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ORIGINAL ARTICLE

Prevalence of hyposmia and hypogeusia in 390 COVID-19 hospitalized patients and outpatients: a cross-sectional study

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Abstract

Anecdotal evidence rapidly accumulated during March 2020 from sites around the world that sudden hyposmia and hypogeusia are significant symptoms associated with the SARS-CoV-2 pandemic. Our objective was to describe the prevalence of hyposmia and hypogeusia and compare it in hospitalized and non-hospitalized COVID-19 patients to evaluate an association of these symptoms with disease severity. We performed a cross-sectional survey during 5 consecutive days in March 2020, within a tertiary referral center, associated outpatient clinic, and two primary care outpatient facilities in Paris. All SARS-CoV-2-positive patients hospitalized during the study period and able to be interviewed ($n = 198$), hospital outpatients seen during the previous month ($n = 129$), and all COVID-19-highly suspect patients in two primary health centers ($n = 63$) were included. Hospitalized patients were significantly more often male (64 vs 40%) and older (66 vs 43 years old in median) and had significantly more comorbidities than outpatients. Hyposmia and hypogeusia were reported by 33% of patients and occurred significantly less frequently in hospitalized patients (12% and 13%, respectively) than in the health centers' outpatients (33% and 43%, respectively) and in the hospital outpatients (65% and 60%, respectively). Hyposmia and hypogeusia appeared more frequently after other COVID-19 symptoms. Patients with hyposmia and/or hypogeusia were significantly younger and had significantly less respiratory severity criteria than patients without these symptoms. Olfactory and gustatory dysfunction occurs frequently in COVID-19, especially in young, non-severe patients. These symptoms might be a useful tool for initial diagnostic work-up in patients with suspected COVID-19.

Keywords COVID-19 · SARS-CoV-2 · Hyposmia · Hypogeusia · Neurovirulence

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Introduction

The most frequent symptoms of coronavirus disease 2019 (COVID-19) are fever, dry cough, fatigue, arthromyalgia, and headache, but in March 2020, during the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic, anecdotal evidence rapidly accumulated from sites around the world that sudden loss of smell (hyposmia) and/or taste (hypogeusia) was also occurring in COVID-19 patients, often without concomitant nasopharyngeal symptoms [1, 2]. In a joint briefing paper by the presidents of the British Rhinological Society and of the UK ear, nose, and throat (ENT) group, loss of sense of smell was said to be a marker of COVID-19 infection and a potential screening tool to help identify otherwise asymptomatic patients [3]. After the publication of several studies reporting hyposmia and hypogeusia as frequent symptoms of COVID-19 [4, 5], the World Health Organization (WHO) included these symptoms in case definition. It has been suggested that these symptoms are related to a neuroinvasion and could be associated with severe forms of COVID-19 [6]. However, no study has focused yet on the difference of prevalence of these symptoms in COVID-19 hospitalized and non-hospitalized patients to investigate the association with disease severity.

Therefore, the aim of our study was to describe olfactory and taste disorder prevalence and compare it between hospitalized and primary care or hospital outpatients with COVID-19, to evaluate an association of these disorders with disease severity.

Methods

Study design and participants

This cross-sectional study was conducted during 5 consecutive days from March 23 to 27, 2020, in three adult COVID-19 patient groups, aged 18 or over. The first group was inpatients cared for in either the infectious and tropical disease, internal medicine, pneumology, or geriatrics department within La Pitié-Salpêtrière Hospital, Paris, France. The second group were patients who had attended the infectious and tropical disease outpatient clinic, also at the same hospital, 1 month prior to and were reachable over phone during the study period. The third group attended one of two primary outpatient clinics near Paris. All inpatients and outpatients who were consulted at the hospital had confirmed positive SARS-CoV-2 result using real-time reverse transcriptase polymerase chain reaction (RT-PCR) acquired from a respiratory sample (nasopharyngeal swab or induced sputum specimen). For patients seen in primary care, COVID-19 diagnosis was strongly suspected according to the treating general practitioner's clinical judgment and available data on COVID-19 infection. Patients with mild symptoms were not being tested at that time in France.

Data collection

A medical physician interviewed inpatients and phoned outpatients consulted in the infectious diseases clinic. For the primary care outpatients, the treating general practitioner collected the data during the consultation.

