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Phenotypes in obstructive sleep apnea: a definition, examples and evolution of approaches

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Summmary

Obstructive sleep apnea (OSA) is a complex and heterogeneous disorder and the apnea hypopnea index alone can not capture the diverse spectrum of the condition. Enhanced phenotyping can improve prognostication, patient selection for clinical trials, understanding of mechanisms, and personalized treatments. In OSA, multiple condition characteristics have been termed "phenotypes." To help classify patients into relevant prognostic and therapeutic categories, an OSA phenotype can be operationally defined as: *"A category of patients with OSA distinguished from others by a single or combination of disease features, in relation to clinically meaningful attributes (symptoms, response to therapy, health outcomes, quality of life)."* We review approaches to clinical phenotyping in OSA, citing examples of increasing analytic complexity. Although clinical feature based OSA phenotypes with significant prognostic and treatment implications have been identified (e.g., excessive daytime sleepiness OSA), many current categorizations lack association with meaningful outcomes. Recent work focused on pathophysiologic risk factors for OSA (e.g., arousal threshold, craniofacial morphology, chemoreflex sensitivity) appears to capture heterogeneity in OSA, but requires clinical validation. Lastly, we discuss the use of machine learning as a promising phenotyping strategy that can integrate multiple types of data (genomic, molecular, cellular, clinical) to identify unique, meaningful OSA phenotypes.

Keywords

obstructive sleep apnea; phenotype; REM related; positional; cluster analysis; personalized medicine

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Introduction

Obstructive sleep apnea (OSA) is increasingly recognized as a complex and heterogeneous disorder [1]. Recent work shows that this heterogeneity exists in the domains of the presenting symptoms [2], physiologic etiology [3], comorbid conditions [4], and important outcomes [5-7]. Despite this recognition, the diagnosis, assessment of severity, and management of OSA remains intimately linked to a single indicator, the apnea hypopnea index (AHI) [8]. An AHI-centered approach, with its lack of stratification by other syndrome characteristics likely contributes to the challenges of better understanding the genetic and biological underpinnings of the disorder [9] as well as to the modest treatment effects found in large randomized trials using continuous positive airway pressure (CPAP) [10-12].

One way to address these challenges is to classify the disorder into smaller, more homogeneous categories. Such classifications, sometimes referred to as “phenotypes,” can be based on clinical, pathophysiologic, cellular, or molecular characteristics [13]. Recent data suggest that patients may respond differently to non-positive airway pressure (non-PAP) treatments depending on their pathophysiologic characteristics such as arousal propensity or ventilatory sensitivity [14]. Successful therapeutic clinical trials can also be designed if patient categories more likely to respond to a given therapy are selected, such as those without complete concentric palatal collapse treated with upper airway neuro-stimulation [15]. These examples suggest that improved phenotyping approaches are an important step towards the goal of personalized medicine for OSA patients.

This manuscript provides an overview of the OSA phenotype literature in the context of various approaches to phenotyping. Specifically, the goals of this review are to:

1. Explore how phenotype identification can improve understanding of heterogeneous disorders (illustrated through other conditions) and propose a working definition of a phenotype in OSA for research and patient care
2. Summarize the OSA “phenotype literature” to-date, using key examples of OSA phenotyping approaches and their utility
3. Identify gaps in the current approaches and propose means to address them with a goal of personalizing care of patients with OSA

Role of phenotyping and lessons from other conditions

The aims of phenotyping include improving understanding of disease mechanisms, predicting response to therapy, risk for adverse events and reducing heterogeneity in clinical trials [16].

Similar to OSA, asthma and chronic obstructive pulmonary disease (COPD) are heterogeneous disorders whose diagnosis and management have been traditionally based on measures of physiological (expiratory volumes) and functional impairment. By better understanding the heterogeneity of these conditions, marked advances have been recently made in understanding mechanisms of disease [17], risk stratification [18] and developing

