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Symptom content analysis of Obstructive Sleep Apnea (OSA) questionnaires: time to identify and improve relevance of diversity of OSA symptoms?

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Abstract (250 mots)

Study Objectives. Obstructive Sleep Apnea (OSA) is a heterogeneous condition covering many clinical phenotypes in terms of the diversity of symptoms. Patient-based OSA screening questionnaires used in routine practice contain significantly varying contents that can impact the reliability and validity of the screening. We investigated to what extent common patient-based OSA screening questionnaires differ or overlap in their item content by conducting a rigorous, methodical, and quantified content overlap analysis.

Methods. We conducted an item content analysis of 11 OSA screening questionnaires validated in adult populations and characterized their overlap using a four-step approach: i) selection of OSA screening questionnaires; ii) item extraction and selection; iii) extraction of symptoms from items; iv) assessment of content overlap with the Jaccard Index (from 0: no overlap to 1: full overlap).

Results. We extracted 72 items that provided 25 distinct symptoms from 11 selected OSA questionnaires. The overlap between them was weak (mean Jaccard Index 0.224, ranging from 0.138 to 0.329). All questionnaires contained symptoms of the “OSA symptom” dimension (e.g., snoring or witnessed apneas). The STOP-BANG (0.329) and the Berlin (0.280) questionnaires exhibited the highest overlap content. Ten symptoms (40%) were investigated in only one questionnaire.

Conclusions. The heterogeneity of content and the low overlap across these questionnaires reflect the challenges of screening OSA. The different OSA questionnaires potentially capture varying aspects of the disorder, with the risk of biased results in studies. Suggestions are made for better OSA screening and refinement of clinical OSA phenotypes.

Keywords: obstructive sleep apnea; sleep disorders; sleep symptoms; questionnaires; content analysis; symptom overlap.

Brief summary (120 words)

Current Knowledge/Study Rational

- Obstructive Sleep Apnea (OSA) is a heterogeneous condition with diverse clinical phenotypes, and existing patient-based OSA screening questionnaires may lack reliability and validity with regard to symptom diversity.
- Several systematic reviews of OSA screening questionnaires have demonstrated variations in contents, but there is still no rigorous, methodical and quantified analysis of the content overlap between them.

Study Impact

- A content overlap analysis of 11 validated OSA screening questionnaires revealed heterogeneity of content and low overlap between them, reflecting how challenging it is to screen OSA.
- This first step towards a broad reappraisal of a set of symptoms and clinical characteristics critical for OSA screening should lead to better OSA screening based on refinement of clinical OSA phenotypes.

Introduction

The prevalence of obstructive sleep apnea (OSA) varies between 9 and 13% in the general population but remains massively underdiagnosed. OSA is characterized by the repetitive occurrence of complete (apneas) or partial (hypopneas) upper airway collapses during sleep, leading to intermittent hypoxia, sleep fragmentation, and swings in intrathoracic pressure¹⁻³. The resulting hypoxic burden, autonomic activation, and sleepiness are the main predictors of poor clinical outcomes and altered quality of life in OSA^{4,5}. OSA is associated with multimorbidity and high mortality rates, in particular owing to an increased risk of cardiometabolic diseases⁶, psychiatric disorders⁷ and motor vehicle accidents^{8,9}. It is now acknowledged that OSA is a heterogeneous condition covering many clinical phenotypes in terms of OSA symptom diversity^{2,10}.

Owing to the high prevalence of OSA and its consequences, several patient-based OSA screening questionnaires have been developed. The STOP-BANG and the Berlin questionnaire are widely used^{11,12} and have the highest sensitivity and specificity, as reported in recent systematic reviews and meta-analyses¹³⁻¹⁷. Three main dimensions can be individualized in OSA questionnaires: specific “OSA symptoms” (e.g., snoring or witnessed apneas), “Sleep-related symptoms” (e.g., sleepiness or insomnia) and “Clinical characteristics” (e.g., age, sex, body mass index or neck circumference)¹¹. Not all three dimensions are present in all OSA questionnaires^{11,13,15-17} and each dimension is assessed by items that vary from one questionnaire to another¹³. In particular, a previous review identifying eight different validated patient-based OSA questionnaires found that the number of items in each questionnaire ranged from 3 to 12 items, with significantly varying contents¹³. Thus, empirical research is needed to refine the symptoms that should be investigated to improve OSA screening and phenotyping at the symptom level, as no consensus has emerged to date regarding the symptoms that should be systematically investigated in questionnaires to screen OSA¹³. As Abrishami et al. noted,

“a standard definition of factors is a prerequisite for standardizing questionnaire components and evaluating their values in different combinations”, and “a lack of standard definition of some factors involved in OSA questionnaire could also result in heterogeneity of the data among the studies”¹³. A rigorous discussion of questionnaires is possible only if the content investigated is well known. However, a rarely tested clinical assumption postulates that questionnaires are interchangeable when evaluating OSA. The lack of standardization and rationale for choosing specific questionnaires in clinical practice and research can potentially impact the reliability and validity of the screening of disorders^{11,13}. Indeed, the item content of a questionnaire can impact the reliability and validity of a questionnaire according to the type of population screened in terms of sex¹⁸, comorbid sleep disorders¹³, or other comorbidities^{7,19–21}. Furthermore, additional symptoms may be required to improve OSA clinical phenotyping^{2,10,22,23}. Thus, more relevant questionnaires are needed to capture the diversity of OSA symptoms. The first step before establishing new OSA questionnaires is to identify and list symptoms in existing OSA screening questionnaires. Such an analysis seems particularly important to understand and visualize the variability in the collection of data concerning OSA screening.

In this line, we need an informative, rigorous, methodical, and quantified approach to item content in existing OSA screening questionnaires. Several systematic reviews of OSA screening questionnaires have been published^{11,13–16,19} but there is still no systematic quantified analysis of the content overlap between them. However, such an approach was developed and validated in 2017 by Fried, who proposed a method for analyzing content overlap based on the Jaccard similarity coefficient to reveal the overlap between widely used patient-based questionnaires²⁴. Such symptom content overlap analysis has since been applied to various disorder questionnaires^{24–32} and we recently used it in sleep medicine by studying patient-based multiple sleep disorder screening questionnaires for adult populations²⁵. Here, we

conducted a systematic quantified analysis comparing item content in widely used adult patient-based OSA screening questionnaires ^{24,25}. We sought to establish to what extent common OSA screening questionnaires differ or overlap in their item content, to identify relevant symptoms that constitute consensual characteristics of OSA, to identify the differences between questionnaires and to pave the way for better evaluations of the diversity of OSA symptoms.

