.7%)	1 (50.0%)	
Rhinorrhea	Yes	4 (10.8%)	0 (0.0%)	1.000
	No	33 (89.2%)	2 (100%)	
Gastrointestinal	Yes	6 (16.2%)	0 (0.0%)	1.000
	No	31 (83.8%)	2 (100%)	
Did the patient's condition worsen or improve after the change in smell and/or taste was observed? N. (%)				
Got worse		28 (75.7%)	2 (100%)	1.000
Improved		9 (24.3%)	0 (0%)	

Comparison between categorical variables: Fisher's exact test.
* = $p<0.05$

Persistent symptoms of COVID-19 (Long COVID)

Of the 53 professionals, 50 had some sign and symptom of COVID-19, with 43 in the positive group and 7 in the negative group (**Table 1**). Of these 50, 31 reported the presence of symptoms lasting longer than 4 weeks, being denominated as patients with Long COVID. Among the most commonly cited lasting symptoms were loss of smell (n=16, 48%), loss of taste (n=16, 48%), weakness/tiredness (n=11, 35%), low mood (n=8, 25%), memory loss or confusion (n=8, 25%), difficulty concentrating (n=6, 19%), and headache (n=5, 16 %) (**Figure 1**).

Figure 1: Symptoms that persisted for more than 4 weeks in individuals reporting Long COVID (n=31)



Assessment of the impact of olfaction and/or taste disturbances on quality of life

The scores of the sQOD-NS did not differ between patients with loss of smell and/or taste and those without these disturbances (P>0.05) (**Table 3**).

Table 3: Analysis of the impact of smell and/or taste disorders on the quality of life of positive individuals with loss of smell and/or taste and loss of smell and/or taste.

Question	IgA and/or IgG positive for SARS-CoV-2 with loss of smell and/or taste (n=37)	Question	IgA and/or IgG positive for SARS-CoV-2 without loss of smell and/or taste (n=7)	Value P
	Mean/CI 95%		Mean/CI 95%	
1) Change in my sense of smell/taste isolated me socially	1/0.76-1.62	1) The positive diagnosis for COVID-19 isolated me socially	0/-0.5-2.21	0.424
2) Problems with my sense of smell/taste had a negative impact on my daily social activities	1/0.90-1.75	2) The positive diagnosis for COVID-19 had a negative impact on my daily social activities	0/-0.62-1.48	0.055
3) Problems with my sense of smell/taste made me more irritable	1/0.97-1.85	3)The positive diagnosis for COVID-19 made me more irritated	0/-0.62-1.48	0.657
4) Because of problems with my sense of smell/taste, I eat less	1/0.95-1.86	4) Because of the positive diagnosis for COVID-19, I ate less	1/0.28-2.86	0.206
5) Because of the problems with my sense of smell/taste I had a loss of apetite	1/0.94-1.76	5) Because of the positive diagnosis for COVID-19, I had a loss of apetite	2/0.93-3.07	0.249
6) Because of problems with my smell/taste I have to make more effort to relax	1/1.07-1.96	6) Because of the positive diagnosis for COVID-19, I had to make more effort to relax	1/0.25-2.61	0.504
7) I am afraid I will never be able to get used to my smell/taste problems	1/1.00-1.87	7) I am afraid that I will never be able to get used to the problems caused by COVID-19	1/0.52-2.62	0.713
Total - SQOD-NOS total score short version	10/7.90-11.94	**Total - SQOD-NOS total score short version**	11/4.25-15.75	0.987

Comparison between variables: Mann-Whitney test.

Assessment of the impact of olfaction and/or taste dysfunctions on eating habits

Fisher's test showed an association between the groups which refers to "liking food". Of the 37 individuals in the positive group with loss of smell and/or taste, 24(64.9%) reported that these disturbances made them like food less, while of the 7 individuals in the control group only 1(14.3%) revealed that the positive diagnosis for COVID-19 made them dislike food (**Table 4**).

Table 4: Analysis of the impact of smell and/or taste disorders on the eating habits of positive individuals for SARS-CoV-2 with loss of smell and/or taste and positive without loss of smell and/or taste.

Question	IgA and/or IgG positive for SARS-CoV-2 with loss of smell and/or taste (n=37)	Question	IgA and/or IgG positive for SARS-CoV-2 without loss of smell and/or taste (n=7)	
1) Since my taste or smell problem started, my appetite has been:		**1) Since the positive diagnosis for COVID-19 my appetite has been:**		
Better	1 (2.7%)	Better	0 (0,0%)	0.319
Not changed	10 (27%)	Not changed	4 (57.1%)	
Worst	26 (70.3%)	Worst	3 (42.9%)	

2) Since the onset of my taste or smell problem, I have enjoyed food:		**2) Since the positive diagnosis for COVID-19 I have liked the food:**		
The same	13 (35.1%)	The same	6 (85.7%)	0.032*
Any less	24 (64.9%)	Any less	1 (14.3%)	
3) Does my taste or smell problem affect the way I (changed types of food, frequency of meals and snacks):		**3) The positive diagnosis for COVID-19 affected the way I eat (it changed the types of food, the frequency of meals and snacks):**		
No	20 (54.1%)	No	6 (85.7%)	0.211
Yes	17 (45.9%)	Yes	1 (14.3%)	
4) Since my taste or smell problem started, I have changed the amount of salt, sugar or spices I add to my food		**4) Since testing positive for COVID-19, I have changed the amount of salt, sugar or spices I add to my food**		
No	34 (91.9%)	No	7 (100%)	1.000
Yes	3 (8.1%)	Yes	0 (0.0%)	
5) Since my taste or smell problem started, I started strongly to dislike or avoid certain foods		**5) Since being diagnosed positive for COVID-19, I have started strongly to dislike or avoid certain foods**		
No	26 (70.3%)	No	6 (85.7%)	0.653
Yes	11 (29.7%)	Yes	1 (14.3%)	
6) Since the onset of my problem with taste or smell, I have had a strong desire or craving for certain foods.		**6) Since being diagnosed positive for COVID-19, I have had a strong desire or craving for certain foods.**		
No	31 (83.8%)	No	7 (100%)	0.568
Yes	6 (16.2%)	Yes	0 (0.0%)	

Comparison between categorical variables: Fisher's exact test.
* = p<0,05

DISCUSSION

According to the Epidemiological Bulletin released by the Brazilian Ministry of Health, by the beginning of March/2021[19], there were 39,510 health professionals infected with SARS- CoV-2. And, according to Muschi (2022)[20], in this same period, at the end of 2020 and first half of 2021, the Gamma variant was considered the predominant SARS-CoV-2 strain in Brazil. It is worth noting that, in this variant, disturbances of smell and taste were often mentioned[20]. SARS-CoV-2 is constantly changing; these changes can lead to the emergence of variants that may have new characteristics[21]. Therefore, we need to emphasize that this study, aimed to assess the prevalence, long-term persistence and impact of olfactory and taste disturbances on the quality of life and eating habits of healthcare professionals, was designed with samples of professionals tested and interviewed in the period from 2020 to 2021.

According to our findings, the positive group showed a higher percentage of olfaction and/or taste disorders compared to the negative group. Similar to that of a study developed in a hospital in Turkey with 128 individuals, where the impairment of smell and taste was approximately 7 times higher in the positive group than in the negative group[15], suggesting that the virus causing COVID-19 impairs the functioning of olfactory and taste organs.

Studies indicate damage to angiotensin-converting enzyme 2 (ACE2)[22] - identified as a cellular receptor of SARS-CoV-2[23], mainly in the olfactory bulb[22]. These receptors are highly expressed in the oral mucosa and epithelial cells of the tongue and are associated with taste perception[24]. Regarding alterations in the smell, research points out that this alteration can be triggered by damage to the cells that support the olfactory neurons, so damage to the support cell that is around the neuron ends up inhibiting its functionality[25]. Another study detected an inversely proportional relationship between changes in olfaction and taste with the levels of interleukin 6 (IL-6); as the olfaction and taste functions returned, there was a

reduction in the levels of IL-6[26]. This association may be linked to the fact that IL-6 has peripheral levels in cell receptors infected by SARS-CoV-2, and also because pro-inflammatory cytokines such as TNF-α, IFN-γ, and IL-6 are capable of reducing the life span of the taste bud cells, which may lead to dysgeusia[26].

In Poerbonegor *et al.* (2021), was found that olfaction disorder was present in 72.4% of individuals before they were diagnosed with COVID-19[27]. Similar to our data, as 97.2% of the participants who tested positive and reported disturbances in smell and/or taste mentioned that they noticed these problems before receiving a diagnosis for COVID-19. This happens because damage to olfactory and taste cells can occur 1-3 days after SARS-CoV-2 infection[28]. In these studie, many participants reported that disturbances in smell and/or taste were the leading reasons for testing for COVID-19. These symptoms made them suspicious as to the possibility of SARS-CoV-2 infection.

According to the CDC (2020) although some patients infected recover their normal health, some may experience symptoms that can last for weeks or months even after recovery from the illness[8]. Cases of long-lasting symptoms of COVID-19 are increasingly recurring.

According to a study in China of 1,733 patients who were hospitalized with COVID-19, three-quarters of them had at least one symptom over a 6-month course even after recovery from the acute phase, with the most persistent and recurrent symptoms being: fatigue 63%, dyspnea 26%, difficulty sleeping 26%, anxiety or depression 23% and smell disorder 11%[29]. Given this, we also wanted to analyze the prevalence of persistent symptoms. In our sample 50 professionals reported some signs and symptoms for COVID-19. Of these, 31 reported symptoms lasting > 4 weeks, classifying them as individuals who have suffered or are suffering from long COVID. And when asked which symptoms persisted, the most mentioned were loss of smell, loss of taste, weakness/tiredness, moodiness, difficulty concentrating, and headache. It can be seen, that olfaction and/or taste dysfunctions besides being characteristic symptoms for COVID-19 are also symptoms that tends to persist the longest. In fact, a national online survey of 321 individuals found that 67% reported that their lack of sense of smell and taste persisted for 6 months or longer[7].

Smell and taste are crucial senses for life. Alterations in these senses can result in eating disturbances, loss of appetite, weight change, reduced enjoyment of food, decreased social engagement and relationships, and difficulty detecting dangerous situations such as gas leaks, smoke, and spoiled food[30,31]. Loss of smell and taste, whether this is a persistent symptom or not, carries with it numerous psychological and emotional consequences, affecting patients' quality of life[10]. Therefore, we decided to investigate the impact of olfactory and taste dysfunctions on quality of life and eating habits.

When analyzing the impact of disturbances on quality of life we found no difference between the group that experienced these dysfunctions and the control group, which tested positive but did not have a loss of smell and/or taste. Different from the study by Shah *et al.* (2020), who used the same questionnaire to analyze quality of life in patients with COVID-19; they found that quality of life scores were lower in patients with anosmia[32]. However, it is worth mentioning that the study by Shah *et al.* (2020), despite using the same protocol, was based on a comparison of the scores between individuals with anosmia and hyposmia[32]. And it is important to consider the context of COVID-19 when analyzing quality of life in the pandemic period, as we did in our study. Shah's (2020) study considered that only the loss of smell brought consequences to quality of life, without taking into consideration the context of the disease and pandemic that were experienced by these participants. Physical or psychological aftereffects, linked to the anxieties brought about by social restriction, either by the pandemic scenario or by having received a positive diagnosis for COVID-19, can also entail a considerable impact on quality of life[33].