Patients who were fit to be interviewed were asked if they had experienced olfactory alteration (hyposmia), taste alteration (hypogeusia), and other symptoms (asthenia, fever, cough, dyspnea, headache, rhinorrhea, nasal obstruction, diarrhea, vomiting, neurological manifestations). The disease onset date, defined as the day when the first symptom of COVID-19 was noticed, was asked to record the time from onset to interview. Symptom persistence, as well as demographic characteristics and comorbidities (hypertension, diabetes, obesity, bronchopathy, cardiopathy, nephropathy, neurologic diseases, cancer, hemopathy, and other immunosuppression), were also asked.

The research protocol was reviewed and approved by the Ethics Committee of the Sorbonne University (CER-SU) under the Institutional Review Board N° 2020–CER-2020-8. According to French law (n° 78-17 of 6 January 1978 on computers, files, and liberties), this study has been registered with the CNIL (French National Agency Regulating Data Protection) and was conducted in compliance with the reference methodology 004.

Statistical analysis

A global comparison of the 3 groups of patients was performed (inpatients, hospital outpatients, and primary care outpatients). Continuous variables were reported as median (interquartile range) qualitative data were reported as numbers (percentages). Categorical variables were compared using Fisher exact tests. To compare distributions of continuous outcomes over the 3 groups, nonparametric Kruskal-Wallis were performed. When a significant difference was identified overall, pairwise Wilcoxon test or Fisher exact test was computed between groups, and corresponding p values were adjusted using the Benjamini-Hochberg method to correct for the multiple comparisons undertaken.

Associations between patient characteristics and presence or absence of hyposmia and/or hypogueusia were investigated through univariate analyses and then using a multivariate logistic regression model. Candidate variables to be included in the final model were those with a univariate p value < 0.05. A stepwise backward method based on the likelihood ratio test was undertaken. Results of the final logistic model were reported as odds ratios (OR) with their corresponding

confidence intervals at 95% (CI 95%). p values of Wald test were also presented.

All statistical tests were two-sided, with p values of 0.05 or less denoting statistical significance. All analyses were performed on the R version3.5.1.

Results

A total of 390 patients were included in the study, of whom 198 were hospitalized, 129 were infectious diseases clinic outpatients, and 63 were primary care outpatients. Thirty-seven hospitalized patients were excluded because they were unable to be interviewed (34 due to dementia, 2 severe psychiatric disorders, and 1 linguistic barrier). Demographics and comorbidities are shown in Table 1. There were significantly older (median age 66 years), male (64%) patients in the hospitalized group than in the two outpatient groups (43% male with median age 43 years in the hospital outpatient group, 32% male with median age 42.5 years in the primary care outpatient group). Hospitalized patients also had significantly more comorbidities (Table 1).

Reports of hyposmia, hypogeusia, and other COVID-19 symptom prevalence in the 3 groups of patients are shown in Table 2. In total, 129 patients (33%) reported hyposmia, of whom 74 (19%) without nasal obstruction or rhinorrhea, 130 patients (33%) reported hypogeusia, and 106 patients reported both (27%). No patients reported isolated hyposmia or hypogeusia without other symptoms. There was significantly fewer reports of hyposmia (12%) and hypogeusia (13%) in hospital inpatients than in primary care outpatients (33% and 43% respectively, $p < 0.05$) which was fewer again than in the hospital outpatients (65% and 60%, respectively, $p < 0.05$). There was a significant association between hyposmia and hypogeusia ($p < 0.0001$), with 23/129 (18%) patients with hyposmia reporting no hypogeusia, and 24/130 (18.5%) patients with hypogeusia reporting no hyposmia. Regarding the timing of hyposmia and hypogeusia onset, they appeared before (5% and 4%, respectively), at the same time (46% and 36%, respectively), or after (49% and 60%, respectively) the other COVID-19 symptoms. Notably, 17 patients did not remember the time of hyposmia onset and 30 patients the time of hypogeusia onset. Among the 38 patients with infection onset > 14 days before interview and an initial hyposmia, 13 patients (34%) still had persistent hyposmia, and 10/34 (29%) had persistent hypogeusia.