Methods

Our method is based on previous content overlap analysis studies^{25–32}. The reference method of content overlap analysis is Jaccard similarity coefficient calculation. If the overlap of symptom content between the scales is high, the questionnaires are interchangeable. If overlap is low, the challenge to develop and validate questionnaires in the context of clinical phenotyping becomes greater. The Jaccard method has not yet been applied to OSA screening questionnaires.

1.1. Selection of OSA screening questionnaires

We included any standardized validated OSA screening questionnaire with at least specific OSA symptoms (e.g., snoring or witnessed apneas) or sleep-related symptoms (e.g., sleepiness or insomnia), used as self-reported questionnaires, which can be completed by patients or clinicians and can be validated against in-laboratory polysomnography (PSG). Following a recently published systematic review¹³, we included eight adult OSA screening questionnaires validated against in-laboratory PSG: the STOP questionnaire (for Snoring, Tiredness, Observed apnea, and high blood Pressure)^{33,34}, the STOP-BANG questionnaire (STOP and BMI, Age, Beck circumference, Gender)³⁵, the Berlin questionnaire^{36–39}, the checklist of the American Society of Anesthesiologists (ASA)³⁷, the Wisconsin sleep questionnaire^{40,41}, the Sleep Apnea scale of the Sleep Disorders Questionnaire (SA-SDQ)^{42,43}, the Haraldsson questionnaire⁴⁴ and the Apnea Score (AS)⁴⁵.

To ensure exhaustiveness in the compilation of these questionnaires, we carried out a PubMed search with the following search terms: [(“Obstructive Sleep Apnea*” OR “OSA*”) AND (“diagnosis*” OR “scale*” OR “questionnaires*” OR “screen*” OR “psychometric*”). We identified four other OSA questionnaires: the NoSAS (for Neck circumference, obesity,

Snoring, Age, and Sex scores)^{46,47}, the Obstructive Sleep Apnea 50 questionnaire (OSA-50)⁴⁸, the GOAL (for Gender, Obesity, Age, and Loud snoring)⁴⁹, and the No-Apnea scale⁵⁰. The NoSAS, the OSA-50 and the GOAL questionnaires were validated against in-laboratory PSG but the No-Apnea scale was not and was excluded⁴⁹. A total of 11 questionnaires were finally included in the analysis.

1.2. Item extraction and selection

An item was defined as any question to be answered by the patient. A total of 72 items from the 11 OSA questionnaires were extracted (items relating to children in the ASA checklist were excluded), see **Supplementary Material 1**.

1.3. Extraction of symptoms from items

Extraction of symptoms from items involved three consecutive steps (see **Supplementary Material 1**). In agreement with previous similar analyses²⁵⁻³², a “symptom” was defined as any unit of analysis from an item. For example, “Daytime sleepiness” is a symptom. We also considered clinical characteristics such as “neck circumference” in this content analysis.

1.3.1. Symptom extraction from items in each questionnaire

Two medical students (MP and PAS) and four sleep experts (SB, AR, CG, and JAM) performed the extraction. In the event of disagreement between experts, consensus was sought by referring to two key sleep opinion leaders (PP and JLP). Some of the symptoms were split or lumped²⁵. For instance, in the STOP-BANG, item 2, “Do you often feel tired, fatigued, or sleepy during daytime?”, the following symptoms were extracted “Tired”, “Fatigued” and “Daytime sleepiness”. “Tired and “Fatigued” was lumped into a “Fatigue” symptom. “Daytime sleepiness” and “Fatigue” were split.

According to the terminology used in previous content overlap analysis studies²⁵⁻³², symptoms were categorized as follows: *compound* symptoms, *specific* symptoms, and *idiosyncratic* symptoms:

- A compound symptom is an item constructed on the basis of at least two distinct symptoms. For example, item 2 of the STOP-BANG questionnaire, “Do you often feel tired, fatigued, or sleepy during daytime?” encompasses both “Fatigue” and “Daytime sleepiness” symptoms.
- A specific symptom derives from an item constructed on the basis of a single symptom. For example, item 1 of the STOP-BANG questionnaire, “Do you snore loudly?” refers only to the symptom of “Loud snoring”. When a symptom can represent both a specific and a compound symptom, it was considered specific.
- Finally, an idiosyncratic symptom is a symptom appearing only once in a questionnaire among all the analyzed questionnaires. For example, the symptom “Waist circumference” appears only in the OSA-50 questionnaire (item 1).

1.3.2. *Harmonization of wording of the extracted symptom*

To better harmonize the wording of the extracted symptoms, we used an original conservative approach based on our previous work extracting and harmonizing symptoms in two international classifications of sleep disorders (ICSD-3 and Sleep-Wake disorders section of the Diagnostic and Statistical Manual of mental disorders (DSM-5)^{25,51-54} and on the previous dimensions identified in the literature^{11,13,37}. First, we harmonized symptoms that were considered as worded similarly between questionnaires. For instance, “Snoring loud enough to be heard through closed doors” in the ASA index (item 6) and “I am told I snore loudly or bother others” in the SDA-SDQ (item 1), were harmonized into one symptom: “Loud snoring”

Second, we organized the extracted symptoms into three main dimensions. The main dimension of “OSA symptoms” was defined as the set of specific symptoms related to the underlying pathophysiological mechanism, i.e., repeated upper airway collapses. The “Sleep-related symptoms” dimension was defined as the set of symptoms related to sleep and daytime disturbances induced by OSA. The “Clinical characteristics” dimension was defined as the set of specific characteristics of the patient that can be identified in clinical practice and have been reported as being related to OSA.

1.3.3. Data aggregation

The last step of data preparation was to code the collected symptoms on a three-point rating scale: specific or idiosyncratic symptoms were coded 1; compound symptoms were coded 2. If a symptom was absent from a specific questionnaire, it was coded 0.