Individuals with olfaction and taste deficits can also suffer with alterations in eating

habits, have problems with cooking, and have decreased appetite[10]. When analyzing the impact of olfaction and/or taste disturbances on eating habits, we found an association regarding "liking food", because the group that had olfaction and taste disturbances mentioned liking food less, compared to the control group. It is worth noting that most of the respondents mentioned that they did not prepare meals themselves; this factor may have influenced the reports about changes in the amount of condiments. When asked which foods they had a preference for, they mentioned spicy, hot, and citrus foods, probably in an attempt to mask their chemosensory disorder.

This study had some limitations. We evaluated the prevalence, long-term persistence, and impact of olfactory and taste disorders on quality of life and eating habits of only health professionals. However, this investigation is important, since them represent a group at high risk of acquiring and transmitting the COVID-19, because they are in direct contact with infected individuals within a weakened health care situation.

CONCLUSION

It can be concluded that there is a high prevalence of short- and long-term smell and/or taste dysfunctions in subjects with COVID-19, suggesting that these symptoms can be used as clinical signs in screening for SARS-CoV-2 infection and Long COVID cases. Loss of smell and taste can appear as the first symptom and persist for weeks or even months, even after the acute phase of the disease has passed. This loss of smell and taste sensation, even persistently, can impact on eating habits resulting in reduced enjoyment of food. This may cause individuals to compensate for the loss of these sensitivities by choosing more palatable and spicy foods in an attempt to mask the change in these senses.

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7 CONSIDERAÇÕES FINAIS

A partir desse estudo é possível concluir que existe uma alta prevalência das disfunções do olfato e/ou paladar, a curto e longo prazo, nos sujeitos com diagnóstico positivo para COVID-19, revelando que esses sintomas podem ser usados como sinais clínicos na triagem para infecção pelo SARS-CoV-2 e casos de *Long* COVID.

A perda do olfato e paladar pode surgir como primeiro sintoma durante a infecção e persistir por semanas ou até meses, mesmo após a fase aguda da doença o que podem resultar na redução do prazer pela comida, podendo acarretar perda de peso e desnutrição; bem como, fazer com que os indivíduos para compensar a perda dessas sensibilidades optem por alimentos mais temperados e palatáveis na tentativa de mascarar a alteração nesses sentidos.

Diante do exposto, ressaltamos a necessidade da continuação dos estudos, a fim de observar os efeitos a longo prazo da Long COVID e até mesmo desenvolver análises de citocinas e genômicas de pacientes que desenvolveram Long COVID em comparação com os pacientes que não tiveram persistência de sintomas a longo prazo.

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APÊNDICE A – PRODUTO CIENTÍFICO PRODUZIDO DURANTE O MESTRADO: RESUMO – XXXII CONGRESSO BRASILEIRO DE VIROLOGIA/2021

LONG COVID: LASTING SYMPTOMS AND THEIR INTERFERENCE WITH DAILY ACTIVITIES

Barbosa DAM[1*]; Conceição EH[1]; Araujo AV[1]; Fernandes MP[2] Gomes ALV[1]; Althoff KNFP[2]

[1] Laboratório Microbiologia e Imunologia, Departamento Enfermagem, CAV/UFPE, Vitória de Santo Antão/PE

[2] Grupo de Pesquisa Nutrição, Atividade Física e Plasticidade Fenotípica, Departamento Pleno de Educação Física e Ciência do Esporte UFPE/CAV, Vitória de Santo Antão/PE

*danielly.alvesb@ufpe.br;

Introduction: Some reports of long-lasting symptoms of COVID-19 (Long COVID), are increasing, but little is known about the prevalence, risk factors or whether it is possible to predict a prolonged course at the onset of the disease. According to the Centers for Disease Control and Prevention (CDC), although patients infected with SARS-CoV-2 regain their normal health, some may experience symptoms that can last weeks or months even after they recover from the disease. Therefore, this study aimed to analyze the long-lasting symptoms of COVID-19 and its interference in daily activities. **Materials and Methods:** This study was approved by the CEP under number: 4,744,490. The survey was carried out with a sample of 40 professionals working on the frontlines of the COVID-19 combat, who were IgG and/or IgA positive for SARS-CoV-2. These professionals were invited to answer the WHO Long Covid questionnaire by telephone. The memo being composed of 2 objective questions: permanence of any symptom of COVID-19 for 4 weeks or more after infection (symptoms not explained for any other reason) the individual should report yes or no. If you reported yes, you should inform if this situation of Long COVID has reduced your ability to perform daily activities compared to the time before having COVID- 19 in: Yes (very, little, not at all). In the 2nd question, the respondent should inform which symptom had persisted in the post-COVID period. **Result:** Of the 40 professionals, 25 reported having symptoms that lasted for more than 4 weeks; of these 25 professionals, 14 people reported that persistent symptoms greatly affected their ability to perform daily activities, 8 reported that lasting symptoms somewhat affected their ability to perform daily activities, and 3 showed that these symptoms did not affect their ability to carry out day-to-day activities. Among the lasting symptoms the most mentioned were: loss of smell 68% (n=17), loss of taste 48% (n=12), weakness/tiredness 36% (n=9), moodiness 28% (n=7), memory loss or confusion 24%(n=6), concentration difficulty 20% (n=5) and headache 20% (n=5). **Conclusion:** Symptoms of loss of smell, loss of taste, fatigue and neuropsychiatric symptoms figured prominently; and these lasting symptoms can affect the individual's quality of life. The cooperation of several lines of studies is necessary to verify the behavior of these symptoms in the long term and learn the best way to treat these patients, implementation of public policies for collective health and reintegration into society.

Keywords: COVID-19; Long Covid; SARS-CoV-2.

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APÊNDICE B - PRODUTO CIENTÍFICO PRODUZIDO DURANTE O MESTRADO: RESUMO – XXXIII CONGRESSO BRASILEIRO DE VIROLOGIA/2022

LEVEL OF PHYSICAL AND MENTAL HEALTH OF INDIVIDUALS WITH COVID-19 IN THE SHORT AND LONG TERM

Danielly Alves Mendes Barbosa [1]; Ewerthon Henrique da Conceição [1]; Renata Emmanuele Assunção Santos [2]; , Mariana Pinheiro Fernades [2]; Alice Valença de Araújo [2]; Isis Didier Lins [4]; Caio Bezerra Souto Maior [3]; Felipe Cavalcanti de Barros Felipe [5]; Kelli Nogueira Ferraz Pereira Althoff [4]; Ana Lisa do Vale Gomes [2]

[1]Discente. R. Alto do Reservatório - Alto José Leal, Vitória de Santo Antão - PE, 55608-680. Universidade Federal de Pernambuco - Centro Acadêmico de Vitória; [2]Docente. R. Alto do Reservatório - Alto José Leal, Vitória de Santo Antão - PE, 55608-680. Universidade Federal de Pernambuco - Centro Acadêmico de Vitória; [3]Docente. Av. Marielle Franco, s/n - Km 59 - Nova, PE, 55014-900- PE, 55608-680. Universidade Federal de Pernambuco - Centro Acadêmico do Agreste; [4]Docente. Av. Prof. Moraes Rego, 1235 - Cidade Universitária, Recife - PE, 50670-901. Universidade Federal de Pernambuco ; [5]Discente. Av. Prof. Moraes Rego, 1235 - Cidade Universitária, Recife - PE, 50670-901. Universidade Federal de Pernambuco

Resumo:
The spread of SARS-CoV-2 was accelerated, reaching a pandemic reality in 2020. The main symptoms in the first patients included fever, cough, myalgia and dyspnea. As the virus spread, new symptoms emerged, and COVID-19 came to be considered a multisystem disease. According to the US Centers for Disease Control and Prevention, although most patients infected with SARS-CoV-2 regain their normal health, some may experience symptoms lasting for weeks or months even after recovery from the acute phase of the disease. This persistence of symptoms, whether physical or psychological, can have a considerable impact on quality of life. Therefore, this study aims to assess the level of physical and mental health of individuals with COVID-19 in the short and long term. This is a case-control study carried out with a sample of 53 health professionals. These professionals performed the anti-SARS-CoV-2 IgG research through ELISA and were divided into 2 groups: positive IgG and negative IgG. They were then invited to answer the PROMIS 10 questionnaire by telephone, which aims to self-assess their quality of life, physical function, general health, mental health, emotional health, relationships, active roles and their ability to perform activities of daily living. This study was approved by the Ethics Committee: 4,744,490. The sample is composed of 53 health professionals from the municipality of Vitória de Santão Antão (Pernambuco/ Brazil) where 44 tested positive and 9 negative. Of the 44 in the positive group, 23 (52.3%) people had high levels for physical health and 21 (19.9%) had low levels for physical health, 31 (70.5%) had high levels for health mental health and 13 (29.5%) had low levels for mental health. As for persistent symptoms, when the 53 professionals were asked about having any long-term symptoms of COVID-19, that is, for more than 4 weeks, 31 reported this condition, classifying them as Long COVID. Of the 31 professionals with Long COVID, 16 (51.6%) were in high physical health and 15 (48.4%) had low levels of physical health; and of the 31 with long COVID, 21 (67.7%) were in high mental health and 10 (32.2%) were in low mental health. The percentages of individuals who had short-term and long-term COVID-19 and fell into low physical and mental health levels are high. Our results highlight the need for more studies linking physical and mental health to COVID-19 in the short and long term to identify its impacts and inform mental health care policy, intervention, and prevention.
Palavras-chave: COVID-19; Health Physics; mental health; Quality of Life;

APÊNDICE C - PRODUTO CIENTÍFICO PRODUZIDO DURANTE O MESTRADO: RESUMO – XXXIII CONGRESSO BRASILEIRO DE VIROLOGIA/2022

ACUTE POST-COVID SYNDROME: PREVALENCE, PERSISTENT SYMPTOMS AND THEIR IMPACT ON DAILY ACTIVITIES

Danielly Alves Mendes Barbosa [1]; Ewerthon Henrique Conceição [2]; Renata Emmanuele Assunção Santos [3]; Mariana Pinheiro Fernades [3]; Alice Valença Araújo [3]; Isis Didier Lins [4]; Caio Bezerra Souto Maior [5]; Felipe Cavalcanti de Barros Felipe [6]; Kelli Nogueira Ferraz Pereira Althoff [4]; Ana Lisa do Vale Gomes [3]

[1]Bolsista. R. Alto do Reservatório - Alto José Leal, Vitória de Santo Antão - PE, 55608-680. Universidade Federal de Pernambuco - Centro Acadêmico de Vitória; [2]Discente. R. Alto do Reservatório - Alto José Leal, Vitória de Santo Antão - PE, 55608-680. Universidade Federal de Pernambuco - Centro Acadêmico de Vitória; [3]Docente. R. Alto do Reservatório - Alto José Leal, Vitória de Santo Antão - PE, 55608-680. Universidade Federal de Pernambuco - Centro Acadêmico de Vitória; [4]Docente. Av. Prof. Moraes Rego, 1235 - Cidade Universitária, Recife - PE, 50670-901. Universidade Federal de Pernambuco; [5]Docente. Av. Marielle Franco, s/n - Km 59 - Nova, PE, 55014-900. Universidade Federal de Pernambuco - Centro Acadêmico do Agreste; [6]Discente. Av. Prof. Moraes Rego, 1235 - Cidade Universitária, Recife - PE, 50670-901. Universidade Federal de Pernambuco