Significantly more hospitalized patients had fever (83%) and dyspnea (58%) than hospital outpatients (71% and 26%, respectively) and primary care outpatients (30% and 41%, respectively), whereas inpatients reported significantly fewer headaches (16%), nasal obstruction (4%), and rhinorrhea (4%) than hospital outpatients (64%, 35%, and 44%, respectively) and primary care outpatients (54%, 33%, and 33%, respectively) ($p < 0.05$) (Table 2). Sixty-three percent of hospitalized

Table 1 Comparison of demographics and comorbidities between hospitalized, hospital outpatients, and primary care outpatients

	Hospitalized patients $N = 198$	Hospital outpatients $N = 129$	Primary care outpatients $N = 63$	p value global	p value-adjusted hospitalized patients vs hospital outpatients	p value-adjusted hospitalized patients vs primary care outpatients	p value-adjusted hospital outpatient vs primary care outpatients
Age (years)	66 (55–77.6)	43 (32–54)	42.5 (33–50.8)	< 0.001	< 0.001	< 0.001	0.832
Female	72 (36%)	73 (57%)	43 (68%)	< 0.001	0.157	< 0.001	< 0.001
HTA	80 (40%)	15 (12%)	16 (25%)	< 0.001	< 0.001	0.049	0.030
Diabetes	52 (26%)	6 (5%)	3 (5%)	< 0.001	< 0.001	< 0.001	1.00
Obesity	22 (11%)	9 (7%)	6 (10%)	0.476			
Bronchopathy	33 (17%)	14 (11%)	5 (8%)	0.127			
Cardiopathy	39 (20%)	2 (2%)	4 (6%)	< 0.001	< 0.001	0.017	0.092
Nephropathy	19 (10%)	1 (1%)	0 (0%)	< 0.001	0.002	0.014	1.00
Neurological diseases	26 (13%)	1 (1%)	1 (2%)	< 0.001	< 0.0001	0.011	0.55
Cancer	23 (12%)	2 (2%)	1 (2%)	< 0.001	0.001	0.019	1.00
Hemopathy	13 (7%)	1 (1%)	2 (3%)	0.0022	0.032	0.534	0.377
Graft	7 (4%)	2 (2%)	0 (0%)	0.269			
Other immunosuppression*	17 (9%)	4 (3%)	3 (5%)	0.106			

* HIV, autoimmune disease, inflammatory disease, sickle cell anemia. Data expressed in median (IQR) for continuous variables or N (%) for qualitative data

Table 2 Comparison of COVID-19 symptoms, hyposmia, and hypogeusia between hospitalized, hospital outpatients, and primary care outpatients

	Hospitalized patients $N = 198$	Hospital outpatients $N = 129$	Primary care outpatients $N = 63$	p value global	p value adjusted-hospitalized patients vs hospital outpatients	p value hospitalized patients vs primary care outpatients	p value hospital outpatient vs primary care outpatients
Time since onset of first symptom (days)	9 (5–12)	14 (10–19)	7 (4–10)	< 0.001	< 0.001	0.030	< 0.001
Asthenia	122 (62%)	108 (84%)	35 (56%)	< 0.001	< 0.001	0.46	< 0.001
Cough	151 (76%)	97 (75%)	51 (81%)	0.676			
Fever	165 (83%)	92 (71%)	19 (30%)	< 0.001	0.013	< 0.001	< 0.001
Headache	31 (16%)	83 (64%)	34 (54%)	< 0.001	< 0.001	< 0.001	0.208
Diarrhea and/or vomiting	70 (35%)	42 (33%)	8 (13%)	0.003	0.635	0.001	0.004
Dyspnea	115 (58%)	34 (26%)	26 (41%)	< 0.001	< 0.001	0.032	0.046
Neurological manifestations	21 (11%)	10 (8%)	1 (2%)	0.056	0.44	0.1	0.156
Nasal obstruction	9 (5%)	37 (29%)	18 (29%)	< 0.001	< 0.001	< 0.001	1.00
Rhinorrhea	9 (5%)	53 (41%)	27 (43%)	< 0.001	< 0.001	< 0.001	0.877
Hyposmia	24 (12%)	84 (65%)	21 (33%)	< 0.001	< 0.001	< 0.001	< 0.001
Persistent hyposmia	22/24 (92%)	26/84 (31%)	19/21 (90%)	0.001	< 0.0001	0.225	0.003
Hyposmia without nasal obstruction nor rhinorrhea	23 (12%)	40 (31%)	11 (17%)	< 0.001	< 0.0001	0.282	0.084
Hypogeusia	26 (13%)	77 (60%)	27 (43%)	< 0.001	< 0.001	< 0.001	0.032
Persistent hypogeusia	22/26 (85%)	26/77 (34%)	22/27 (81%)	< 0.001	< 0.001	0.309	0.002