1.4. Statistical analysis

1.4.1. Number and frequency of sleep symptoms

Three types of analyses were performed: i) the frequency of symptoms identified in the questionnaires (from the most frequent to the least frequent on all dimensions and regarding the three dimensions: OSA symptoms, Sleep-related symptoms and Clinical characteristics), ii) the distribution of the symptoms found in each questionnaire across the three dimensions, and iii) the identification of the questionnaires with the highest number of symptoms and with the highest number of specific and compound symptoms in each questionnaire (to assess the lack of precision due to items constructed on the basis of at least two distinct symptoms).

1.4.2. Content overlap analysis

The Jaccard Index (or “Jaccard similarity coefficient”) measures the similarity between binary data, with values ranging from 0 (no overlap among questionnaires) to 1 (complete overlap). It is calculated by the following equation: $s/(u_1 + u_2 + s)$, with s representing the number of symptoms shared by two questionnaires, and u_1 and u_2 the number of symptoms that are unique to each one ²⁴. In line with previous studies that used this type of content analysis ^{25–32} and considering the absence of well-cited guidelines on the strengths and weaknesses of the Jaccard similarity coefficient, we used the *Evans’ Straightforward Statistics for the Behavioral Sciences* rule of interpretation for the Jaccard Index ⁵⁵: very weak: (0.00-0.19), weak: (0.20-0.39), moderate: (0.40-0.59), strong: (0.60-0.79), and very strong: (0.80-1).

We conducted three Spearman correlations of the Jaccard Index, one with the total number of symptoms captured by a questionnaire (to investigate whether the length of the questionnaire played a role in the overlap), one with the number of specific symptoms and one with the number of compound symptoms (to investigate whether the presence of specific or compound symptoms played a role in the overlap). Finally, we calculated the Jaccard Index for each dimension to evaluate content overlap on each of the three dimensions of the OSA questionnaires. We also calculated pairwise overlaps to analyze the overlap between each questionnaire.

1.4.3. Data visualization of content overlap

We provide two graphical representations of the distribution across the categories of the symptoms measured in each questionnaire using the Python package *plotly*¹. The first one, plotted in **Figure 4**, is an interactive radar plot that represents the different symptoms identified in each questionnaire. It demonstrates the symptom overlap between questionnaires, each concentric circle representing a questionnaire and each point representing a symptom (when

¹<https://github.com/plotly/plotly.py>

there are several “points” on the same “radius”, this means that there is significant overlap between several OSA questionnaires). The second one, plotted in **Figure 5**, is a sunburst plot, that visualizes the hierarchical arrangement of the symptoms within the three dimensions and proposes subdimensions. This hierarchization of symptoms, subdimensions and dimensions is a purely exploratory proposal for making it easier to visualize symptoms.

1.4.4. Availability and reproducibility of results

Based on a previous sleep overlap study and with a view to openness and sharing, all our data, results, figures, tables, and code are available in a GitHub repository². This repository contains the analysis notebook already executed and saved in html format³. To foster reproducibility of these results, we set up a Binder repository⁴, allowing any interested researcher to reproduce our results fully online.

²<https://github.com/vincentpmartin/OSAS.content.analysis>

³https://raw.githubusercontent.com/vincentpmartin/OSAS.content.analysis/main/jupyter_notebook_OSAS_content_analysis.html

⁴https://mybinder.org/v2/gh/vincentpmartin/OSAS.content.analysis/HEAD?labpath=jupyter_notebook_OSAS_content_analysis.ipynb

Results

1.1. Number and frequency of symptoms and clinical characteristics

The 11 questionnaires were composed of 72 items, representing 25 distinct symptoms from the 74 extracted from all the questionnaires. **Figure 1** shows the frequency of each symptom from the most frequent to the least frequent overall, further classified according to the three dimensions: OSA symptoms, Sleep-related symptoms and Clinical characteristics. The most common symptoms were “Stop breathing observations” (appearing in 9 questionnaires out of 11 – 81.8%), “Loud Snoring” (appearing in 8 questionnaires out of 11 – 72.0%) and “Snoring” (appearing in 6 questionnaires out of 11 – 54.5%), all of them belonging to the “OSA symptom” dimension.