novel treatments for these conditions [19, 20]. In asthma for example, cluster analysis (described later) identified two new categories of patients: 1) late-onset, inflammatory, obese and female, and 2) very severe, mixed inflammatory phenotypes, both with high morbidity and healthcare utilization [18]. Additionally, clinical and molecular based phenotyping methods have classified individuals based on levels of T helper cell (T_H2) inflammation, with augmented corticosteroid responsiveness noted among T_H2 high individuals [17]. This challenged the paradigm that all asthma is allergic, eosinophilic, and T_H2 mediated. Phenotyping patients by markers of high T_H2 inflammation resulted in clinical trials of new biological agents that demonstrated significant improvement in lung function and exacerbation frequency [20, 21]. These "positive" trials of better phenotyped patients stand in marked contrast to the early "negative" trials of such agents using unselected, more heterogeneous, asthma patients [13]. Another example from the COPD literature, characterizes patients according to a radiographic phenotype of emphysema identifying patients who benefit from lung volume reduction therapy (upper lobe predominant) and endobronchial valve placement (lack of collateral ventilation) [19].

Although improved phenotyping has clearly resulted in tangible improvements for patients with heterogeneous disorders, there are lessons to be learned from these approaches. Several of the patient phenotypes in asthma and COPD have been overlapping, not always reproducible, changed over time, and have not consistently pointed to greater mechanistic understanding or treatments [16, 22]. This may be due to disparate populations studied, lack of relevant features used for phenotyping, or a situation in which clinical phenotypes alone may not capture relevant biology. The absence of a consistent definition for the term "phenotype" in some cases may also lead to lack of clarity.

OSA phenotype, a definition

Ideally, the phenotype serves as an expression of an "endotype," a subtype of disease defined by "a unifying and consistent natural history, clinical and physiological characteristics, an underlying pathobiology with identifiable biomarkers and genetics and a predictable response to general and specific therapies that impact relevant patient outcomes" [13]. Current categorizations of OSA patients, however, have not yet advanced to the status of endotype definition. At this point we believe that identifying meaningful phenotypes of OSA can be accomplished by anchoring them to relevant patient outcomes. Akin to the phenotype definition proposed for COPD [23], we propose the following operational definition for OSA phenotype:

> "A category of patients with OSA distinguished from others by a single or combination of disease features, in relation to clinically meaningful attributes (symptoms, response to therapy, health outcomes, quality of life)."

Phenotypes lacking all of the qualities of an endotype can advance toward that status as supportive data (biologic markers, genomic, and genetic) are generated (Figure 1). This refinement may offer opportunities for even more targeted prognostication and treatments. The outcomes used in phenotype identification should be carefully defined, given that some features such as excessive daytime sleepiness, sleep fragmentation, or treatment-resistant hypertension may be viewed as either outcomes or phenotypes.

An advantage of the proposed definition is that it offers the flexibility to identify phenotypes in situations where biological or genetic mechanisms of categorization may not yet be known but patient stratification may have prognostic or therapeutic utility. For example, complete concentric collapse of the palate in OSA patients predicts failure to respond to upper airway neuro-stimulation therapy [24]. Although the biological underpinnings of this OSA feature are not fully understood, meaningful benefits can accrue from using this phenotype to augment clinical trial design [15] and patient care [25]. The definition also provides a basis for deeper characterization of physiological or molecular mechanistic investigations. Those exhibiting similar clinical outcomes may behave so because of a similar underlying physiological or biological mechanism.

Phenotyping approaches

Phenotyping strategies can be grouped by features (e.g., clinical vs. molecular) and by experimental approaches (e.g., supervised vs. unsupervised) (Table 1) [16]. Clinical phenotyping focuses on identifying unique patient categories based on measures such as signs, symptoms, demographics, comorbidities, physiological and anatomic measures, or treatment responsiveness. Molecular phenotyping aims to classify individuals based on molecular features: DNA, RNA, mRNA, miRNA, proteins, metabolites and other biological products. Additionally, the number of features considered in the approach can vary from one (e.g., sex) to thousands (e.g., single nucleotide polymorphisms).

Supervised analytic methods evaluate a prespecified phenotype based on single or multiple features (Table 1). The premise is that the features differentiating subjects into specific subcategories represent biological/mechanistic differences between them [26]. In terms of complexity, these methods vary from standard regression analyses to machine learning algorithms incorporating complex, highly dimensional data [26].

Unsupervised analytic methods, such as cluster analysis, require no *a priori* classification of the data [27]. They are designed to organize information about features so that patients are classified into relatively homogeneous categories [28]. They have the advantage of generating new phenotypes based on unique associations between features not readily apparent in highly multidimensional data. As such, they are hypothesis generating rather than confirming. Ultimately, anchoring to outcomes using supervised analyses is necessary to establish the relevance of the newly identified phenotype.