Resumo:
The American Autonomic Society has termed the ongoing symptoms of COVID-19 "acute post-COVID syndrome" (PACS), characterizing individuals who remain with a range of ongoing symptoms, even after being diagnosed with improvement in the acute phase of the disease. Cases of lasting symptoms of COVID-19 are increasingly recurrent, so research is needed to understand the social and health impacts of these persistent symptoms. Thus, this study aims to analyze the prevalence, persistent symptoms and their impact on daily activities. The survey was carried out with 44 health professionals who worked on the front lines of the fight against COVID-19, who presented positive IgG and/or IgA for SARS-CoV-2, they were invited to answer the questionnaire: WHO Long Covid question , by telephone, the collection period of this study was from April 2021 to January 2022. The WHO Long Covid questionnaire from WHO is composed of 3 questions: 1. permanence of any symptoms of COVID-19 for 4 weeks or more after the infection, 2. whether the persistent symptom reduced their ability to perform daily activities, and finally 3. which symptom had persisted in the post-COVID period. This study was approved by the Ethics Committee: 4,744,490. As a result, we found that of the 44 participants, 29 developed symptoms that persisted for more than four weeks. Among the most cited persistent symptoms are: loss of smell 55.17%(n=16), loss of taste 55.17%(n=16), weakness 34.48%(n=10), depressed mood 20.69 %(n=6), memory loss or confusion 24.13%(n=7), difficulty concentrating 20.69%(n=6) and headache 13.79%(n=4). Among the 29 who developed PACS, 34.48% (n=10) mentioned that this condition had a moderate impact on their daily activities, and 55.17% (n=16) reported that they had persistent symptoms for more than 4 weeks greatly impacted their daily activities. Weakness, loss of smell and loss of taste were the most mentioned among those who rated PACS as having an intense impact on daily activities. The chi-square test showed a dependence relationship between having loss of smell and/or taste with the PACS, with p=0.001. Symptoms of loss of smell, loss of taste, fatigue and neuropsychiatric symptoms figured prominently. The cooperation of several lines of studies is necessary to verify the behavior of these symptoms in the long term, to provide the best care to patients who live with lasting sequelae, to know the best way to treat these patients and to implement public policies.
Palavras-chave: COVID-19; Long Covid; SARS-CoV-2; ;

APÊNDICE D - PRODUTO CIENTÍFICO PRODUZIDO DURANTE O MESTRADO: RESUMO – 30º CONGRESSO BRASILEIRO DE FONOAUDIOLOGIA

IMPACTO DAS ALTERAÇÕES DO OLFATO E PALADAR, A CURTO E LONGO PRAZO, NOS HÁBITOS ALIMENTARES DE PACIENTES COM COVID-19

Celiane de Farias[1], Danielly Alves Mendes Barbosa[2], Nilian Cerqueira Azevêdo[1], Renata Emmanuele Assunção Santos[2], Maria Caroline Barbosa do Monte Silva[3], Cynthya Myllena Martins Silva[3], Isabeli Lins Pinheiro[2,5], Ana Lisa do Vale Gomes[2], Kelli Nogueira Ferraz Pereira Althoff[1,2,4]

1. Programa de Pós-graduação em Saúde da Comunicação Humana – Universidade Federal de Pernambuco.
2. Programa de Pós-Graduação em Nutrição, Atividade Física e Plasticidade Fenotípica. Universidade Federal de Pernambuco – Centro Acadêmico de Vitória – Universidade Federal de Pernambuco
3. Programa de Pós-Graduação em Nutrição – Universidade Federal de Pernambuco.
4. Departamento de Fonoaudiologia - Universidade Federal de Pernambuco
5. Cursos de Educação Física – Centro Acadêmico de Vitória – Universidade Federal de Pernambuco.

Introdução: Sintomas duradouros da COVID-19, o chamado *Long* COVID, estão cada vez mais recorrentes, podendo-se destacar alterações no olfato e paladar como um deles. Sabe-se a importância das funções sensoriais supracitadas como componentes protetores, entretanto, deve-se destacar as repercussões que alterações nesses sentidos podem influenciar nos hábitos alimentares, em especial, a relação do olfato e paladar na alimentação. O estímulo dessas funções sensórias também promove o aumento da produção salivar, que ao entrar em contato com o alimento, contribui para a produção do bolo alimentar, refletindo em pontos positivos para o processo mastigatório e deglutição. Quando tais funções estão ausentes ou alteradas, podem refletir em desinteresse, recusa alimentar e alterações nos processos mastigatórios, provocando perda de peso, desnutrição, limitações nutricionais/funcionais. **Objetivo:** Avaliar o impacto das alterações do olfato e paladar, a curto e longo prazo, nos hábitos alimentares de pacientes com COVID-19. **Métodos:** Estudo aprovado pelo CEP: 4.744.490. Participaram 53 profissionais da saúde da linha de frente do combate da COVID-19. Estes foram divididos em 2 grupos: IgG/IgA positivo para SARS-CoV-2 (n=44) e IgG/IgA negativo para SARS-CoV-2 (n=9), os quais, responderam 3 questionários por contato telefônico: *Anosmia Reporting Tool; WHO Long Covid question* e Questões de aceitabilidade de comportamento alimentar. O primeiro questionário apresenta 17 questões, mas foi selecionado apenas o quadro sintomatológico e a classificação do comprometimento do olfato e paladar para os resultados deste estudo. O segundo questionário, contém 2 perguntas: permanência de sintoma de COVID-19 por $\geq$ 4 semanas após a infecção e qual sintoma persistente. E o terceiro questionário contava com 6 perguntas direcionadas aos hábitos alimentares. **Resultados:** Dos 53 participantes, 9 testaram negativo e 44 positivo para COVID-19. Dos negativos 2(28,6%) relataram alterações no olfato e/ou paladar e dos positivos 37(86,1%) relataram tais sintomas. Dos 37 positivos com alteração do olfato e/ou paladar, apenas 1 pessoa relatou o comprometimento isolado do paladar. Todos os demais (n=36) mencionaram o comprometimento integrado do olfato e paladar. Desses, 32(86,5%) classificaram seu comprometimento do olfato como anosmia, e 29(78,4%) classificaram seu comprometimento do paladar como ageusia. Quanto aos sintomas persistentes, 31(58,5%) desenvolveram sintomas que duraram por mais de quatro semanas, classificando-os com *Long* COVID. Entre os sintomas persistentes mais citados estão: perda do olfato (n=16, 51,6%) e paladar (n=16, 51,6%). O teste do qui-quadrado mostrou relação de dependência entre ter perda do olfato e/ou paladar com a *Long* COVID. Quanto a análise do impacto das alterações sobre os hábitos alimentares descobriu-se que o grupo positivo com perda de olfato e/ou paladar apresentou redução do gosto/prazer pela comida. **Conclusão:** Alterações de olfato e paladar constituem-se componentes importantes em pacientes com COVID e apresentam-se de forma duradoura no *Long* COVID. As alterações nas funções olfativas e gustativas podem refletir em impactos negativos a qualidade de vida dos indivíduos, apresentando ligação direta na adequada função do sistema motor oral e do sistema gastrointestinal no que se refere ao processo da alimentação, tornando-se de fundamental importância a atuação fonoaudiológica, na intervenção do sistema sensorial, evitando repercussões negativas nas diferentes funções do sistema estomatognático.

APÊNDICE E - PRODUTO CIENTÍFICO PRODUZIDO DURANTE O MESTRADO: ARTIGO DE REVISÃO SISTEMÁTICA

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Onset and duration of symptoms of loss of smell/taste in patients with COVID-19: A systematic review

Renata Emmanuele Assunção Santos [a,d], Maria Giselda da Silva [d,e], Maria Caroline Barbosa do Monte Silva [d,e], Danielly Alves Mendes Barbosa [c,d], Ana Lisa do Vale Gomes [c,e], Ligia Cristina Monteiro Galindo [d,e,f], Raquel da Silva Aragão [a,b,d,e], Kelli Nogueira Ferraz-Pereira [b,d,e,*]

[a] Graduate Program in Nutrition, Universidade Federal de Pernambuco, Recife, PE, Brazil
[b] Physical Education and Sports Sciences Nucleus, Universidade Federal de Pernambuco, Vitória de Santo Antão, PE, Brazil
[c] Nursing Department, Universidade Federal de Pernambuco, Vitória de Santo Antão, PE, Brazil
[d] Phenotypic Plasticity and Nutrition Studies Unit, Universidade Federal de Pernambuco, Recife, PE, Brazil
[e] Graduate Program in Nutrition, Physical Activity and Phenotypic Plasticity, Universidade Federal de Pernambuco, Vitória de Santo Antão, PE, Brazil
[f] Department of Anatomy, Universidade Federal de Pernambuco, Recife, PE, Brazil

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ABSTRACT

Objective: The aim of the study was to conduct a systematic review of the literature to investigate the time of onset and duration of symptoms of loss of smell and taste in patients diagnosed with COVID-19.
Methods: Two independent authors performed a systematic review of the Medline/PubMed, SCOPUS, COCHRANE, Lilacs and Web of Science electronic databases. The time of onset and duration of symptoms were considered primary outcomes. The sex and age of individuals, the geographical location of the study, the prevalence of symptoms, other associated symptoms, associated comorbidities, and the impact on quality of life and eating habits were considered secondary outcomes.
Results: Our search generated 17 articles. Many of the studies reported that the onset of anosmia and ageusia occurred 4 to 5 days after the manifestation of other symptoms of the infection and that these symptoms started to disappear after one week, with more significant improvements in the first two weeks.
Conclusion: The present study concludes that the onset of symptoms of loss of smell and taste, associated with COVID-19, occurs 4 to 5 days after other symptoms, and that these symptoms last from 7 to 14 days. Findings, however, varied and there is therefore a need for further studies to clarify the occurrence of these symptoms. This would help to provide early diagnosis and reduce contagion by the virus.

1. Introduction

COVID-19 (Coronavirus 2019 disease), which is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was first registered in China in December 2019, being associated with severe acute respiratory syndrome [1]. The spread of the virus was very rapid, reaching pandemic status in early 2020 [2]. By the end of August 2020, the World Health Organization (WHO) had registered 24,021,218 confirmed cases and 821,462 confirmed deaths [3]. Brazil was the first country in Latin America to diagnose a patient with COVID-19, on February 25, 2020, in the city of São Paulo. According to the WHO, by the end of August 2020, Brazil had registered 3,669,995 confirmed cases and 116,580 deaths [3].

The most prevalent symptoms in the first patients included fever, cough, myalgia and shortness of breath [4]. However, as the pandemic spread to more countries and the numbers of infected individuals increased, other signs and symptoms came to be viewed as clinical manifestations of the disease [5]. One unusual symptom in particular began to appear in an increasing number of patients: dysfunction of smell and taste - loss of sensitivity to taste and smell [6]. In South Korea, China and Italy, a large percentage of infected patients developed anosmia or hyposmony [4]. In Italy, about 33.9% of patients reported

* Corresponding author at: Núcleo de Educação Física e Ciencias do Esporte, Universidade Federal de Pernambuco, Centro Academico de Vitória, R. Alto do Reservatório, S/n - Bela Vista, Vitória de Santo Antão, PE CEP 55608-680, Brazil.
E-mail address: kelliferraz@hotmail.com (K.N. Ferraz-Pereira).

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changes in smell and taste and 11% reported both disorders [6]. In South Korea, where tests were performed on a large scale, 30% of patients had loss of smell as the main sign in mild cases of infection [4]. More than two-thirds of those infected in Germany developed anosmia [4]. In Brazil, a study carried out with 253 recovered patients, showed that 212 had experienced sudden-onset anosmia and 196 had developed loss of smell accompanied by nonspecific inflammatory symptoms [6]. Sudden changes in smell thus came to be seen as initial signs of COVID-19 [7] and, anosmia, in the absence of other symptoms, such as rhinorrhea or nasal congestion, may be an indicator of SARS-CoV-2 infection [8–12].