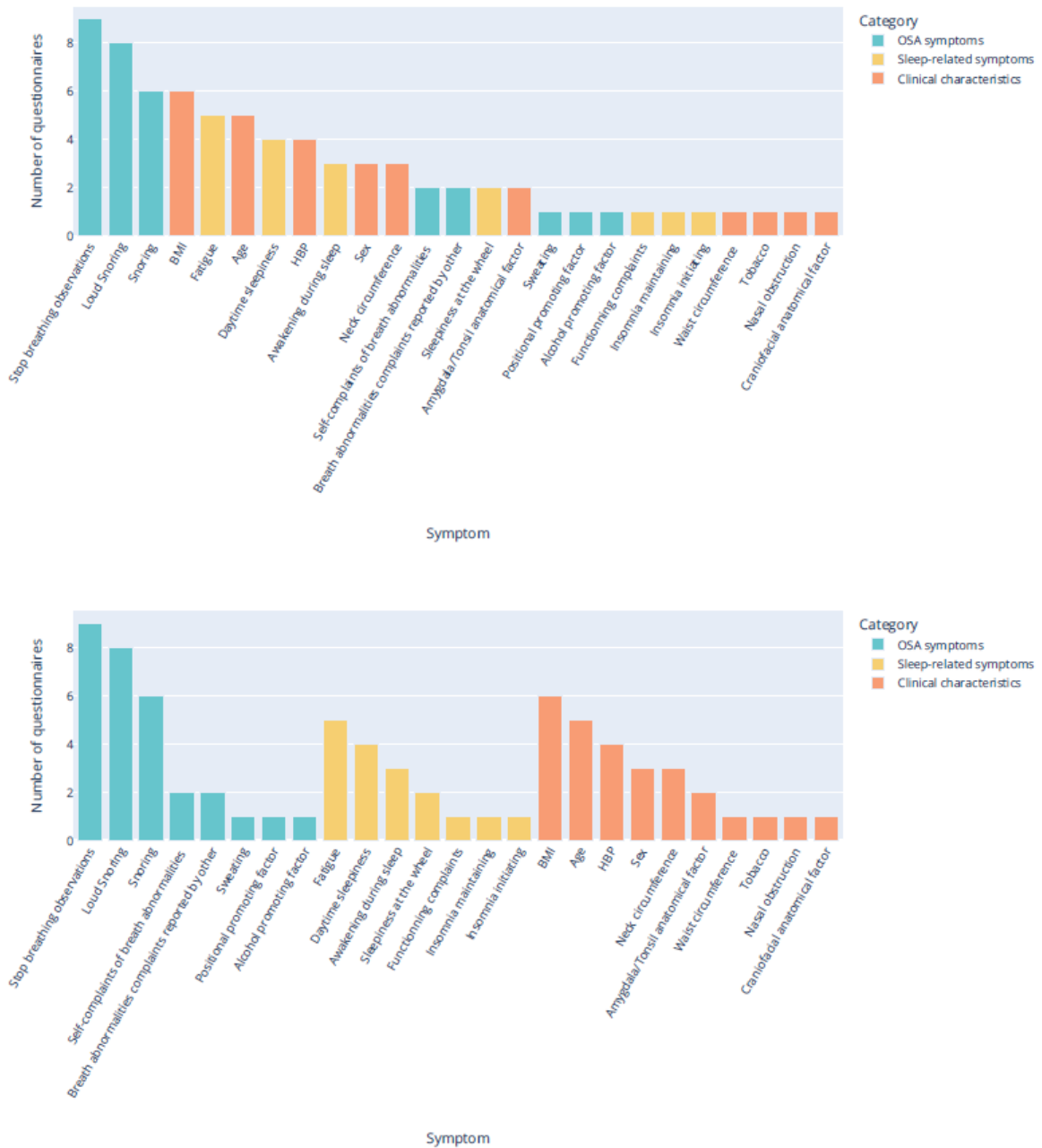


Figure 1—Frequency of symptoms and clinical characteristics identified in the 11 OSA questionnaires. (**Top**) Plot organized from the most frequent to the least frequent for all dimensions. (**Bottom**) Plot organized from the most frequent to the least frequent regarding the three dimensions as identified previously^{53,54,61}.

Figure 2 shows the graphical representation of the distribution of the symptoms and clinical characteristics found in each questionnaire across the three dimensions. Five questionnaires do not contain any symptom from the “Sleep-related symptoms” dimension (NoSAS, GOAL,

OSA-50, AS, Wisconsin questionnaires)^{41,45,46,48,49}; and two questionnaires do not contain any symptom from the “Clinical characteristics” dimension (Haraldsson and Wisconsin questionnaires)^{41,44}. All questionnaires have symptoms of the “OSA symptoms” dimension. The number and the distribution of OSA symptoms across all dimensions for each questionnaire are available in our online analysis notebook⁵.

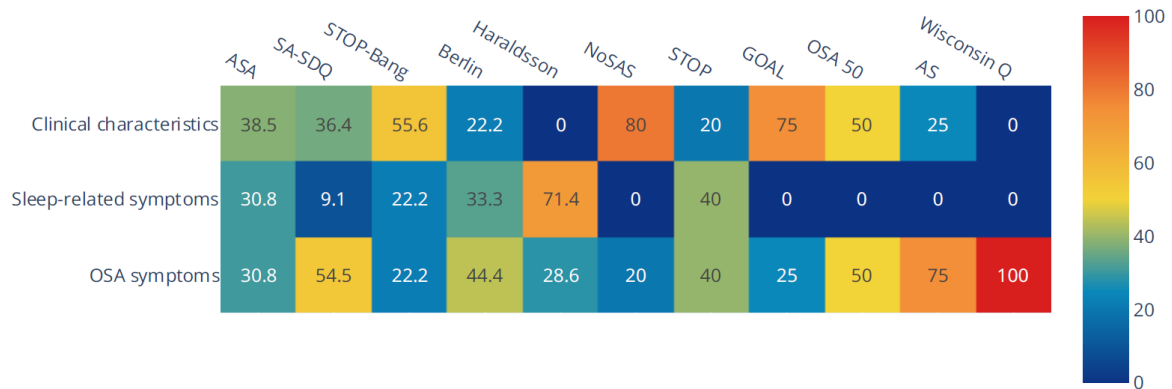


Figure 2–Distribution of the symptoms found in each questionnaire across the three dimensions. The color bar corresponds to the percentages of symptoms per questionnaire according to the three dimensions. ASA: American Society of Anesthesiologists checklist; SA-SDQ: Sleep Apnea scale of the Sleep Disorders Questionnaire; STOP-BANG: Snoring, Tiredness, Observed apnea, high blood Pressure, BMI, Age, Beck circumference, Gender); NoSAS: Neck Circumference, Obesity, Snoring, Age, and Sex scores); STOP: Snoring, Tiredness, Observed apnea, high blood Pressure; GOAL: Gender, Obesity, Age, Loud snoring; OSA-50: Obstructive Sleep Apnea 50 questionnaire; AS: Apnea Score.

The questionnaires containing the largest number of symptoms were the ASA (N = 13/25), the SA-SDQ (N = 11/25), and the STOP-BANG and the Berlin questionnaires (N = 9/25) (Table 1). Among the 74 symptoms extracted from the questionnaires, 16 were compound symptoms (21.6%) and 58 were specific symptoms (78.4%). Among the 25 distinct symptoms, 10 symptoms were idiosyncratic (40%), appearing only in one questionnaire. The questionnaires

⁵

https://raw.githubusercontent.com/vincentpmartin/OSAS.content.analysis/main/jupyter_notebook_OSAS_content_analysis.html

with the largest number of compound symptoms were the ASA and the Haraldsson (resp. 4/7 and 4/13), followed by the STOP-BANG (7/9), the STOP (3/5) and the AS (2/4) (**Table 1**).