Examples of these approaches and their corresponding methods are noted in Table 1, all of which have advantages and disadvantages related to underlying assumptions, hypotheses tested, and computational burden [29]. This schema will be used as a framework to review key examples of phenotyping in OSA in order of increasing analytical complexity. We start with phenotypes described using supervised, single feature analyses and end with multi-feature unsupervised and supervised approaches to OSA phenotypes. Given the relative paucity of publications in the molecular domain of OSA, this review focuses primarily on clinical phenotyping.

Potential, clinically relevant OSA phenotypes

Literature search

A literature search for key concepts related to sleep apnea and phenotypes was performed (see Supplement [Part A], for methods and article inclusion/exclusion criteria). Table of potential phenotypes and their characteristics can be viewed in the Supplement (Part B).

Single feature phenotypes (supervised analytic methods)

Symptom and demographics based features: The concept that differing presenting symptoms may have implications for pathogenesis and outcomes has been used to phenotype OSA individuals for decades. Up to sixty percent of OSA patients can be excessively sleepy [30] and report higher rates of impaired concentration, mood lability, and other neurocognitive difficulties [31]. Epidemiologic studies demonstrate that excessive daytime sleepiness (EDS) modifies the relationship between AHI and incidence of hypertension [32], glucose metabolism [33], and mortality [34]. This provided a ready target for treatment with CPAP and mandibular advancement devices which improve EDS [35]. Compared to those without sleepiness, treatment of patients with EDS has also been shown to reduce blood pressure, vascular risk [5, 10, 11], and improve quality of life [36]. Thus it has been proposed that OSA with EDS is a unique phenotype [37]. OSA with EDS phenotype appears to have clinical relevance but it is unlikely that it represents a true endotype given the multitude of contributors to EDS [38].

Age, gender, and race-ethnicity are increasingly recognized as factors impacting OSA presentation and implications [7, 39, 40]. For example, compared to younger patients with the same AHI, OSA in older patients is associated with less sleepiness [41] and often presents with enuresis, cognitive dysfunction, and mood impairments [42]. Additionally, with increasing age there is increased upper airway collapsibility as measured by pharyngeal critical closing pressure (P_{crit}), decreased lung volume and ventilatory chemosensitivity. These observations have led some to suggest that OSA in the elderly may represent distinct physiological phenotype [43]. Supporting this claim, is a consistent lack of association between OSA and increased risk of hypertension [44] or atrial fibrillation [45] among older adults. Conflicting results exist, however, with regard to risk for coronary artery disease [46, 47], cognitive impairment [48-50] and death [47, 51]. The potential reasons for such variability are many, including differing definitions of OSA used in these studies and differing measures employed to characterize OSA severity (AHI, oxygen desaturation index [ODI], time spent below 90% oxygen saturation).

Age related differences in OSA are also gender dependent. OSA is less prevalent among premenopausal women, but postmenopausal women have a similar risk to that of men. Women tend to have longer sleep latency and more slow wave sleep [40]. Overall, their AHIs are lower, especially during NREM (non-rapid eye movement) sleep and respiratory events tend to cluster in REM sleep [40]. Such findings suggest that OSA in women is a separate phenotype, further supported by differences in predisposing factors for OSA. Fat distribution may play a role, with truncal obesity measured by waste to hip ratio (lower in women) mediating some of the association between gender and AHI [40]. Men have a larger

[52], but more collapsible airway then women [53] and retrusive movement of the mandible decreases cross-sectional area of the oropharynx-pharynx in men, but not in women [54]. Although it is clear that OSA prevalence and pathogenesis differ by gender, the mechanisms and implications of these differences are not well understood. Studies of known determinants of upper airway stability such as pharyngeal fat content, upper airway muscle responsiveness, ventilatory sensitivity to hypoxia or hypercapnia, and upper airway resistance all show conflicting results when comparing men to women [40, 53]. Perhaps more importantly, the clinical implications for the gender differences are uncertain, with investigators reporting conflicting risk differences of incident hypertension [55, 56], congestive heart failure [7, 46], stroke [57, 58], treatment responsiveness [59], neurocognitive outcomes [12] or death [51, 60].