In view of this, the Center for Disease Control and Prevention (CDC) added the loss of taste and smell to the list of signs and symptoms that may arise from the second to the fourteenth day after exposure to the virus. During this time, there are generally no specific clinical manifestations, because it is the viral incubation period [1]. The Brazilian Academy of Rhinology and the Brazilian Association of Otorhinolaryngology and Cervical-Facial Surgery duly issued a warning that cases of anosmia, with or without concomitant ageusia, may indicate the presence of infection by COVID-19 [6]. However, despite being a very prevalent symptom in patients with COVID-19, the onset time and duration of these symptoms has not been well established. Understanding of this issue would contribute greatly to early diagnosis, thereby enabling prevention of further contagions and possible complications. We thus performed a systematic review of the literature to investigate the time of onset and duration of symptoms of loss of smell and taste in patients diagnosed with COVID-19.

2. Materials & methods

The present systematic review was carried out in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [13]. Our review was conducted using a protocol submitted to the International Prospective Registry for Systematic Reviews (PROSPERO) and published under registration number: CRD42020186114.

2.1. Research strategy

The literature search was carried out in May 2020 using the Medline/PubMed (Online System for Research and Analysis of Medical Literature), SCOPUS, COCHRANE, Lilacs (Latin American and Caribbean literature in health sciences) and Web of Science electronic databases. Variations of the following descriptors were used: COVID-19; SARS-COV-2; smell; taste; olfaction disorders; anosmia; taste disorders; dysgeusia.

The bibliographic search in the electronic databases was carried out by two independent reviewers (SANTOS REA and DA SILVA, MG), using a pre-established protocol. A third reviewer (BARBOSA, DAM) was consulted when necessary and acted as a mediator in decisions regarding inclusion or exclusion criteria, on occasions when there was no agreement between the reviewers. Data extraction was performed according to the eligibility criteria established for the study.

2.2. Inclusion and exclusion criteria

The present review included human studies that assessed the symptoms of loss of smell and/or taste in patients diagnosed with COVID-19, regardless of laboratory confirmation and other symptoms related to the disease. Studies were excluded if they did not explain in detail the outcomes investigated in the present review or if they did not provide detailed explanation of their methodology. Case-reports, letters to the editor, literature reviews, systematic reviews, meta-analyses, and in vitro and animal studies were also excluded. There were no restrictions regarding language or year of publication.

2.3. Evaluation of articles

The assessment of the risk of bias in the studies was performed independently by two reviewers using the Modified Health Care Research and Quality Agency (AHRQ) instrument [14]. The studies were evaluated using a list of twenty-six items, divided into nine evaluation criteria: study question, study population, subject comparability, exposure or intervention, measured results, statistical analysis, results, discussion, and funding or sponsorship [14,15].

The primary outcomes for reviewing the literature on loss of smell and taste in patients diagnosed with COVID-19 were the time of onset and duration of symptoms. Secondary outcomes included the sex and age of individuals, the geographical location of the study, prevalence of symptoms, other associated symptoms, associated co-morbidities, and the impact on quality of life and eating habits.

The level of agreement between the reviewers and the quality of the studies (risk of bias) were analyzed using the kappa coefficient on the Statistical Package for the Social Sciences - SPSS version 20 for Windows (IBM SPSS Software, Armonk, NY, USA).

3. Results

The initial database search identified a total of 298 articles, 122 in Medline/PubMed, 157 in Scopus, one in LILACS, 18 in Web of Science and none in Cochrane. Removal of duplicate articles reduced the total to 200, which title and abstract screening reduced further to 22 articles. These 22 studies underwent full-text analysis, resulting in the exclusion of 5 studies and generating a final total of 17 articles included for analysis, as shown in the flowchart presented in Fig. 1.

3.1. Quality assessment of articles

Table 1 shows the evaluation of the articles according to the points highlighted by West [14]. Evaluation of quality criteria revealed methodological shortcomings in some articles, including: failure to justify the sample size (all articles included in the review); failure to detail inclusion and exclusion criteria [8,9,12,16–24]; analysis of individuals who were not tested for COVID-19 [18–21]; failure to address the limitations of the study [15,21]; and failure to cite sources of financing, even if these did not exist [8,10,15,19,20,24–27]. The level of agreement between reviewers regarding analysis of data extraction and risk of bias was almost perfect (Kappa: 0.8824) [28].

The results of studies of the time of onset and duration of symptoms of loss of smell and taste in patients diagnosed with COVID-19, as well as the sex and age of individuals, the geographical location of the study, the prevalence of symptoms, associated symptoms, associated comorbidities, and the impact on quality of life and eating habits, are summarized in Table 2.

3.2. Characterization of the studies

3.2.1. Sex and age of individuals

All 17 articles provided data on the age and sex of individuals, although only five articles found an association between sex and alterations in the sense of taste or smell [10,12,15,24,25], with women presenting a higher prevalence of such alterations. Only four articles found an association between age and olfactory and gustatory symptoms, [10,15,24,25], although these results were inconsistent. Two studies found that younger people presented a higher prevalence of these symptoms [10,25]; one study found that adults with a mean age of 36.5 were more affected [24]; and one study showed that symptoms were more prevalent in individuals over 50 years of age [15].

3.2.2. Geographical location of studies

The studies covered by the present review provided data for countries on three continents, three articles were from Asia [21,23,24], five

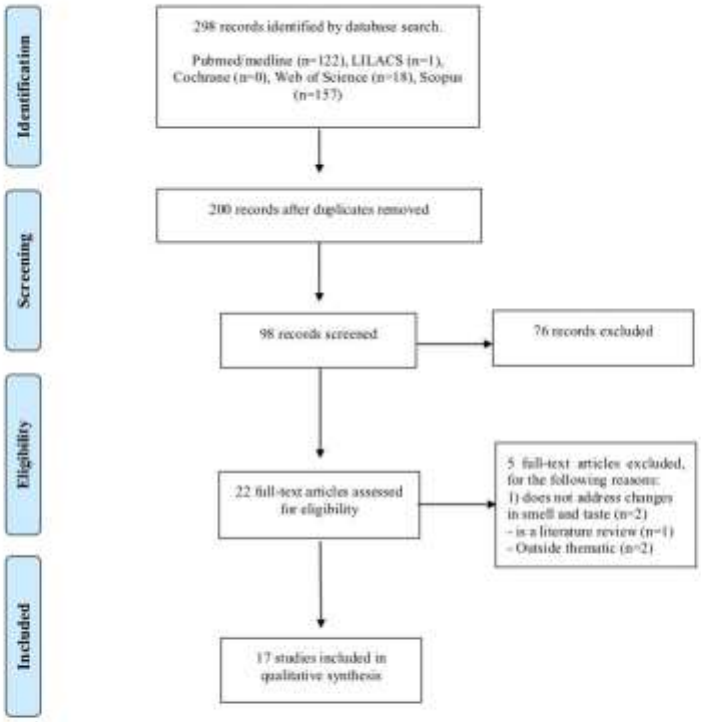

Fig. 1. Selection of articles.

from North America [9,16,17,20,22], and 10 from Europe [8–10,12,15,18,19,25–27]. All articles reported alterations in the sense of smell and taste in patients with COVID-19, although, in Asian countries, the prevalence of olfactory and gustatory dysfunction reported was lower compared to North America and Europe. In China, the prevalence of such symptoms was 5.6%, in Korea, 15%, and, in Singapore, 22%. In North America and Europe, the prevalence varied from 18.6% to 90%.

3.3. Time of onset of symptoms

The articles reviewed reported conflicting results regarding the time of onset of symptoms of loss of smell and/or taste in patients diagnosed with COVID-19. Many studies, however, reported that the onset of anosmia and ageusia occurred 4 to 5 days after the appearance of other symptoms of the infection [15,26,27]. Analysis of the prevalence of the appearance of changes in smell and/or taste before, simultaneously with or after other symptoms as reported in these articles found that the prevalence of such symptoms emerging prior to other symptoms varied between 13% [19] and 73% in patients (before diagnosis) [9]; the prevalence of such symptoms emerging at the same time as other symptoms, varied from 13.5% [8] to 38.4% [19]; and that of such symptoms appearing after other symptoms from 27% [9] to 48.6% [19].

3.4. Duration of symptoms

The duration of symptoms of loss of smell and/or taste in patients diagnosed with COVID-19 was addressed in eight articles [9,10,15,17–19,24,26]. The findings were inconsistent but, generally speaking, the symptoms begin to disappear after one week [9,15,24], and, in the first two weeks, significant improvement occurred [17–19]. In addition, two studies found that 34% [15] and 37.5% [10] of the subjects continued to show symptoms for at least 7 days, even after recovery from the disease.

3.5. Prevalence of symptoms

Only one of the studies reviewed did not assess the prevalence of symptoms of loss of smell and/or taste in patients diagnosed with COVID-19. This study looked only at individuals who had already presented with anosmia [9]. Six combined the prevalence for symptoms of loss of smell and taste, reporting a minimum prevalence of 19% [22] and a maximum of 73.6% [15]. Regarding olfactory disorders alone, six studies found a prevalence of over 68% [10,12,16,17,25,27] and two found a prevalence of less than 7.27% [23,24]. In relation to taste disorders, six studies reported a prevalence greater 54.2% [10,16,17,19,25,27] and two registered a prevalence of below 5.1% [23,24].

3.6. Associated symptoms

Many studies also showed that changes in smell and/or taste may occur concomitantly with other symptoms. The most commonly mentioned were: fever [8,12,16,17,19–23,25–27], cough [8,10,12,15,19–23,25–27], headache [8,10,15,20,22,26,27], and fatigue [12,16,17,26]. Some studies also reported gastrointestinal symptoms [8,15–17,20,22,26,27]., Six studies found that smell and taste disorders occurred together with nasal obstruction [10,12,15,20,25,26].

Table 1
Characterization of studies according to evaluation criteria highlighted by West et al. (2002).

Author/ Year	DOMAINS								
	Study Question	Study Population	Comparability of Subjects	Exposure/ Intervention	Outcome Measure	Statistical Analysis	Results	Discussion	Funding
Spinato et al., 2020	●	◑	◑	●	●	●	●	●	●
Yan et al., 2020	●	◑	◑	●	●	●	●	●	●
Lechien et al., 2020a	●	◑	●	●	●	●	●	●	○
Kaye et al., 2020	●	◑	◑	●	●	●	●	●	●
Hopkins et al., 2020a	●	◑	◑	◑	●	●	●	●	●
Vaira et al., 2020	●	◑	●	●	●	●	●	◑	○
Lechien et al., 2020b	●	◑	●	●	●	●	●	●	○
Hopkins et al., 2020b	●	◑	◑	◑	●	●	●	●	○
Giacomelli et al., 2020	●	◑	◑	●	●	●	●	●	○
Roland et al., 2020	●	◑	◑	◑	●	●	●	●	○
Wee et al, 2020	●	◑	◑	◑	●	●	●	◑	●
Aggarwal at al., 2020	●	◑	◑	●	●	●	●	●	●
Klopfenstein et al., 2020	●	◑	●	●	●	●	●	●	○
Mao at al., 2020	●	◑	◑	●	●	●	●	●	●
Luers et al., 2020	●	◑	●	●	●	●	●	●	○
Yan et al., 2020	●	◑	◑	●	●	●	●	●	●
Lee et al., 2020	●	◑	◑	●	●	●	●	●	○

●–Yes; ◑–Partial; ○–No information. Kappa: 0.8824.