1.2. *Content overlap analysis*

Table 1 presents the mean Jaccard Index, the number of items, and the number of specific and compound symptoms per questionnaire. The mean overlap between the questionnaires evaluated with the Jaccard Index was 0.237 (SD = 0.054), indicating a low similarity. The questionnaire with the highest mean Jaccard index was the STOP-BANG (0.329), followed by the Berlin questionnaire (0.280), the ASA checklist (0.257) and the STOP questionnaire (0.267). These four questionnaires are also those with symptoms belonging to the three dimensions. Nevertheless, the correlations between the Jaccard Index and the total number of symptoms or the number of specific symptoms or compound symptoms were not significant (respectively: $\rho = 0.115$, $p = 0.735$, $\rho = 0.0$, $p = 1$, and $\rho = 0.245$, $p = 0.467$), suggesting that neither the length of the questionnaire nor the presence of specific or compound symptoms played a role in the overlap.

Regarding the dimensions, the mean overlap was the highest for the “OSA symptoms” dimension (0.393), followed by the “Sleep-related symptoms” dimension (0.319). The lowest overlap between questionnaires was found for the “Clinical characteristics” dimension (0.213). Lastly, concerning the pairwise analysis, the STOP-BANG and the STOP had a high pairwise overlap (0.556). The Wisconsin and the AS had the highest pairwise overlap (0.750), followed by the GOAL and the NoSAS (0.500) and the GOAL and the STOP-BANG (0.444). (**Figure 3**).

Table 1. Average Jaccard Index, number of items and of specific and compound symptoms in the OSA questionnaires. ASA: American Society of Anesthesiologists checklist; SA-SDQ: Sleep Apnea scale of the Sleep Disorders Questionnaire; STOP-BANG: Snoring, Tiredness, Observed apnea, high blood Pressure, BMI, Age, Beck circumference, Gender); NoSAS: Neck Circumference, Obesity, Snoring, Age, and Sex scores); STOP: Snoring, Tiredness, Observed apnea, high blood Pressure; GOAL: Gender, Obesity, Age, Loud snoring; OSA-50: Obstructive Sleep Apnea 50 questionnaire; AS: Apnea Score.

	Average Jaccard Index	Number of items	Specific symptoms	Compound symptoms	Total number of symptoms
ASA	0.257	12	9	4	13
SA-SDQ	0.210	12	10	1	11
STOP-BANG	0.329	8	7	2	9
Berlin	0.280	11	8	1	9
Haraldsson	0.192	5	3	4	7
NoSAS	0.189	6	5	0	5
STOP	0.267	4	3	2	5
GOAL	0.209	4	4	0	4
OSA 50	0.138	4	4	0	4
AS	0.261	3	2	2	4
Wisconsin	0.274	3	3	0	3
MEAN / TOTAL	0.237 (mean)	72 (total)	58 (total)	16 (total)	74 (total)



Figure 3–Jaccard Index overlap of item content of the 11 OSA questionnaires for each pair of questionnaires. The numbers from 0 to 1 in the color bar refer to the corresponding percentages. ASA: American Society of Anesthesiologists checklist; SA-SDQ: Sleep Apnea scale of the Sleep Disorders Questionnaire; STOP-BANG: Snoring, Tiredness, Observed apnea, high blood Pressure, BMI, Age, Beck circumference, Gender); NoSAS: Neck Circumference, Obesity, Snoring, Age, and Sex scores); STOP: Snoring, Tiredness, Observed apnea, high blood Pressure; GOAL: Gender, Obesity, Age, Loud snoring; OSA-50: Obstructive Sleep Apnea 50 questionnaire; AS: Apnea Score.

1.3. Data visualization of content overlap

Figure 4 shows the analysis of the content overlap of OSA symptoms in the 11 questionnaires (see <https://chart-studio.plotly.com/~vincent.martin/41/#/> for an interactive version online).

A hierarchical arrangement of the symptoms according to the proposed dimensions and subdimensions is given in the sunburst plot in **Figure 5** (see <https://chart->

studio.plotly.com/~vincent.martin/43/#/ for an interactive version online). The proposed subdimensions should not be considered as definitive. These subdimensions illustrate how such visualization helps in grasping the organization and the wording of symptoms with a view to improving the nosology of sleep disorders.



OSA symptoms

S001: Snoring
 S002: Loud snoring
 S003: Self-complaints of breath abnormalities
 S004: Breath abnormalities complaints reported by other
 S005: Sweating
 S006: Stop breathing observations
 S007: Positional promoting factor
 S008: Alcohol promoting factor

Sleep-related symptoms

S009: Daytime sleepiness
 S010: Fatigue
 S011: Sleepiness at the wheel
 S012: Functioning complaints
 S013: Awakening during sleep
 S014: Insomnia maintaining
 S015: Insomnia initiating

Clinical characteristics

S016: Age
 S017: Sex
 S018: Neck circumference
 S019: Waist circumference
 S020: BMI
 S021: HBP
 S022: Tobacco
 S023: Nasal obstruction
 S024: Amygdala/Tonsil anatomical factor
 S025: Craniofacial anatomical factor

Figure 4—Content overlap of the Obstructive Sleep Apnea (OSA) symptoms in the 11 selected OSA questionnaires. The figure illustrates the symptom overlap between questionnaires: each concentric circle represents a questionnaire, and each point represents a symptom. When there are several “points” on the same “radius”, this means that there is significant overlap between several OSA questionnaires. Colored circles for a symptom indicate that this is a specific symptom, while empty circles indicate that this is a compound symptom. See also the interactive version of this Figure online: <https://chart-studio.plotly.com/~vincent.martin/41/#/>. ASA: American Society of Anesthesiologists checklist; SA-SDQ: Sleep Apnea scale of the Sleep Disorders Questionnaire; STOP-BANG: Snoring, Tiredness, Observed apnea, high blood Pressure, BMI, Age, Beck circumference, Gender); NoSAS: Neck Circumference, Obesity, Snoring, Age, and Sex scores); STOP: Snoring, Tiredness, Observed apnea, high blood Pressure; GOAL: Gender, Obesity, Age, Loud snoring; OSA-50: Obstructive Sleep Apnea 50 questionnaire; AS: Apnea Score. HBP: High Blood Pressure. BMI: Body Mass Index.