Polysomnographic and physiological features: Anisotropy of the upper airway collapse observed with positional changes has resulted in categorization of some individuals as positional OSA. Reports suggest that over 50% of those referred for OSA evaluation exhibit supine AHI that is at least twice that in non-supine position [61]. Patients with positional (supine-predominant) OSA tend to be younger, have lower body mass indices (BMI), and lower AHIs compared to their non-positional counterparts [61]. The characteristics and prevalence vary depending on the definition used (i.e., ratio of supine to non-supine events, lower limit of non-supine AHI, etc…) [62]. A consistent finding in is that pharyngeal collapsibility (P_{crit}), markedly improves in lateral position [63], suggesting that smaller lateral wall size, decreased fat content, and lower facial height are associated with velopharyngeal patency while lateral [64]. Despite the high prevalence and plausible physiological mechanisms, conflicting data exists on clinical presentation and treatment responsiveness. The two largest studies (425 and 630 patients) examining treatment success (defined as residual AHI < 10 and ≥ 50% reduction) with mandibular advancement devices (MAD) showed conflicting results [65, 66]. Short-term studies (1 month follow up) suggest that auto-set PAP use is associated with improved sleepiness and wakefulness among supine-predominant patients in comparison to CPAP [67, 68], lending credence to idea that fixed PAP may not be optimal in all OSA patients with similar AHIs. Multiple position altering devices are efficacious at reducing time spent in supine position and AHI, but devices vary significantly in patient comfort and adherence with only short-term data available [69].

In addition to position, distribution of respiratory disturbance within sleep stages has been used to categorize OSA, with REM-predominant OSA being most studied. Patients with REM-predominant OSA tend to be younger women and have reduced sleep time, sleep efficiency, and REM duration. Decreased genioglossal muscle activity in REM [70], lower respiratory drive [71], longer duration events and more severe hypoxia combined with increased sympathetic activity during REM sleep [72] have led to hypotheses that events during this stage may have unique clinical implications. Similar to supine predominant OSA, prevalence of REM-predominant OSA depends on the definition used [73]. Despite the physiological and polysomnographic differences, large cross-sectional analyses comparing REM-predominant to NREM (or stage independent) OSA have failed to show differences in sleepiness, functional outcomes, PAP adherence, or quality of life [74-76]. Although lower response rates to MAD have been noted in REM-predominant OSA, REM-predominance

was not a predictor of MAD responsiveness when age, BMI, and AHI were considered [66]. Limited data exist on neurocognitive, metabolic, or cardiovascular outcomes, but findings from the Wisconsin cohort demonstrate that a REM AHI ≥ 15 was associated with both prevalent and incident risk of hypertension [6]. The increased risk was present even among those with an overall AHI < 5. This suggests that some patients not meeting the current criteria for diagnosis and treatment of OSA may stand to benefit from treatment.

Studies of other polysomnographic and physiological features such as severity measures of airway obstruction, event duration, type (i.e., central, mixed, or obstructive), NREM predominance, and hypoxic load have been differentially associated with outcomes (see Supplement, Part B). Overall, the features discussed above do seem to capture parts of symptomatology, pathophysiology, and outcome heterogeneity among OSA patients, but it remains to be seen whether they represent true phenotypes or features of latent phenotypes yet to be identified. Focusing on individual features in isolation likely probes the same latent structure from different perspectives, much like using a single lead of an electrocardiogram to assess cardiac conduction. Comprehensive studies simultaneously considering feature interactions and their impact on outcomes are lacking. To address these challenges, some investigators have focused on outcomes and measured multiple features simultaneously to predict salient phenotypes.

Outcome based “reverse engineering” phenotypes (supervised analytic methods)—An example of this approach, includes use of drug-induced sleep endoscopy (DISE) to identify patients who benefit from upper airway neuro-stimulation therapy (UAS). A DISE study of 1249 patients showed that the collapse pattern is heterogeneous with respect to the level within the airway (e.g., tongue base vs velopharynx), direction (anterior–posterior, lateral vs. concentric), and degree of collapse (complete vs. partial) [77]. In another study, those with complete concentric collapse (CCC) at level of the palate (~ 30%), showed no improvement in AHI with UAS therapy, compared to 81% of patients without CCC in whom success was achieved. [24]. A subsequent randomized trial of 126 patients without CCC showed marked improvement in AHI, sleepiness, and functional outcomes that persisted through 2 years of follow-up [15, 25]. This work serves as an example of “reverse engineering” by developing a targeted intervention and matching it with a corresponding clinically important phenotype.