3.7. Associated comorbidities

Five of the studies covered by our review investigated co-morbidities present in patients diagnosed with COVID-19 [10,22,23,25,26]. The most prevalent co-morbidities were systemic arterial hypertension [10,22,23,25,26], rhinitis [10,25], asthma [10,25,26], and cardiovascular disease [22,23,26].

4. Discussion

The spread of COVID-19 around the world has been accompanied by the appearance of symptoms that differ from a common flu [29,30]. Changes in smell and taste have been strongly associated with a positive diagnosis of infection by the new coronavirus [31]. This association is confirmed by the prevalence of more than 50% for anosmia and/or agneusia in patients with COVID-19 [10,12,15,16,27]. However, the time of onset time and duration of these symptoms has yet to be clearly established. Adequate quantification of loss of smell and/or taste, and identification of the temporal relationship between COVID-19 contagion and olfactory and/or gustatory dysfunctions would provide great assistance in arriving at an early diagnosis and thereby avoiding further contagion and possible complications [32]. The present systematic review thus aimed to establish the time of onset and duration of symptoms of loss of smell and taste in patients diagnosed with COVID-19.

The tool used to assess risk of bias (AHRQ) [14] found that the articles reviewed were effectively addressed the proposed study question. Some, however, were marred by methodological shortcomings, especially with regard to the "study population", since they did not calculate the sample size. However, this probably occurred due to the lack of information on the prevalence of this novel disease. We also observed that the studies analyzed employed a variety of different methods and presented their findings in different ways, making it impossible to carry out a meta-analysis.

All articles included in this review investigated both female and male individuals, but only five articles found any association between sex and changes in taste and smell [10,12,15,24,25]. Although men have a less favorable prognosis for COVID-19 [33], the prevalence in women of changes in smell and taste was higher in the five studies reviewed [10,12,15,24,25]. The average age range was 38 to 65 years, with a predominance of adults and elderly people affected by the infection. This is the age group that appears to be most affected by COVID-19 [34–36]. One study cited working outside the home during the pandemic as an important risk factor for the transmission of the disease among adults, as this occasions more contact with people and, consequently, greater exposure to the virus [37].

The prevalence of smell and taste dysfunction appeared to be lower in Asia, compared to North America and Europe. It is thus possible to identify a change in the profile of the main symptoms as the disease passes through different countries. This may be related to the different strains of the virus that have been circulating since the beginning of the COVID-19 pandemic. Around 93 mutations have been observed throughout the SARS-CoV-2 genome in different geographic regions [38]. A meta-analysis carried out with cases of COVID-19 in China, the country that presented the first cases of the disease, showed that the main symptoms were fever, cough, fatigue, sputum and dyspnea [39]. When the disease reached European countries, a change in symptoms occurred and olfactory and gustatory changes began to appear as clinical signs. Such signs may prove a great aid to diagnosis of COVID-19, since they are predominant symptoms in people affected by the virus [40]. Most patients with Sars-CoV-2 infection are considered asymptomatic and do not require hospitalization [10]. Symptomatic patients have symptoms such as fever, dry cough, shortness of breath, gastrointestinal symptoms and also symptoms that mainly affect smell and taste, in which there is a significant reduction in these senses. Such symptoms

Table 2
Characteristics of studies included.

Author (year)	Sample characterization	Methodological design	Investigated outcomes	Results
Hopkins et al., 2020a	382 female and male adults were included. 74.6% of the sample was composed of women. The median age range was 40 to 49 years. 46.8% of those evaluated were younger than 40 years old. The study was carried out in London, UK.	- Online survey of patients diagnosed during the COVID-19 pandemic, who sought advice by e-mail on smell and taste disorders and were followed up for one week.	1.Duration of symptoms 2.Prevalence of symptoms	1. In one week, 80.1% of individuals reported lower severity scores on follow-up, 17.6% remained unchanged and 1.9% were worse. There seems to have been a significant improvement in the first two weeks, but thereafter the recovery rate seems to taper off. 2. 86.4% of patients reported complete anosmia and another 11.5% reported severe loss of smell.
Hopkins et al., 2020b	2428 female and male adults were included. 73% of the sample was composed of women. 64% of respondents were under 40 years old. The median age was 30 to 39 years. The study was carried out in London, UK.	- A simple questionnaire regarding the onset of anosmia and associated symptoms was designed and sent to patients sought advice by email on symptoms of anosmia (cohort). The questionnaire was also widely applied throughout the population that did not contact the counseling service (cross-sectional study)	1.Time of onset of symptoms 2.Duration of symptoms 3.Prevalence of symptoms 4.Associated symptoms	1. 13% of individuals reported anosmia before other symptoms appeared. 38.4% at the same time as other symptoms, and 48.6% after other symptoms. 2. Symptoms lasted between 1 and 4 weeks. There seemed to be a significant improvement in the first 2 weeks. 3. 74.4% of individuals reported complete loss of smell, another 17.3% reported very severe loss. 90% reported that their sense of taste was reduced, but 61% of the entire group reported that they could still differentiate between sweet, salty, sour and bitter flavors. 4. Of the cohort, 17% of individuals reported no other symptoms associated with COVID-19. In patients who reported other symptoms, 51% reported cough or fever.
Spinato et al., 2020	202 female and male adults were included. The average age of the individuals was 56 years. The study was carried out in Italy.	- Patients were contacted 5 to 6 days after the swab for diagnosis of COVID-19 - A telephone interview was conducted, using the Respiratory Tract Infection Questionnaire. - Patients had performed the Sino-nasal Test 22 (SNOT-22). SNOT-22 classifies the severity of symptoms of changes in smell and taste.	1.Time of onset of symptoms 2.Sex and age of individuals 3.Prevalence of symptoms 4.Associated symptoms	1. The change in sense of smell or taste occurred before other symptoms in 24 patients (11.9%); at the same time as other symptoms in 46 patients (22.8%); and after other symptoms in 54 patients (26.7%); 6 patients (3.0%) reported that altered sense of smell or taste had been the only symptom. 2. Altered sense of smell or taste was found in 105 women (72.4%) and in 97 men (55.7%). No comparison was made between age and changes in smell and taste. 3. Changes in sense of smell or taste were reported by 130 patients (64.4%). 4. Of the 130 patients who reported altered sense of smell or taste, 45 (34.6%) also reported nasal obstruction. Other common symptoms were: fatigue (68.3%), dry or productive cough (60.4%) and fever (55.5%).
Yan et al., 2020[9]	262 adults were included, 161 women, 98 men, and 1 person of indeterminate sex. The age profile of the individuals was as follows: 18–29 years: 36 individuals; 30–39 years: 78 individuals; 40–49 years: 56 individuals; 50–59 years: 45 individuals; 60–69 years: 26 individuals; 70–79 years: 15 individuals; > 80+ years: 5 individuals. The study was carried out in the United States, in the State of California.	- Adult patients, diagnosed or not with COVID-19, reported their symptoms, focusing on smell and taste, by way of an internet platform (Qualtrics, Provo, UT). The sample was divided into "COVID positive" and "COVID negative" patients. A comparison was made between these two groups.	1.Prevalence of symptoms 2.Associated symptoms	1. Among patients testing positive for COVID-19, 68% reported loss of sense of smell and 71% loss of sense of taste. 4. Other self-reported symptoms associated with testing positive for COVID-19 were: fatigue (81%), fever (70%), myalgia or arthralgia (63%), diarrhea (48%) and nausea (27%).
Lechien et al., 2020a	A total of 1420 individuals (over 15 years of age), male and female, were included, 458 men and 962 women. The average age of the individuals was 39.17 years. This was a multicentre European study carried out with data from France (Paris, Marseille), Italy (Milan, Verona, Naples, Genoa, Florence, Forli), Spain (Seville, Santiago de Compostela, San Sebastian), Belgium (Mons, Brussels, Charleroi, Saint-Ghislain) and Switzerland (Geneva).	- Patients and health professionals diagnosed with COVID 19 were identified through the database of hospital laboratories, and underwent an interview, using a standardized questionnaire containing questions about clinical or epidemiological outcomes. - The questionnaire was applied in the patient's room or by telephone, to infected home patients or health professionals.	1.Duration of symptoms 2.Sex and age of individuals 3.Prevalence of symptoms 4.Associated symptoms 5.Associated comorbidities	1. The average duration of symptoms in patients with mild to moderate COVID-19 was 11.5 ± 5.7 days. Loss of smell persisted at least 7 days after the disease in 37.5% of cured patients. 2. The symptom of loss of smell was more prevalent in women. Young patients had greater loss of smell. 3. 70.2% of the individuals had loss of smell and 54.2% of the individuals had loss of taste. 4. The most common symptoms were headache (70.5%), nasal obstruction (67.8%), cough (63.2%), asthenia (63.3%), myalgia (62.5%), rhinorrhea (60.1%) and sore throat (52.9%). Fever was reported by 45.4%. 5. Allergic rhinitis (13.4%), hypertension (9.2%), reflux (6.9%) and asthma (6.5%) were the most prevalent comorbidities.

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Table 2 (*continued*)