Data expressed in median (IQR) for continuous variables or N (%) for qualitative data

patients had respiratory severity criteria defined as a hypoxemia-requiring oxygen therapy, with 37% needing an oxygen therapy ≥ 3 l, 6% needing non-invasive ventilation, and 6% who had been in intensive care unit with necessity of invasive ventilation before they were transferred to medicine departments upon clinical improvement. Four outpatients seen in the health centers showed signs of respiratory severity and were transferred to hospital after their consultation, of which 2 reported hyposmia and 3 hypogeusia.

Univariate analysis revealed that patients with hyposmia and/or hypogeusia were significantly more frequently female (55%) and younger (46.5 years old in median) and had significantly less comorbidities than patients without hyposmia nor hypogeusia (44% of female and 60 years old in median) (Table 3). They had had COVID-19 symptoms significantly longer (11 vs 9 days), with significantly more asthenia and headaches, but with significantly less signs of respiratory severity. In the multivariate analysis, hyposmia and/or hypogueusia were significantly more frequent in younger patients (OR = 0.97 [0.96–0.99], $p < 0.001$), in the absence of bronchopathy (OR = 0.44 [0.21–0.94], $p = 0.034$), of neurological disease (0.27 [0.08–0.95], $p = 0.047$), and of respiratory severity (0.51 [0.29–0.91], $p = 0.023$). They were more frequently present in patients reporting asthenia (OR = 4.83 [2.7–8.65], $p < 0.001$) and headache (OR = 1.88 [1.11–3.19], $p = 0.018$).

Discussion

This cross-sectional study found that one-third of COVID-19 patients reported hyposmia and/or hypogeusia, which occurred significantly more frequently in non-severe outpatients. Olfactory and taste disorders were associated with absence of signs of respiratory severity and of other neurological symptoms. A previous study among 45 hospitalized COVID-19 patients found as well that anosmia was not a predictor of a severe COVID-19 manifestation, with no difference of outcome at day 15, or by counting the worst outcome during the hospital stay defined by a rating on a 6-point ordinal scale, between patients with and without anosmia or hyposmia [7]. Moreover, as previously described [5, 6, 8], women reported hyposmia or/and hypogueusia more often, but the difference was not significant in multivariate analysis. It has already been shown that women were at lower risk of severe forms of COVID-19 and less frequently hospitalized than men [9, 10].

Although viral upper respiratory infections account for up to 30% of hyposmia cases [11], sensorineural viral anosmia is

Table 3 Comparison of demographics, comorbidities, symptoms, and severity criteria between patients with hyposmia and/or hypogeusia and patients without hyposmia nor hypogeusia

Variables	Univariate analysis			Multivariate analysis	
	No hyposmia nor hypogeusia $N = 237$	Hyposmia and/or hypogeusia $N = 153$	p value	OR (95% CI)	p value
Age (years)	60 (47–75)	46.5 (33–56)	< 0.001	0.97 (0.96–0.99)	< 0.001
Female	104 (44%)	84 (55%)	0.038		
HTA	79 (33%)	32 (21%)	0.011		
Diabetes	45 (19%)	16 (10%)	0.032		
Obesity	25 (11%)	12 (8%)	0.48		
Bronchopathy	40 (17%)	12 (8%)	0.014	0.44 (0.21–0.94)	0.034
Cardiopathy	37 (16%)	8 (5%)	0.002		
Nephropathy	17 (7%)	3 (2%)	0.032		
Neurological diseases	25 (11%)	3 (2%)	0.001	0.27 (0.08–0.95)	0.042
Cancer	22 (9%)	4 (3%)	0.011		
Hemopathy	14 (6%)	2 (1%)	0.034		
Graft	7 (3%)	2 (1%)	0.49		
Other immunodepression*	17 (7%)	7 (5%)	0.39		
Time since onset of first symptom (days)	9 (5–13)	11 (8–15)	0.001		
Asthenia	132 (56%)	133 (87%)	< 0.001	4.83 (2.7–8.65)	< 0.001
Cough	178 (75%)	121 (79%)	0.39		
Fever	170 (72%)	106 (69%)			
Headache	60 (25%)	88 (58%)	< 0.001	1.88 (1.11–3.19)	0.018
Diarrhea and/or vomiting	69 (29%)	51 (33%)	0.43		
Dyspnea	119 (50%)	56 (37%)	0.009		
Neurological manifestations	18 (8%)	14 (9%)	0.58		
Signs of respiratory severity	101 (43%)	28 (18%)	< 0.001	0.51 (0.29–0.91)	0.023
Oxygen therapy ≥ 3 l	60 (25%)	15 (10%)	0.0002		
Non-invasive ventilation	12 (5%)	0 (0%)	0.004		
Invasive ventilation	8 (3%)	3 (2%)	0.54		