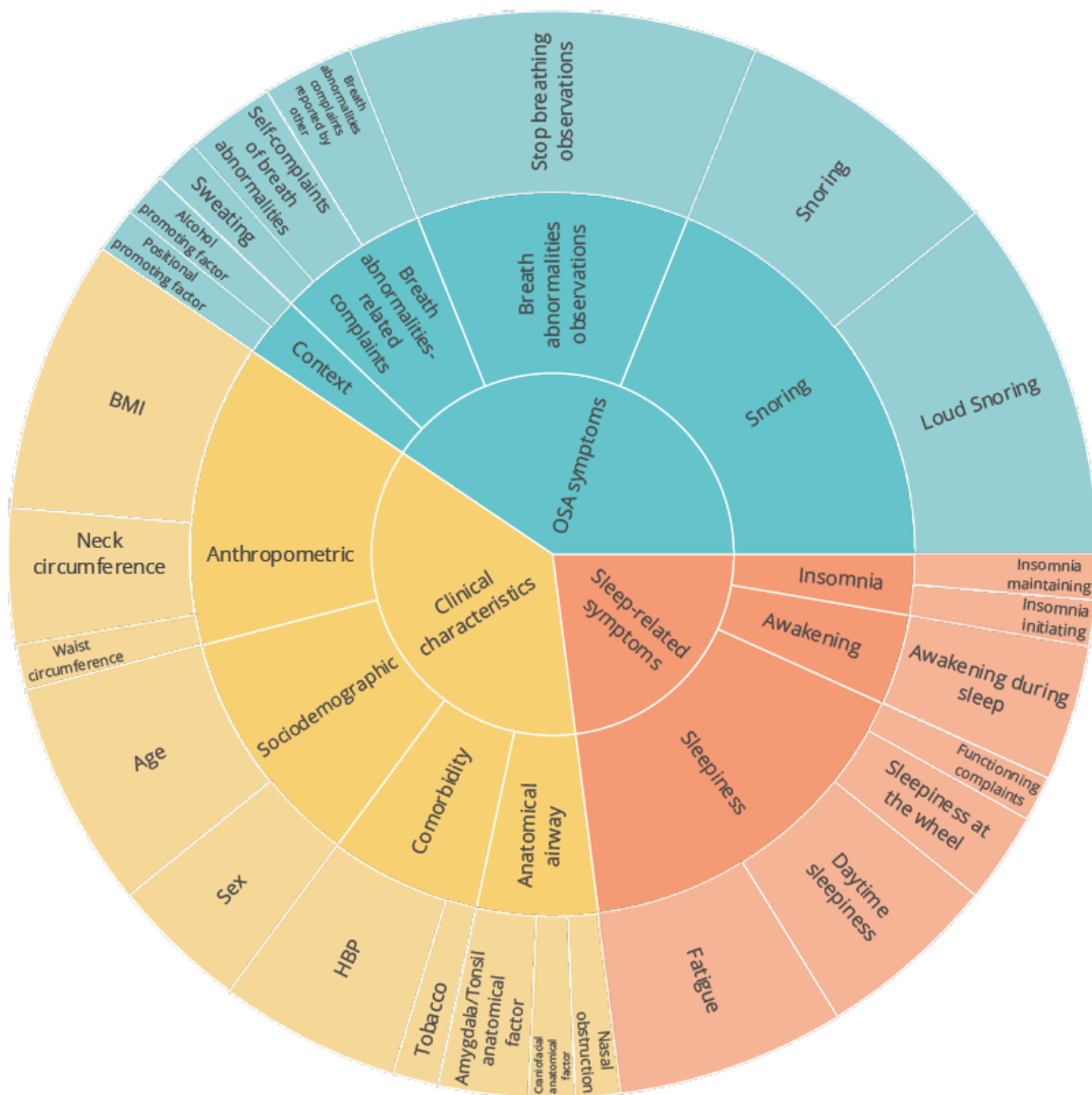


Figure 5—Sunburst plot indicating the hierarchical arrangement of the symptoms according to subdimensions and dimensions. This hierarchization of symptoms, subdimensions and dimensions is a purely exploratory proposal for making it easier to visualize symptoms. Yellow: Clinical characteristic dimension; Red: Sleep-related symptom dimension; Blue: OSA symptom dimension. OSA: Obstructive Sleep Apnea; HBP: High Blood Pressure; BMI: Body Mass Index. Please also see the interactive version of this Figure online: <https://chart-studio.plotly.com/~vincent.martin/43/#/>.

Discussion

This is the first rigorous, methodical and quantified symptom content analysis in widely used patient-based screening OSA questionnaires for adult populations. The “OSA symptoms” dimension (e.g., snoring or witnessed apneas) was found in all questionnaires, confirming their central role in the definition of OSA¹⁻³. The STOP-BANG questionnaire, considered as the most accurate OSA screening questionnaire^{13,14,35,38,38}, was the questionnaire with the highest overlap content analysis, confirming that the choice of items exploring a range of symptoms in the three main dimensions of OSA (“OSA symptoms”, “Sleep-related symptoms” and “Clinical characteristics”) constitute consensual characteristics of OSA^{11,13}.

Nevertheless, our analysis highlights the considerable heterogeneity between the 11 selected OSA questionnaires (i.e., a weak overlap – with a mean Jaccard Index at 0.237). Our analysis found that 40% of symptoms were covered by only one questionnaire. When investigating by dimension, the heterogeneity was the lowest for “OSA symptoms” (with a mean Jaccard Index of 0.393, close to the threshold considered as moderate), but was high for “Sleep-related symptoms” and “Clinical characteristics”. This heterogeneity is due to the presence or absence of items exploring symptoms (**Figure 2**), but also to the choice of the symptoms selected to investigate such a dimension (e.g. “Snoring” or “Loud snoring”) (**Figure 4 and 5**). It is thus important to identify the differences between questionnaires. The STOP-BANG questionnaire and the Berlin questionnaire explore all the main dimensions of OSA, but they do not contain any item probing the symptoms of insomnia, despite its importance for classifying OSA severity and treatment indications⁵⁶, in line with the concept of Comorbid Insomnia and OSA (COMISA)⁵⁷⁻⁶⁰. The Haraldsson questionnaire is composed of seven main symptoms belonging to the “Sleep-related symptoms” dimension, including interestingly insomnia symptoms, but four of these sleep-related symptoms are compound, thus limiting the precision of symptom evaluation⁴⁴. The anatomical airways clinical characteristics subdimension

(amygdala/tonsil and craniofacial anatomical factors, nasal obstruction) was found in only two questionnaire (the ASA³⁷ and the AS⁴⁵). Lastly, except for hypertension, which was found in four questionnaires (the STOP³³, the STOP-BANG³⁵, the Berlin³⁸ and the SA-SDQ^{42,43} questionnaires), the other main cardiometabolic comorbidities of OSA were absent from our content analysis.