Multiple feature phenotypes (with supervised methods)—Based on accumulating data suggesting that multiple pathophysiological processes are involved in genesis of sleep apnea [78], a framework for deeper phenotyping of sleep apnea based on physiology has been developed [3]. With this approach, simultaneous measurement of multiple causative traits (anatomical predisposition [passive P_{crit}], arousal threshold [ventilation prior to arousal], respiratory controller stability [loop gain], and upper airway muscle responsiveness [upper airway gain], designated as “PALM”) is performed using a modified polysomnography technique [3]. Eckert and colleagues showed marked heterogeneity of these traits among 75 OSA patients, with non-anatomic features such as high loop gain, low arousal threshold, and low upper airway gain being abnormal in over 50% of the patients [3]. Utilizing this framework, investigators demonstrated that disparate groups of OSA patients

(e.g., elderly, supine predominant) differentially express the PALM causative traits (or their combinations) [43, 63]. Small studies show that individual traits are modifiable. For example, esczopiclone increases arousal threshold, acetazolamide reduces loop gain, and weight loss or uvulopalatopharyngoplasty lower P_{crit}, and all are associated with reductions in AHI [79-83]. An integrative model developed using the PALM framework features can classify patients as with or without OSA and determine how many and which patients may benefit from trait modification [14]. The sensitivity and specificity for OSA were 88% and 80% respectively. Importantly, modification of a single trait with above treatments showed that the proportion of patients that could be successfully treated (NREM AHI < 10) ranged between 19 and 38%, while honing in on the predominantly abnormal trait in each patient, improved the success to 48%. Notably, combination of trait modifications (e.g., loop gain, arousal threshold, and anatomical collapsibility) was predicted to alleviate OSA in 81%. These findings are notable because they suggest that OSA patients can be meaningfully categorized based on heterogeneity of their physiology, and targeted non-PAP treatments can alleviate respiratory events. Furthermore, this approach provides new targets for treatment and means to stratify patients for clinical trials.

Although clearly an important step forward in personalizing approaches to OSA, important questions regarding this framework remain. Multiple traits can be measured simultaneously, yet it is unclear whether such traits change independently as ventilatory drive changes [84]. With some stimuli (e.g., hypoxia) for example, loop gain, upper airway gain, and arousal threshold are all affected [81]. Replication of this work is needed, as conflicting results of the traits' association with OSA risk factors (gender [53, 85]) and treatments (trazodone) aimed at modifying individual traits (arousal threshold [86, 87]) have been found. Despite efforts to make measurements of these traits more accessible to the greater research community [88, 89], the technology and expertise required are complex and not yet available even in most academic centers. Finally, the use of this framework remains largely theoretical and the impact on OSA severity and most importantly relevant patient outcomes (e.g., cardiovascular, metabolic, neurocognitive, functional) is a needed area of future investigation.

Another approach to characterizing OSA physiology uses electrocardiography (ECG)-based measures of autonomic and respiratory interaction (cardiopulmonary coupling). An example of this approach integrates cardiac inter-beat (R-R interval) and respiratory (ECG-lead axis variation) dynamics to generate a map of coupled sleep oscillations, a sleep spectrogram [90]. The spectrographic measures correlate with electroencephalographic markers of sleep stability, not ordinarily captured by conventional sleep stage distributions [90]. Transitions occur between periods of high frequency coupling (HFC, putative "stable" sleep), low frequency coupling (LFC, "unstable" sleep) and very low frequency coupling (VLFC, wake or REM sleep). A subset of LFC, termed elevated narrow band LFC (e-LFCnb) was found to be a marker of increased chemoreflex activation. This is suggested by correlation with central apneas and increased risk of treatment emergent central sleep apnea (TE-CSA) [91]. e-LFCnb is heritable [92], and has been associated with prevalent hypertension and stroke in the sleep heart health study in adjusted analyses, including the AHI [93]. No associations with incident outcomes have been reported and treatment implications of this phenotype require investigation. In a single study e-LFCnb did not predict adaptive servo ventilator

responsiveness among patients with TE-CSA [94]. It remains to be investigated how measures such as e-LFCnb are integrated into individual patient phenotyping and whether targeted interventions improve outcomes.