* HIV, autoimmune disease, inflammatory disease, sickle cell anemia. Data expressed in median (IQR) for continuous variables or N (%) for qualitative data

rare in the absence of rhinosinusitis and oedema in the nasal vault or olfactory cleft, with one to two new-onset patient each year in general ENT practice [12]. However, previous reports highlighted that hyposmia in COVID-19 patients occurs often suddenly, in the absence of nasal obstruction. In our series, 57% of patients who reported hyposmia did not have nasal obstruction or rhinorrhea (19% of all patients). In a European, multicenter study on 417 mild-to-moderate hospitalized or outpatient COVID-19-confirmed patients, 76 patients (18.2%) did not suffer from rhinorrhea or nasal obstruction, of which 79.7% reported nonetheless sudden smell disorders (14% of all patients) [5]. In a French study on 252 patients tested for SARS-CoV-2, of whom 68 were positive, the combination of hypogeusia and hyposmia in patients with no medical history of ENT disorders had a sensitivity of 42% (95% CI 27–58) and a specificity of 95% (95% CI 90–98) for COVID-19 diagnosis [13]. Even though other respiratory viruses are known to cause post-viral olfactory dysfunction, the sudden onset of hyposmia and hypogeusia in a patient seems therefore quite specific for COVID-19 in the current context.

As previously described [5, 8], timing of olfactory and taste disorders onset in respect of other symptoms seems rather variable, predominantly at the same time or after the other symptoms in our series. Hyposmia and hypogeusia may go

unnoticed early in their development. The question of recovery of olfactory and gustatory function is an important issue that remains unsolved. In our series, among patients with an infection onset > 14 days before interview and initial hyposmia or hypogeusia, 34% of patients still had persistent hyposmia and 29% persistent hypogeusia. In the study by Lechien et al., 56% of patients with an infection onset > 14 days before and a resolution of general COVID-19 symptoms still had persistent olfactory dysfunction [5].

This sudden loss of smell without nasal obstruction and its higher frequency in non-severe patients raises questions about the underlying pathogenetic mechanism of hyposmia in COVID-19. Indeed, as already described with other coronaviruses (CoVs) causing post-viral olfactory loss (PVOL) [14], local nasal inflammation resulting in mucosal edema and nasal obstruction do not appear to be the only etiological factors underlying olfactory dysfunction in COVID-19. An involvement of the central nervous system (CNS) has been suspected, as it is known that CoVs can invade it inducing neurological diseases [15], and SARS-CoV particles have been detected in cerebrospinal fluid and in the brain [16, 17]. Likewise, a growing body of evidence shows that SARS-CoV-2 has a neurotropism, with 36.4% of 214 COVID-19-confirmed patients hospitalized in Wuhan hospitals, China, showing neurological manifestations, including 25% with central neurological manifestations, such as acute cerebrovascular disease, impaired consciousness, ataxia and epilepsy, and 9% with peripheral neurological signs, such as hypogeusia (5.6%) and hyposmia (5.1%) [18]. An increasing number of cases of various COVID-19-related neurological diseases are now being reported, such as meningitis, encephalitis, and Guillain-Barré syndrome [19].