This low overlap between the questionnaires underlines the challenge and need to develop and validate new questionnaires that improve clinical screening accuracy while capturing the diversity of OSA symptoms. Indeed, a consensual list and definition of disorder-related symptoms is a prerequisite for standardizing the contents of questionnaires and evaluating their performance in different combinations^{13,61}. Although the objective of this study was not to propose a new questionnaire, the present results are a first step to support research questions about OSA screening so that the diversity of clinical phenotypes may be readily grasped^{2,10}. By making it possible to select more explicitly specific items from dimensions and sub-dimensions found in existing OSA screening questionnaires, the development of specific questionnaires to screen OSA in specific populations will be facilitated, especially with regard to sex¹⁸, comorbid sleep disorders (in particular insomnia and hypersomnolence)¹³, and other comorbidities^{7,19-21}. It will thus be easier to evaluate specific clinical phenotypes. For instance, this overlap analysis can support the search for sex-related phenotypes^{18,62-64} by identifying the most relevant symptoms of certain characteristics in a group, e.g. neck circumference^{65,66}. A putative explanation of the considerable heterogeneity between the 11 questionnaires is that they were not developed to investigate the same construct. In particular, some important symptoms related to the construct defined by the ICSD-3 (i.e., “non-restorative sleep”, called “unrefreshing sleep” in the ICSD-2, and replaced by “impaired sleep-related quality of life” in the ICSD-3-TR), by the ICSD-1-TR (i.e., “morning headaches”, “dry mouth upon awakening”) or by the classical description of the disorder by OSA experts^{1-3,67-69} (i.e., “headache”, “dry

mouth”, “nocturia”, “sexual dysfunction”, “mood alteration”, or “attentional alteration”) do not seem to have played an important role in delineating the construct screened by the questionnaires, as they were not found in any of the 11 questionnaires. We suggest that the questionnaires evaluate two different constructs. Five questionnaires seem to have been developed to screen for OSA as defined by the apnea-hypopnea index (AHI) and exhibit high pairwise overlap (the NoSAS ⁴⁷, the GOAL ⁴⁹, the OSA-50 ⁴⁸, the AS ⁴⁵ and the Wisconsin ⁴¹). Six questionnaires seem to have been developed with a more symptom-based phenotypic approach but exhibit less pairwise overlap (the STOP-BANG ³⁵, the STOP ³³, the Berlin ³⁸, the ASA ³⁷, the SA-SDQ^{42,43}, and the Haraldsson ⁴⁴). Nevertheless, these 6 questionnaires are of interest in regard to the fact that the consensual AHI metric may not be adequate for predicting OSA outcomes and representing the diversity of pathophysiological mechanisms ^{68,70-72}, and that it was recently proposed to combine symptom-based phenotypic approaches with the AHI and other markers of the pathophysiological consequences of OSA such as hypoxic burden and autonomic activation ^{10,72,73 10,74}.

Such overlap analysis may thus prove particularly useful for the future refinement of OSA clinical phenotypes in terms of OSA symptom diversity. Several stratification studies have been performed in OSA to define phenotypes in order to predict risk and treatment outcomes and response ²². When these studies investigated symptoms in stratification analyses, they generally identified three clinical phenotypes: “disturbed sleep”, “excessive daytime sleepiness” and “minimally symptomatic” ^{22,23,68,75-80}. However, the symptoms were investigated neither with common validated OSA screening questionnaires (analyzed in the current study) nor with the same list of questions and symptoms across studies of clinical phenotypes. They were investigated in the Icelandic Sleep Apnea Cohort (ISAC) cohort ^{23,81,82} by the Basic Nordic Sleep Questionnaire (BNSQ) ⁸³, which is more focused on sleep complaints than on OSA screening ⁸³, or by a questionnaire similar to the BNSQ in the Sleep

Heart Health Study (SHHS) cohort ^{77,79} and the Sleep Apnea Global Interdisciplinary Consortium (SAGIC) cohort ⁷⁸. Various OSA symptom questionnaires were used in two different French cohorts ^{84,85} and a Korean cohort ⁸⁶. Such variability highlights the need for a symptom correspondence matrix between cohorts in order to better compare the stratification of clinical phenotypes. Interestingly, in the article by Mazzotti et al. on the SHHS cohort ⁷⁷, the supplementary material provides such a correspondence matrix between the SHHS, ISAC and SAGIC cohorts, but it is not sufficiently meaningful visually to be useful for the community. The results of our content analysis therefore illustrate the need to pursue the search for a consensus regarding the combination of symptoms. Moreover, the proposed visualization of an explicit symptom correspondence matrix would make it possible to compare the relevant clinical phenotypes in the era of stratified medicine for OSA ^{68,75}.

Among the clinical phenotypes proposed in clinical practice, the phenotypic approach of the Baveno classification was designed by the working group of the Sleep-Disordered Breathing Group of the European Respiratory Society and the European Sleep Research Society (ESRS) ^{56,72,87}. It is the first attempt for a consensus clinical phenotype-based approach of OSA based on a two-dimensional scheme divided into four groups. In this consensus, the severity of symptoms (mild or severe) is combined with the presence and severity of comorbidities (minor or major end-organ impact). This classification requires an investigation of sleep-related symptoms (e.g., non-restorative sleep, insomnia, or sleepiness symptoms), and clinical characteristics (e.g. hypertension, cardiovascular disease). In our content analysis, interestingly, daytime sleepiness or sleepiness at the wheel were found in only five questionnaires (the STOP ³³, the STOP-BANG ³⁵, the Berlin ³⁸, the ASA ³⁷ and the Haraldsson ⁴⁴ questionnaires) and insomnia symptoms were found in only one (the Haraldsson questionnaire ⁴⁴), as compound symptoms in both cases. Both symptoms of sleepiness and insomnia in the Baveno classification were found only in the Haraldsson questionnaire⁴⁴. The

combination of sleep-related symptoms and clinical characteristics (in terms of end-organ damages) was found in only three questionnaires (the STOP³³, the STOP-BANG³⁵ and the Berlin³⁸) but was limited to hypertension. Our content analysis highlights the gap between OSA screening questionnaires and symptom-based phenotypic studies^{22,23}, or the Baveno classification⁷², and the value of better evaluating and visualizing OSA symptoms and characteristics by using dedicated OSA questionnaires to establish clinical phenotypes.