Complementary to the work on non-anatomical OSA risk factors, cephalometric measures have been used to characterize OSA in the domain of craniofacial skeletal and soft tissue morphology. Mandibular retrusion, maxillary deficiency, and inferior displacement of the hyoid bone and cranial base are commonly reported risk factors for OSA [95]. Cephalometric measures have been reported to explain some of the racial, ethnic, and gender variance in risk for sleep apnea [39]. Additionally, cephalometric analyses show that abnormalities in the soft tissue morphology predominate among obese OSA patients, in contrast to skeletal structure changes in non-obese OSA individuals [96]. Certain dimensions, including lower facial height, mandibular length and angles between sella-nasion and anterior points of maxilla/mandible are heritable among OSA patients [97]. The observed variability in cephalometric measures in OSA individuals has not, however, been translated into ability to predict clinically relevant outcomes. From treatment standpoint, most literature exists on MAD therapy. In one study using multivariate analyses and controlling for age, BMI and sex, only a long soft palate and large cranial base angulation [98] predicted failure of MAD (negative predictive value 98%). While some reports support these findings, others identify alternate correlations of treatment success, and most are limited by small and heterogeneous sample sizes without consideration of known important factors (BMI, sex, neck circumference) [99]. Similar conclusions have been made regarding cephalometric data on prediction of surgical outcomes [100].

Newer and less costly methods of capturing skeletal and adipose tissue morphologic heterogeneity from digital photography termed “facial phenotyping” have been recently reported. Shorter, retruded jaw, smaller mandibular enclosure area, wider and flatter mid-lower face predict OSA independent of BMI and sex [95]. Features of facial structure were highly correlated to magnetic resonance imaging cephalometric measures known to be risk factors for OSA. Some (maxillary-mandibular relationship, lower face height and mandibular length) were obesity independent, while others (tongue volume) were not, suggesting that the approach may be able to capture both skeletal and soft tissue risk factors for OSA [101]. No studies relating these measures to outcomes have been reported.

Characterization of OSA using features beyond those routinely measured in clinical practice and focusing on the putative causative mechanisms of OSA, may have important implications. Termed intermediate phenotypes, measures of physiological and anatomical mechanisms in pathogenesis of OSA highlighted above may help link genetic and biological pathways to the clinical expression of OSA (a domain where use of AHI and standard demographic data as phenotypes has led to limited success), and identify more robust phenotypes amenable to targeted interventions.

Multiple feature phenotypes (unsupervised methods with or without supervised outcome association)—Although approaches described above have resulted in identification of potentially clinically relevant OSA categories, they are based on a priori (usually clinical) observations, thus potentially missing more complex, and as yet

unidentified phenotypes [102]. Recently, several groups began phenotyping OSA in a more statistically based manner with cluster analysis being most commonly employed technique.

Examples of this approach in OSA literature are few so far [2, 4, 103-106]. While most studies are relatively large (881 to 5983 patients), they vary widely by features and populations selected and only two used similar methodology. Ye et al., identified three clusters of patients in a predominantly male Iceland sleep apnea cohort: “excessive daytime sleepiness” 42%, “disturbed sleep/insomnia’’ 33% and ‘‘minimally symptomatic’’ 25% of those studied [2]. Although traditional risk and severity factors such as gender, BMI and AHI were equivalent in these clusters, measures of mental and physical health, as well as prevalence of cardiovascular disease (notably highest in the “minimally symptomatic” cluster) differed significantly. A more gender balanced study by Gagnadoux et al., [103] identified similar symptom based clusters with comparable distributions of comorbidities. Two additional patient categories were identified: 1) middle aged, obese women with marked insomnia, depression, and comorbidities, and 2) older, obese men with typical nocturnal and diurnal OSA symptoms, depression, and a marked comorbidity burden. Notably, the minimally symptomatic, the male disturbed sleep/insomnia (identified in both studies) and obese female OSA with insomnia clusters (identified only by Gagnadoux et al. [103]) exhibited 50 – 75% lower rates of successful CPAP treatment at six months in comparison to the “excessive daytime sleepiness” phenotype (noted in both studies). The differences were independent of socioeconomic status, sleepiness and AHI. These findings suggest that use of simple indicators such as AHI and sleepiness alone is insufficient to understand OSA’s clinical presentation, implications for treatment, and quality of life. They suggest for example, that in OSA patients with insomnia, combination therapy (e.g., cognitive behavioral therapy and CPAP) or non-PAP therapies rather than CPAP could be explored. Supporting this notion, are studies of insomnia timing subtypes in OSA, with both sleep initiation and late night insomnia patients being less sleepy, less adherent and responsive to CPAP therapy, in contrast to patients with middle of the night insomnia [107, 108]. In addition, these studies provide a basis for more rational patient selection in clinical trial design.