The volume of the olfactory bulb (OB) is known to be decreased in patients with PVOL and is inversely related to the duration of olfactory loss [20]. Four reports of the findings on nasal cavity and brain magnetic resonance imaging (MRI) in patients with COVID-19 and sudden olfactory loss found various results: no abnormality [21], bilateral obstructive inflammation of olfactory clefts without anomalies of the OB and tracts [22], bilateral transient OB edema [23], and transient cortical hyperintensity in the right gyrus rectus and in the OB [24]. Furthermore, a report of a decreased metabolic activity in the orbitofrontal cortex on a ^{18}–FDG PET/CT scan of a patient with COVID-19-related anosmia suggested that there could be an impaired neural activity in olfactory pathways despite normal morphology [25].

Peripherally located olfactory dendrites within receptor cells that connect to the OB may provide SARS-CoV-2 a retrograde trans-synaptic route for neuroinvasion. SARS-CoV have demonstrated in a mice model a neuroinvasion through the olfactory bulb via transneural route [26]. Moreover, angiotensin converting enzyme 2 receptor (ACE2), which is used by SARS-CoV-2 to bind and penetrate into the human host cells, is widely expressed on the epithelial cells of the oral and nasal mucosa [27]. Therefore, there could be a direct contact and interaction with a possible cytopathic effect of SARS-CoV-2 on ACE2-expressing neurosensory receptor cells [28]. Given the prevalence of hyposmia in COVID-19 and the higher frequency in non-severe patients that appears in our study, damage to olfactory receptors in the epithelium of the nasal mucosa or in the olfactory bulbs seems more likely than central cortical involvement [25].

This study has some limitations. First, the comparison of the 3 groups of patients should be interpreted with caution as the patients were not interviewed at the same stage of the disease progression. Hospitalized patients may have been less aware about smell or taste changes due to their age, general condition, other symptoms, and context of hospitalization. Primary care outpatients, who reported fewer hyposmia and hypogeusia than the hospital outpatients, were seen sooner in the disease evolution, and some of them may not have had COVID-19 as they were not all tested. On the contrary, hospital outpatients were interviewed later in the evolution of the disease, were all COVID-19 confirmed, and were perhaps more attentive to their symptoms, being confined to the home at the time of the interview (they also reported more asthenia and headaches than other patients). In addition, the inpatient and outpatient groups may not correspond exactly to severe and non-severe groups, as some patients were hospitalized due to heavy comorbidities or difficult home support, and some ambulatory patients may have developed signs of severity afterwards. Second, given the diffusivity of the disease and the emergency context, we did not perform specific examinations for olfactory and gustatory functions, such as a more structured questionnaire associated with validated olfactory tests or electrophysiological methods. However, we distinguished patients who reported hyposmia together with nasal obstruction or rhinorrhea, reflecting an inflammation of the nasal mucosa, which could be a different mechanism than that of patients with sudden loss of smell without nasal complaints. We also did not specify if the four taste modalities (bitter, sour, sweet, salty) were impaired in themselves in patients who reported taste disorders; therefore, there could be a confusion related to the retro-olfaction. However, nearly 20% of our patients with hypogeusia did not report associated olfactory disorder, suggesting that retro-olfaction impairment is not the only mechanism underlying taste disorders in COVID-19. Third, the lack of follow-up of our patients limits us from inquiring into the recovery time of olfactory and gustatory functions, and, therefore, the rate of permanent hyposmia or hypogeusia.

In conclusion, hyposmia and hypogeusia are frequent COVID-19 symptoms, more common than what was initially reported in China, especially in younger, non-severe patients. These symptoms should alert physicians when seeing a patient with influenza-like illness in the current epidemiological context and might be a useful tool for initial diagnostic work-up in patients with suspected COVID-19. Future epidemiological,

clinical, and basic science studies must elucidate the mechanisms underlying the development of these symptoms, its predictive value of disease severity, the frequency of persistence overtime, and their long-term consequences.

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Compliance with ethical standards

The research protocol was reviewed and approved by the Ethics Committee of the Sorbonne University (CER-SU) under the Institutional Review Board N° 2020–CER-2020-8. According to French law (n° 78-17 of 6 January 1978 on computers, files, and liberties), this study has been registered with the CNIL (French National Agency Regulating Data Protection) and was conducted in compliance with the reference methodology 004.

Conflict of interest The authors declare that they have no conflicts of interest.

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