Another way of refining the clinical phenotypes of OSA is to take into account precise anatomical (airways characteristics) and physiological traits (inadequate responsiveness of the genioglossus dilating muscle, low respiratory arousal threshold, and instability of the respiratory control system), namely “endotyping” in the era of precision medicine for OSA^{68,76}. Of course, it is more difficult for questionnaires, which are constructed on a symptom-based phenotypic approach, to contribute to the identification of endotypes. These questionnaires were not constructed on the basis of physiological traits but rather on anatomical traits for some of them, as in the ASA³⁷ and the AS⁴⁵. Awakening during sleep was found in three questionnaires (the Haraldsson⁴⁴, the ASA³⁷ and the SA-SDQ^{42,43}), and might be related to one of the physiological traits, i.e., low respiratory arousal threshold, but this needs to be further validated. Nevertheless, the results of our content analysis demonstrate why it is important to better assess the relationships between some symptoms or characteristics and some specific endotypes.

This study has some limitations. First, questionnaires focusing on OSA symptoms but not designed specifically for OSA screening (e.g., the BNSQ⁸³) and screening approaches based on probability score calculations were not included, as recommended by Abrishami et al.¹³. Nevertheless, the confluence of probability score calculations with OSA screening questionnaires could be of interest^{14,88,89}, and the content overlap analysis of predictive models should be cross-analyzed with patient-based screening questionnaires in further studies.

Moreover, OSA questionnaires with patient-reported outcomes (PRO) were not analyzed^{74,90}. However, five OSA questionnaires investigate symptoms which can be considered as PRO for sleep disturbances and sleep-related impairments⁹¹ (the STOP-BANG³⁵, the STOP³³, the Berlin³⁸, the ASA³⁷ and the Haraldsson⁴⁴). Following on from the work of Abma et al.⁹⁰ regarding the importance of PRO for developing clinical markers measuring the views of patients on their health and health-related quality-of-life symptoms, a systematic overlap content analysis of OSA PRO questionnaires should be conducted in subsequent research. Secondly, regarding the split and lump procedure, the items were separated or grouped together while remaining as conservative as possible²⁴. This split and lump was constrained by clinical relevance²⁴. Nevertheless, the impact of the granularity of the extraction of the symptoms in terms of precision should be further analyzed (*i.e.*, the split between, “Snoring” and “Loud snoring”, or the split between “Stop breathing observation” and “Breath abnormalities complaints reported by others” for witnessed apneas). Lastly, regarding overlap content analysis, we did not investigate the specific characteristics of the populations that were studied when OSA screening questionnaires were validated. Questionnaires validated in different specific populations (e.g. relative to sex¹⁸, comorbid sleep disorders¹³, or other comorbidities^{7,19–21}) should therefore be compared.

In conclusion, our analysis offers an informative, rigorous, methodical, and quantified approach to item content in existing OSA screening questionnaires. It is a first step towards a broad reappraisal of a set of symptoms and clinical characteristics critical for OSA screening and diagnosis in the era of stratified and precision medicine for OSA. The heterogeneity of content and the low overlap across these questionnaires reflect how challenging it is to screen OSA. Beyond the quest for refining clinical OSA phenotypes in OSA screening, the analysis demonstrates that the current questionnaires potentially capture different aspects of the disorder, with a resulting risk of bias. If the combinations of the contents of OSA questionnaires

could be evaluated more precisely, research findings could be compared more accurately, and bias could be reduced. In this line, further research should better explicit the list of symptoms and clinical characteristics collected in the shift towards stratified and precision medicine for OSA. The principle of prudent conservatism ⁹², whereby a clinical picture of OSA is shared thanks to a consensual core of symptoms that overlap between several questionnaires (e.g. snoring and witness apneas), should be combined with the quest for permanent innovation ⁹², in the view of a personalized symptom-based approach for evaluating OSA.

Abbreviations :

AS: Apnea Score

ASA: American Society of Anesthesiologists checklist

GOAL: Gender, Obesity, Age, Loud snoring

Comorbid association between Insomnia and OSA: COMISA

ESRS: European Sleep Research Society

NoSAS: Neck Circumference, Obesity, Snoring, Age, and Sex scores

OSA: Obstructive Sleep Apnea

PRO: Patient-Reported Outcomes

SA-SDQ: Sleep Apnea scale of the Sleep Disorders Questionnaire

STOP: Snoring, Tiredness, Observed apnea, high blood Pressure

STOP-BANG: Snoring, Tiredness, Observed apnea, high blood Pressure, BMI, Age, Beck circumference, Gender

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Author Contributions

Conceptualization, C.G., V.M., J.C. and J.-A.M.-F.; methodology, C.G., V.M., J.C., S.B. and J.-A.M.-F.; software, C.G., V.M., A.R., M.P., and P.A.S.; validation, J.-A.M.-F., S.B, J.C., A.R. and J.-L.P.; formal analysis, C.G., V.M. and J.-A.M.-F.; writing—original draft preparation, C.G., V.M. and J.-A.M.-F.; writing—review and editing, S.B., R.L., M.P., P.S.A, P.P., J.-L.P. and J.-A.M.-F.; supervision J.-A.M.-F. All authors have read and agreed to the published version of the manuscript.

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Supplementary Materials

Supplementary Material 1: Item extraction and selection for each questionnaire, and symptom extraction and terminology harmonization between questionnaires.

Supplementary Material 2: Online analysis notebook containing all the results and interactive figures, available at:

https://raw.githubusercontent.com/vincentpmartin/OSAS.content.analysis/main/jupyter_notebook_OSA_S_content_analysis.html.

All our code, data, figures and tables and a dedicated repository to reproduce our results online with custom data is available at: <https://github.com/vincentpmartin/generic.content.analysis>.

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