Author (year)	Sample characterization	Methodological design	Investigated outcomes	Results
Kaye et al., 2020	237 adults were included, 108 men and 129 women. The average age of the individuals was 39.6 years. The study was conducted using data from the United States, Mexico, Italy, the United Kingdom and other countries.	- Input data from the "COVID-19 Anosmia Report to Clinicians" was analyzed. This tool enables health professionals to submit a confidential report of cases of anosmia and dysgeusia related to COVID 19.	1.Time of onset of symptoms 2.Duration of symptoms	1. The time taken for anosmia to improve was 7.2 ± 3.2 days. 2. Anosmia was observed in 175 (73%) of individuals before diagnosis of COVID 19, and 65 (27%) of individuals after diagnosis of COVID 19.
Vaira et al., 2020	72 adults were studied, 27 men and 45 women. The average age of the individuals was 49.2 years. The study was carried out in Italy.	- Medical records were evaluated and some general information was recorded: age, sex, previous medical history and positive swab. - The olfactory function was evaluated using the CCCRC orthonasal olfaction test.	1.Time of onset of symptoms 2.Duration of symptoms 3.Sex and age of individuals 4.Prevalence of symptoms 5.Associated symptoms	1. Ageusia and anosmia were the first symptoms of COVID-19, usually occurring within the first 5 days of the beginning of the clinical period. In 13 patients (18.1%), impaired taste and smell were the first clinical manifestations of the disease. 2. At the time of the assessment, the majority of these patients (66%) reported complete recovery of chemosensitive functions, which occurred within 5 days in 19 cases, and more than 5 days in the remaining 16 cases. 18 patients (34%) reported lasting impairment of taste and smell. 3. No differences were found in relation to sex and smell and/or taste disorders. Olfactory and gustatory scores were worse in patients over 50 years of age. 4. Fifty-three patients (73.6%) reported experiencing chemosensory disorders in the period during which they were infected with COVID-19. Taste disorders alone were reported in nine cases (12.5%), while 14 individuals (14.4%) reported olfactory dysfunctions alone. Thirty patients (41.7%) reported that they experienced disorders of both senses. 5. Other symptoms reported were: fever (95.8%), cough (83.3%), nasal obstruction (15.3%), rhinorrhea (18.1%), sore throat (51.4%), headache (41.6%), asthenia (66.7%), abdominal symptoms (11.1%), and pneumonia (30.6%).
Lechien et al., 2020b	417 adults were studied, 154 men and 263 women. The average age was 36.9 years. The study was carried out in 12 European hospitals, in Italy, Spain, Belgium and France.	- Patients diagnosed with COVID-19 were recruited from 12 European hospitals. - The following epidemiological and clinical outcomes were studied: age, sex, ethnicity, comorbidities and general and otorhinolaryngological symptoms. - Patients completed olfactory and taste questionnaires based on the olfactory and taste component of the National Survey on Health and Nutrition Examination and the short version of the Questionnaire on Negative Declarations of Olfactory Disorders (sQOD-NS).	1.Time of onset of symptoms 2.Sex and age of individuals 3.Prevalence of symptoms 4.Associated symptoms 5.Associated comorbidities	1. The average time between the beginning of the infection and the evaluation was 9.2 ± 6.2 days. Olfactory dysfunction appeared before other symptoms in 11.8% of cases. 2. Women were proportionally more affected by dysfunctions in smell and taste compared to men. No comparison was made between age and changes in smell and taste. 3. 85.6% of individuals reported dysfunctions of smell and 88.0% of individuals reported dysfunctions in taste. 4. The most prevalent general symptoms were: cough, myalgia, and loss of appetite. Facial pain and nasal obstruction were the otorhinolaryngological symptoms most commonly related to the disease. 5. The most prevalent comorbidities were: allergic rhinitis, asthma, hypertension, and hypothyroidism. There was no significant association between comorbidities and the development of olfactory or gustatory disorders.
Giacomelli et al., 2020	59 adults were studied, 40 men and 19 women. The average age was 60 years. The study was carried out in Italy	- All patients hospitalized at L. Hospital Sacco, Milan, with positive SARS-CoV-2, completed a simple questionnaire, including questions about the presence or absence of ATD, its type and time of onset in relation to hospitalization.	1. Time of onset of symptoms 2. Sex and age of individuals 3.Prevalence of symptoms 4.Associated symptoms	1. Twelve patients (20.3%) had symptoms before hospitalization, while eight (13.5%) had symptoms during hospitalization. Changes in taste were more frequent (91%) before hospitalization, while, after hospitalization, taste and olfactory changes appeared with equal frequency. 2. Women reported smell and taste disorders more frequently than men. Patients with at least one of these senses affected were younger than patients without the disorders. 3. 20 patients (33.9%) reported either impaired taste or an olfactory disorder and 11 (18.6%) reported both disorders. 4. Fever 43 (72.8%), cough 22 (37.3%), dyspnea 15 (25.4%), sore throat 1 (1.7%),

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Table 2 (*continued*)

Author (year)	Sample characterization	Methodological design	Investigated outcomes	Results
				asthralgia 3 (5.1%), runny nose 1 (1.7%), headache 2 (3.4%), asthenia 1 (1.7%), abdominal symptoms 5 (8.5%).
Roland et al., 2020	302 adults were studied, 88 men and 214 women. The mean age of the individuals was 40 years for the positive COVID-19 group, and 38 years for the negative COVID-19 group. The study was carried out in the United States, in the State of California.	- An anonymous survey was released by various media (Facebook, Twitter, Reddit and Nextdoor), looking for volunteer participants who had been tested or quarantined for the symptoms of COVID-19. Self-reported anonymous responses were collected - Groups of health professionals who care for patients with COVID - 19 were also targeted. Participants recruited included those who identified themselves as over 18 and had a history of previous COVID - 19 tests or a history of quarantine for symptoms of COVID - 19.	1.Prevalence of symptoms 2.Associated symptoms	1. 60% of individuals with COVID 19 had a change in smell or taste. 2. Other symptoms reported were: body pain 112 (77%), fever 106 (73%), sore throat 59 (41%), shortness of breath 50 (34%), headache 93 (64%), cough 79 (54%), nasal obstruction 68 (47%), nausea or diarrhea 64 (44%), rhinorrhea 52 (36%)
Wee et al., 2020	860 adult males and females were included in the study. No detailed data on sex and age of the individuals were provided. The study was carried out in Singapore.	- During a two-week period, a questionnaire was administered to patients diagnosed with COVID 19, including questions about respiratory symptoms, self-reported OTD, and epidemiological and travel risk factors in screening for ED to stratify the risk of hospitalization.	1.Prevalence of symptoms 2.Associated symptoms	1. Of the patients testing positive for COVID-19, approximately one fifth (22.7%) had impaired smell and taste. 2. Fever was the most common concomitant symptom (60.0%), followed by cough (28.5%) and rhinorrhea (28.5%).
Aggarwal et al., 2020	16 adults were included, 12 men and 4 women. The average age was 65.5 years. The study was conducted in the Midwest region of the United States.	- The medical records of patients hospitalized for COVID-19 in the health system of a medium-sized city in the Midwest region of the USA were analyzed. - Data on symptoms were analyzed on the initial presentation of the patient or on admission. - Data were collected on medical history and previous comorbidities, and vital signs on admission - All laboratory values on the day of hospitalization and during hospitalization were collected.	1.Prevalence of symptoms 2.Associated symptoms 3.Associated comorbidities	1. 3 patients (19%) reported loss of smell and taste. 2. Fever (94%), cough (88%) and dyspnea (81%), chest pain (6.3%), headache (25%) and diarrhea (6.3%). 3. 6 patients (38%) had chronic kidney disease; 1 (6%) end-stage kidney disease; 2 (13%) had a history of chronic obstructive pulmonary disease (COPD); 9 patients (56.3%) had a history of hypertension; 3 (19%) had a history of coronary artery disease; 3 (19%) with a history of congestive heart failure and 2 (13%) with a history of stroke.
Klopfenstein et al., 2020	114 adult female and male patients were included. Of these, only 54 were studied, as the objective of the study was to evaluate only those who had anosmia. Thus, a total of 36 women and 18 men with impaired sense of smell were evaluated. The average age of the individuals was 47 years. The study was carried out in France.	- The medical records of all adult patients with COVID-19 between March 1 and March 17, 2020, who were examined in the consultation for infectious diseases or hospitalized in the hospital, and who reported anosmia were analyzed. - Data were collected on: age, sex, comorbidities, characteristics of anosmia (date of appearance since the onset of symptoms, duration of anosmia), other symptoms, physical signs and outcome.	1.Time of onset of symptoms 2.Duration of symptoms 3.Prevalence of symptoms 4.Associated symptoms 5.Associated comorbidities	1. Anosmia started 4.4 ± 1.9 days after infection started. 2. The average duration of anosmia was 8.9 days, with ≥ 7 days for 55% of individuals and ≥14 days for 20% of individuals. 3. 47% of individuals diagnosed with COVID 19 had anosmia. Of these, 85% also had dysgeusia. 4. Anosmia was associated with dysgeusia 85%; rhinorrhea (57%); nasal obstruction (30%); fatigue (93%); cough (87%); headache (82%); fever (74%); myalgia (74%); arthralgia (72%) and diarrhea (52%). 5. The most frequent comorbidities were: asthma (13%), high blood pressure (13%) and cardiovascular diseases (11%).
Mao et al., 2020	214 adults were studied, 127 women and 87 men. The average age was 52.7 years. The study was conducted in Wuhan, China.	- Data were collected from January 16, 2020 to February 19, 2020 at three special service centers designated for COVID-19 in China. - Clinical data were extracted from electronic medical records and data on all neurological symptoms and verified by two trained neurologists.	1.Prevalence of symptoms 2.Associated symptoms 3.Associated comorbidities	1. 12 patients had a change in taste and 11 patients had a change in smell. 19 patients had manifestations in the peripheral nervous system. In these patients, the most common symptoms were impaired taste (5.6%) and impaired smell (5.1%). 2. Fever (61.7%); cough (50%) and anorexia (31.8%). 3. The most frequent comorbidities were: hypertension (23.8%); diabetes (14%); heart or cerebrovascular diseases (7%) and malignancies (6.3%).
Lüers et al., 2020	72 adults were studied, 31 women and 41 men. The average age of the individuals was 38 years. The study was conducted in Germany.	- Medical records of outpatients, diagnosed with COVID 19, identified retrospectively by the records of the University Hospital of Cologne, Cologne, Germany, were analyzed.	1.Time of onset of symptoms 2.Prevalence of symptoms 3.Associated symptoms	1. Both symptoms occurred on average on the fourth day after the first symptoms. In 9 patients (13%), reduced smell and loss of meaning occurred together on the first day that they noticed any symptoms. 2. 53 individuals (74%) had reduced smell and 50 individuals (69%) had reduced taste. 3. Other symptoms included headache (78%), cough (75%) and muscle pain (71%) and diarrhea (31%). - Nasal symptoms included nasal congestion

(continued on next page)

Table 2 (*continued*)

Author (year)	Sample characterization	Methodological design	Investigated outcomes	Results
				(54%); sneezing (50%); rhinorrhea (53%); nasal itching (11%).
Yan et al., 2020b	260 adults were included, 161 women, 98 men, and one person of unidentified sex. The age profile of the individuals was: 18–29 years: 36 individuals; 30–39 years: 78 individuals; 40–49 years: 56 individuals; 50–59 years: 45 individuals; 60–69 years: 26 individuals; 70–79 years: 15 individuals; > 80+ years: 5 individuals. The study conducted in the United States, in the city of San Diego.	- A retrospective review was conducted of all patients who in a San Diego Hospital system with laboratory-confirmed COVID-19 infection. - Data on olfactory and gustatory function and the clinical course of the disease were examined.	1.Duration of symptoms 2.Prevalence of symptoms 3.Associated symptoms	1. Regarding the improvement in the loss of smell, 29 out of 40 (72.5%) reported improvement at the time of the survey (18% in < 1 week, 37.5% in 1 to 2 weeks, 18% in 2 to 4 weeks). Most of the patients testing positive for COVID-19 showed improvement in the senses of smell and taste that correlated temporally with clinical resolution of the disease. 2. In positive COVID-19 patients, 68% and 71% had impaired smell and taste, respectively. 3. Fatigue (81%), fever (70%), myalgia or arthralgia (63%), diarrhea (48%) and nausea (27%).
Lee et al., 2020	3191 adults were studied, 2030 women and 1161 men. The average age of the individuals was 44 years. The study was carried out in Daegu, Korea.	- Doctors prospectively interviewed patients diagnosed with COVID-19 who were awaiting hospitalization or isolation concerning the presence of anosmia or ageusia. - Additional telephone calls were made after admission to assess the duration of symptoms among those who reported that anosmia or ageusia persisting until hospitalization or isolation.	1.Duration of symptoms 2.Sex and age of individuals 3.Prevalence of symptoms	1. Most patients with anosmia or ageusia recovered within 3 weeks; with the average recovery time was 7 days for both symptoms. 2. Impaired sense of smell or taste was found in 336 women (68.9%) and in 152 men (31.1%), and the average age of individuals with such changes was 36.5 years. Younger individuals, particularly those aged between 20 and 39 years, showed a tendency to experience longer duration of anosmia 3. Of 3191 patients, 232 (7.27%) had anosmia and 143 (4.48%) had ageusia.

have been reported mainly in countries in Europe and America [25].

In the studies evaluated the prevalence of changes in both taste and smell in patients with COVID-19 ranged from 19% to 73%. Furthermore, a survey of 204 patients found a prevalence of these symptoms of 56.9% among adults [41]. Another study found that 19% of patients experienced loss of both olfactory and gustatory functions concomitantly [42]. Even with these divergences, the presence of the two associated symptoms in individuals with suspected COVID-19 is of great importance for the diagnosis of this infection, It can, in fact, be seen from the articles included in this review that, in patients with a positive or negative diagnosis, these changes in smell and taste were more likely to be present in patients with a positive diagnosis of the disease. This association has also been observed in other studies of adult individuals with a positive diagnosis of COVID-19 [42,43].

Regarding the time of onset of smell and/or taste changes in patients with COVID-19, it was difficult to establish a relationship between the findings of the studies reviewed, because of the extent to which they differ from one another. Some of the authors indicate that these changes may precede the development of other common symptoms of the disease, such as fever, shortness of breath, dry cough and fatigue [8,10,12]. It is important to note that, in the context of a pandemic, tracking symptoms of loss of smell and/or taste in non-hospitalized patients may prove to be a useful clinical screening tool [15], helping to direct patients towards testing services and thus helping to commence care early on and hence reduce transmission of the disease.

The results of the studies also diverged regarding the duration of symptoms of loss of smell and/or taste. This ranged from five days to four weeks, with an average of one to two weeks for recovery. In addition, a case-control study with 119 individuals found that the average duration of smell and/or taste disorders was 7.5 ± 3.2 days, and that 40% of individuals recovered completely 7.4 ± 2.3 days after the onset of symptoms, without having to seek hospital care [31]. More detailed investigation of the duration of these symptoms is, however, still required. Two of the studies reviewed reported persistence of symptoms, even after recovery from the disease [10,15]. Furthermore, the impact of this persistence of olfactory and gustatory loss after the end of COVID-19 infection is still unclear. We therefore stress the importance of conducting research that analyzes the time and persistence of symptoms associated with olfactory and gustatory disorders in patients with COVID-19, since the results found in the literature are scarce and present divergent findings.

The scientific literature considers a number of hypotheses regarding the pathogenic mechanisms associated with changes in smell and taste in patients with COVID-19 and some of these takes into account the duration of sensory dysfunctions. One such hypothesis is that these disorders occur due to direct damage caused by the virus to olfactory and gustatory receptors [44]. It is believed that changes in smell can be caused by damage caused by the virus to the olfactory bulb [44], or to the olfactory nerve [24]. In the case of taste disorders, studies have hypothesized that this may be associated with damage to the angiotensin-converting enzyme 2 (ACE2) [15], which was recently identified as the SARS-CoV-2 cell receptor [45]. ACE2 receptors are present in the oral cavity [46] and have been associated with the modulation of taste perception [46]. Furthermore, Cazzolla et al. [47] have observed a correlation between the occurrence of smell and taste disorders and IL-6 levels. Recovery of olfactory and gustatory functions is associated with reduced levels of IL-6 and one probable explanation for this finding concerns the role that IL-6 plays at the peripheral level in cell receptors infected by the virus. At the central level, IL-6 also plays a role in the intermediate stages on the gustatory and olfactory pathways, especially in the thalamus [47]. Further studies, however, are needed to shed light on the physiological mechanisms associated with these symptoms, both in cases where changes in smell and/or taste are transient and in those where they are permanent.

It was also observed that changes in smell and/or taste may occur concomitantly with other symptoms. The other symptoms most commonly mentioned by the studies under review were: fever, cough, headache, fatigue and gastrointestinal symptoms. These are classic symptoms of the mildest form of COVID-19. The literature indicates that the most severe symptoms of the virus include respiratory distress, fever, cough and fatigue [39,48]. Other, less prevalent symptoms that may appear are diarrhea, nausea and vomiting [49,50]. Of the thirteen studies, only six reported individuals presenting changes in smell and taste who also experienced nasal obstruction [10,12,15,20,25,26]. This corroborates case reports showing that anosmia and ageusia can be found in patients testing positive for COVID-19, even when other

respiratory symptoms are absent [29,50]. Vaira et al. [44] thus claim that sudden changes in smell and taste, usually not accompanied by symptoms of nasal obstruction or rhinitis, are strongly suggestive of ongoing COVID-19 infection and should be treated with care.

The most prevalent comorbidities in individuals with COVID-19 experiencing loss of smell and/or taste were: systemic arterial hypertension [10,16,24–26], rhinitis [10,25], asthma [10,25,26] and cardiovascular diseases [16,24,26]. Furthermore, Chen et al. compared the characteristics of patients diagnosed with COVID-19 who died with those who recovered, and observed that those who died were more likely to have a comorbidity, such as hypertension, diabetes, cardiovascular disease or chronic lung disease [51]. No study mentioned the impact of smell and/or taste dysfunction on the quality of life and eating habits of patients with COVID-19.

Taste and smell play an important role in the selection of diet, metabolism, and quality of life. Anosmic individuals may present changes in eating habits, such as increased seasoning and use of sugar [52]. In addition, increased consumption of salt, sugar, and fat in patients with changes in smell or taste may complicate issues relating to hypertension, diabetes and cardiovascular diseases [53]. A longitudinal cohort study with subjects self-reporting impaired sense of taste and smell showed these individuals to have greater increases in systolic blood pressure and mean arterial pressure compared to individuals without impaired taste and smell [54]. In view of the high prevalence of co-morbidities such as arterial hypertension and cardiovascular diseases associated with dysfunctions of smell and/or taste in patients diagnosed with COVID-19, studies are therefore needed to investigate the influence of changes in smell and/or taste on quality of life and eating habits in patients diagnosed with COVID-19, especially those with co-morbidities such as hypertension, diabetes, obesity, cardiovascular disease, and others.

4.1. Study limitations

The main limitation of the present study was the heterogeneity of the selected articles, which employed a variety of different methodologies. Some used virtual questionnaires, while others used the medical records of hospitalized patients or telephone interviews. These factors may have influenced the findings regarding the exact duration of olfactory and gustatory symptoms, since most of the studies were based on patient reports and conducted with no prior explanation as to what these symptoms are or how they may change over time. This may lead to a lack of accurate information regarding the reported symptoms.

5. Conclusion

The present study concluded that the onset of symptoms of loss of smell and taste, associated with COVID-19, was 4 to 5 days after other symptoms, and that these symptoms lasted from 7 to 14 days. Findings, however, varied and there is therefore a need for further studies to clarify the occurrence of these symptoms. This would help to provide early diagnosis and reduce contagion by the virus. Furthermore, loss of the sense of smell and taste, in the absence of symptoms indicative of nasal obstruction, to provide a strong indication for a diagnosis of COVID-19. We should also note the need for nutritional monitoring of patients with olfactory and gustatory changes, to avoid excessive consumption of salt and sugar. Finally, it is recommended that a molecular diagnostic test for SARS-CoV-2 be performed in all individuals with sudden, severe loss of smell and taste, and no other symptoms.

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CRediT authorship contribution statement

KNFP conceptualized and designed the study, drafted, and critically revised the manuscript. REAS, MGS, MCBMS, and DAMB performed literature reviews, critically reviewed, interpreted data/literature reviews, drafted, and revised the manuscript. ALVG, LCMG and RSA conceptualized and designed the study, critically reviewed the manuscript draft and revisions.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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ANEXO A - FERRAMENTA DE RELATÓRIO DE ANOSMIA DA ACADEMIA AMERICANA DE OTORRINOLARINGOLOGIA - CIRURGIA DE CABEÇA E PESCOÇO (AAO-HNS) - ANOSMIA REPORTING TOOL

Positivo

Nome:
Telefone:
Idade: Sexo:

1. Liste todos os fatores de risco para a presença de infecção por COVID-19:
   - ○ Nenhum
   - ○ Profissional de Saúde
   - ○ Contato próximo com um caso confirmatório
   - ○ Sem casa
   - ○ Vida em congregação
   - ○ Viajou para áreas com ampla transmissão
   - ○ Outros
2. Comorbidades:
   - ○ Nenhum
   - ○ Fumar
   - ○ Trauma na cabeça
   - ○ Sinusite/alergia
   - ○ Doenças respiratórias crônicas/asma
   - ○ Doenças cardíacas
   - ○ Doenças neurológicas (por ex. Parkinson)
   - ○ Outros
3. Sinais e Sintomas:
   - ○ Nenhum
   - ○ Febre
   - ○ Arrepios
   - ○ Mal-estar
   - ○ Tosse
   - ○ Dor de cabeça
   - ○ Congestão nasal
   - ○ Rinorreia
   - ○ Desconforto gastrointestinal
4. A origem da infecção COVID-19 é identificável
   - ○ Sim
   - ○ Não
5. Qual é o estado atual de infecção por COVID-19 do paciente?
   - ○ Ativo
   - ○ Recuperado
6. O paciente recebeu tratamento
   - ○ Sim
   - ○ Não
7. Apresentou alteração do olfato/paladar?
   - ○ Sim
   - ○ Não
8. Definição da deficiência do olfato (se presente)
   - ○ Anosmia (diminuição ou perda absoluta do olfato)
   - ○ Hiposmia (diminuição do olfato)
   - ○ Parosmia (percepção alterada)
9. Por favor, indique o grau de hiposmia na escala 10 VAS (indicar número)
   0 1 2 3 4 5 6 7 8 9 10 (10 indica normal)
10. Definição da alteração do paladar (se presente)
    - ○ Ageusia (perda absoluta do paladar)
    - ○ Hipogeusia (diminuição do paladar)
    - ○ Disgeusia (percepção alterada)
11. Indique o grau de hipogeusia na escala 10 VAS (indicar número)
    0 1 2 3 4 5 6 7 8 9 10 (10 indica normal)
12. Qual era a condição da infecção COVID-19 no momento em que a alteração do olfato/paladar foi observada?
    - ○ Paciente interno/hospitalizado
    - ○ Ambulatorial

13. Quando a alteração do cheiro/paladar foi notada pela primeira vez pelo paciente
    - ○ Antes do diagnóstico
    - ○ Após o diagnóstico
14. O paciente apresentava algum outro sintomas antes do desenvolvimento do comprometimento do olfato/paladar?
    - ○ Sim
    - ○ Não
15. Que sintomas o paciente apresentou no momento da alteração do olfato/paladar?
    - ○ Nenhum ○ Febre ○ Arrepios ○ Mal-estar ○ Tosse
    - ○ Dor de cabeça ○ Congestão nasal ○ Rinorréia ○ Pneumonia
    - ○ Desconforto Gastrointestinal ○ Outros
16. A condição do pacientes piorou ou melhorou após a observação do comprometimento do olfato/paladar?
    - ○ Piorou
    - ○ Melhorou
17. A alteração do olfato/paladar foi resolvida?
    - ○ Sim
    - ○ Não

ANEXO B - FERRAMENTA DE RELATÓRIO DE ANOSMIA DA ACADEMIA AMERICANA DE OTORRINOLARINGOLOGIA - CIRURGIA DE CABEÇA E PESCOÇO (AAO-HNS) - ANOSMIA REPORTING TOOL – GRUPO NEGATIVO

Negativo

Nome:

Telefone:

Idade: Sexo:

1. Liste todos os fatores de risco para a presença de infecção por COVID-19:
   - ○ Nenhum
   - ○ Profissional de Saúde
   - ○ Contato próximo com um caso confirmatório
   - ○ Sem casa
   - ○ Vida em congregação
   - ○ Viajou para áreas com ampla transmissão
   - ○ Outros
2. Comorbidades:
   - ○ Nenhum
   - ○ Fumar
   - ○ Trauma na cabeça
   - ○ Sinusite/alergia
   - ○ Doenças respiratórias crônicas/asma
   - ○ Doenças cardíacas
   - ○ Doenças neurológicas (por ex. Parkinson)
   - ○ Outros
3. Sinais e Sintomas:
   - ○ Nenhum
   - ○ Febre
   - ○ Arrepios
   - ○ Mal-estar
   - ○ Tosse
   - ○ Dor de cabeça
   - ○ Congestão nasal
   - ○ Rinorreia
   - ○ Desconforto gastrointestinal
4. Apresentou alteração do olfato/paladar?
   - ○ Sim
   - ○ Não
5. Definição da deficiência do olfato (se presente)
   - ○ Anosmia (diminuição ou perda absoluta do olfato)
   - ○ Hiposmia (diminuição do olfato)
   - ○ Parosmia (percepção alterada)
6. Por favor, indique o grau de hiposmia na escala 10 VAS (indicar número)
   0 1 2 3 4 5 6 7 8 9 10 (10 indica normal)
7. Definição da alteração do paladar (se presente)
   - ○ Ageusia (perda absoluta do paladar)
   - ○ Hipogeusia (diminuição do paladar)
   - ○ Disgeusia (percepção alterada)
8. Indique o grau de hipogeusia na escala 10 VAS (indicar número)
   0 1 2 3 4 5 6 7 8 9 10 (10 indica normal)
9. O paciente apresentava algum outro sintomas antes do desenvolvimento do comprometimento do olfato/paladar?
   - ○ Sim
   - ○ Não
10. Que sintomas o paciente apresentou no momento da alteração do olfato/paladar?
    ○ Nenhum ○ Febre ○ Arrepios ○ Mal-estar ○ Tosse
    ○ Dor de cabeça ○ Congestão nasal ○ Rinorréia ○ Pneumonia
    ○ Desconforto Gastrointestinal ○ Outros
11. A condição do pacientes piorou ou melhorou após a observação do comprometimento do olfato/paladar?
    - ○ Piorou
    - ○ Melhorou
12. A alteração do olfato/paladar foi resolvida?
    ○ Sim ○ Não

ANEXO C - QUESTIONÁRIO SQOD-NS – GRUPO NEGATIVO E POSITIVO COM PERDA DE OLFATO E PALADAR

Questionário de Transtornos Olfatórios-Declarações Negativas (sQOD-NS).

1. Mudanças no meu olfato/paladar me isolaram socialmente
   0 1 2 3 (3=nenhum impacto)

2. Os problemas com meu olfato e/ou paladar tiveram um impacto negativo em minhas atividades sociais diárias
   0 1 2 3 (3=nenhum impacto)

3. Os problemas com meu olfato e/ou paladar me deixaram mais irritado
   0 1 2 3 (3=nenhum impacto)

4. Por causa dos problemas com meu olfato e/ou paladar me alimento menos
   0 1 2 3 (3=nenhum impacto)

5. Por causa dos problemas com meu olfato/paladar tive perda de apetite
   0 1 2 3 (3=nenhum impacto)

6. Por causa dos problemas com meu olfato e/ou paladar tenho que fazer mais esforço para relaxar
   0 1 2 3 (3=nenhum impacto)

7. Tenho medo de nunca ser capaz de me acostumar com os problemas com meu olfato e/ou paladar
   0 1 2 3 (3=nenhum impacto)

   PONTUAÇÃO TOTAL DA VERSÃO CURTA QOD-NOS:

ANEXO D - QUESTIONÁRIO SQOD-NS – GRUPO POSITIVO SEM PERDA DE OLFATO E PALADAR

Questionário de Transtornos Olfatórios-Declarações Negativas (sQOD-NS).

1. O diagnóstico positivo para covid-19 me isolaram socialmente
   0 1 2 3 (3=nenhum impacto)

2. O diagnóstico positivo para covid-19 teve um impacto negativo em minhas atividades sociais diárias
   0 1 2 3 (3=nenhum impacto)

3. O diagnóstico positivo para covid-19 me deixaram mais irritado
   0 1 2 3 (3=nenhum impacto)

4. Por causa do diagnóstico positivo para covid-19 me alimentei menos
   0 1 2 3 (3=nenhum impacto)

5. Por causa do diagnóstico positivo para covid-19 tive perda de apetite
   0 1 2 3 (3=nenhum impacto)

6. Por causa do diagnóstico positivo para covid-19 tive que fazer mais esforço para relaxar
   0 1 2 3 (3=nenhum impacto)

7. Tenho medo de nunca ser capaz de me acostumar com os problemas acarretados pela covid-19
   0 1 2 3 (3=nenhum impacto)

PONTUAÇÃO TOTAL DA VERSÃO CURTA QOD-NOS:

ANEXO E - (QUESTÕES DE ACEITABILIDADE DE COMPORTAMENTO ALIMENTAR)– GRUPO NEGATIVO E POSITIVO COM PERDA DE OLFATO E PALADAR

Questionário validado (Questões de aceitabilidade de comportamento alimentar)

1. Desde que meu problema de paladar ou olfato começou, meu apetite tem sido:
   A) Eu não tenho problema de gosto ou cheiro
   B) Melhor
   C) Não alterado
   D) Pior
2. Desde o início do meu problema de paladar ou olfato, tenho gostado da comida:
   A) Não tenho problema de gosto ou cheiro
   B) Mais
   C) O mesmo
   D) Menos
3. Meu problema de gosto ou cheiro afeta a maneira como (alterou os tipos de alimentos, a frequência das refeições e lanches):
   A) Não tenho problema de gosto ou cheiro
   B) Não
   C) Sim (descreva a mudança)

4. Desde que meu problema de gostou ou cheiro começou, alterei a quantidade de sal, açúcar ou especiarias que adiciono à minha comida

   A) Não tenho problema de gosto ou cheiro
   B) Não
   C) Sim (descreva a mudança)

5. Desde que meu problema de paladar ou cheiro começou, comecei fortemente não gostar ou evitar certos alimentos

   A) Não tenho problema de gosto ou cheiro
   B) Não
   C) Sim (especificar alimentos)

6. Desde o início do meu problema com o paladar ou cheiro, sinto um forte desejo ou anseio por determinados alimentos.

   A) Não tenho problema de gosto ou cheiro
   B)Não
   C) Sim (descreva a mudança)

ANEXO F - (QUESTÕES DE ACEITABILIDADE DE COMPORTAMENTO ALIMENTAR) – GRUPO POSITIVO SEM PERDA DE OLFATO E PALADAR

Questionário validado (Questões de aceitabilidade de comportamento alimentar)

1. Desde o diagnóstico positivo para covid-19 meu apetite tem sido:
   A) Melhor
   B) Não alterado
   C) Pior
2. Desde o diagnóstico positivo para covid-19 tenho gostado da comida:
   A) Mais
   B) O mesmo
   C) Menos
3. O diagnóstico positivo para covid-19 afetou a maneira que como (alterou os tipos de alimentos, a frequência das refeições e lanches):
   A) Não
   B) Sim (descreva a mudança)

4. Desde o diagnóstico positivo para covid-19, alterei a quantidade de sal, açúcar ou especiarias que adiciono à minha comida

   A) Não
   B) Sim (descreva a mudança)

5. Desde o diagnóstico positivo para covid-19, comecei fortemente não gostar ou evitar certos alimentos
   B) Não
   C) Sim (especificar alimentos)
6. Desde o diagnóstico positivo para covid-19, sinto um forte desejo ou anseio por determinados alimentos.
   A) Não
   B) Sim (descreva a mudança)

ANEXO G - QUESTIONÁRIO SOBRE *LONG* COVID

New CIS question on long COVID

1. Você se descreveria como tendo "long COVID", ou seja, ainda está experimentando sintomas mais de 4 semanas depois de ter tido COVID-19 pela primeira vez, que não são explicados por outra coisa?

( ) SIM ( ) NÃO

1.1. Se sim: (a) Isso reduz sua capacidade de realizar atividades do dia-a-dia em comparação com o tempo antes de você ter COVID-19? (selecione uma)

( )SIM, MUITO ( )SIM, UM POUCO ( )DE JEITO NENHUM

2. Quais sintomas persistiram por mais do que 4 semanas?

Febre ( ) SIM ( ) NÃO
Dor de cabeça ( ) SIM ( ) NÃO
Dor muscular ( ) SIM ( ) NÃO
Fraqueza/cansaço ( ) SIM ( ) NÃO
Náuseas/vomito ( ) SIM ( ) NÃO
Dor abdominal ( ) SIM ( ) NÃO
Diarreia ( ) SIM ( ) NÃO
Perda do apetite ( ) SIM ( ) NÃO
Perda de Paladar ( ) SIM ( ) NÃO
Perda do Olfato ( ) SIM ( ) NÃO
Dor de garganta ( ) SIM ( ) NÃO
Tosse ( ) SIM ( ) NÃO
Falta de ar ( ) SIM ( ) NÃO
Dor no peito ( ) SIM ( ) NÃO
Palpitações ( ) SIM ( ) NÃO
Vertigem/tontura ( ) SIM ( ) NÃO
Apreensão/preocupação ( ) SIM ( ) NÃO
Mau humor ( ) SIM ( ) NÃO
Problemas para dormir ( ) SIM ( ) NÃO
Perda ou confusão de memória ( ) SIM ( ) NÃO
Dificuldade de concentração ( ) SIM ( ) NÃO

ANEXO H - COMITÊ DE ÉTICA EM PESQUISA

UFPE - CENTRO ACADÊMICO DE VITÓRIA DA UNIVERSIDADE FEDERAL DE PERNAMBUCO - CAV/UFPE

PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: LONG COVID: PREVALÊNCIA E IMPACTO NA QUALIDADE DE VIDA E NOS HÁBITOS ALIMENTARES.
Pesquisador: DANIELLY ALVES MENDES BARBOSA
Área Temática:
Versão: 2
CAAE: 45588621.9.0000.9430
Instituição Proponente: UNIVERSIDADE FEDERAL DE PERNAMBUCO
Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 4.744.490

Apresentação do Projeto:
Trata-se de um projeto de dissertação da mestranda Danielly Alves Mendes Barbosa, vinculada ao programa de pós-graduação em nutrição, atividade física e plasticidade fenotípica da UFPE, sob orientação da profª Kelli Ferraz e co-orientação da profª Ana Lisa do Vale.
As informações elencadas nos campos "Apresentação do Projeto","Objetivo da Pesquisa" e "Avaliação dos Riscos e Benefícios" foram retiradas do arquivo Informações Básicas da Pesquisa (INFORMAÇÕES_BÁSICAS_DO_PROJETO_1724703.pdf de 17/05/21) e/ou do Projeto Detalhado (ProjetoCEPLongCOVID.pdf de 17/05/21) e/ou da Carta Resposta (CartaRespostaPendenciaCEP.pdf): Resumo, Metodologia, Critérios de inclusão e exclusão.
Os pesquisadores pretendem avaliar a prevalência e o impacto da Long COVID na qualidade de vida e nos hábitos alimentares de profissionais atuantes na linha de frente ao combate da COVID-19. Os pesquisadores caracterizam o estudo como do tipo caso-controle, que será realizado com uma amostragem por conveniência de 500 profissionais atuantes na linha de frente ao combate da COVID-19, que já fazem parte do projeto "Diagnóstico sorológico ANTI-SARS-CoV-2 ELISA (IgA, IgM e IgG) e perfil de citocinas em profissionais de saúde" sob o Número do Parecer: 4.244.984, no qual foi realizado o diagnóstico sorológico semiquantitativo a partir da pesquisa de IgA, IgM e IgG em soro desses profissionais. Estes profissionais já foram submetidos ao teste diagnóstico sorológico ANTI-SARS-CoV-2 ELISA (IgA, IgM e IgG); e a partir do resultado eles serão divididos