Vavougios et al., showed that a wide range of comorbidities can vary markedly within equivalent, AHI-based OSA severity categories [4]. A highly comorbid cluster and one without significant comorbidity were identified within both, moderate and severe OSA patient groups. Notably, both low comorbidity clusters were similar in age, BMI, sleepiness, and daytime oxygen saturation but exhibited a 2-3 fold difference in AHI, ODI, and arousal index [46]. Further work in this domain has the potential to explain factors responsible for “resiliency” to the increasing OSA severity.

Studies using the above approaches provide insights into symptomatic heterogeneity and identify potentially clinically relevant phenotypes. Further investigation however is needed. Most analyses are cross-sectional, lacking the ability to discern temporal relationships. It remains unknown when these phenotypes first manifest, whether they are stable over time, (single night or longer scales) and if/how individuals transition between them. Furthermore, many features capturing the known risk factors for and etiologic mechanisms in OSA are missing from the designs.

Summary and future directions

Evidence is accumulating and consensus is building that AHI alone is insufficient for diagnosis and management of individuals with OSA. Complementary to molecular phenotyping, clinical phenotyping may serve as an intermediate step towards personalized medicine in OSA. Emerging themes from current literature include needs for: 1) improved anchoring of phenotypes to clinically relevant outcomes and 2) addressing the interplay of features important in pathogenesis of OSA though advanced analytic methods.

Linking phenotypes to meaningful, longitudinal outcomes can facilitate their selection and refinement (e.g., REM-related OSA). Focus on outcomes distal to AHI reduction such as blood pressure or neurocognitive performance is prudent given examples in the literature that lowering AHI may not translate to benefit [5] or may even be harmful in some patients [109]. Expanding the outcome domain beyond “hard” endpoints such as mortality to include functional and patient-centered outcomes [110] may capture phenotypes with importance to our patients that would otherwise be missed.

Because of the inherent correlation of the features used to characterize OSA patients, applying machine learning approaches like cluster analysis or neural networks to simultaneously assess the clinical and the novel promising phenotype measures (e.g. PALM model, facial analysis and cardiopulmonary coupling features) will be important. Such approaches may not only provide phenotypic classification using a single level of data (e.g., clinical, biologic, genomic) but also show promise integrating data between levels to identify mechanistic distinctions [111] more closely resembling endotypes.

In the context of systems biology, clinical and pathophysiologic OSA features constitute just some levels of the data to be integrated to predictively model disease expression and response to therapy [112]. Figure 2 illustrates the levels of OSA characterization (risk factor/environmental, clinical, pathophysiologic, biologic, genomic/genetic) and the potential benefits of translating the new knowledge at each level for research and clinical practice. At the clinical level, for example, a better understanding of the relationships between comorbidities can improve strategies for integrated care. In addition, examples of clinical (EDS) and intermediate (CCC) phenotypes predicting response to CPAP exist [11, 15]. Similarly, better understanding of the genomic and biologic levels can help determine risk of future complications and response to treatment. For example, in OSA patients with resistant hypertension, a cluster of miRNAs discriminated between those with and without favorable blood pressure response to CPAP [113].

Knowledge from each of the above levels can enable targeted patient selection in OSA clinical trials, reduce resource use and lessen the burden on patients unlikely to benefit from treatment. Phenotype identification and validation will likely require an iterative process (Figure 3), with multiple points of entry, as research is advancing in several domains simultaneously. One way to integrate phenotype information has been proposed in COPD [114] and an analogous approach may be applicable to OSA. It organizes the actionable information available for individualized treatment for a patient (e.g., symptom phenotype, polysomnographic phenotype, physiological trait measures, airway collapse pattern, co-

morbid disease responsiveness to treatment, etc.) into domains of syndrome severity, causative factors, and impact. Biomarker and genomic data can be incorporated as our concepts of OSA phenotypes evolve, enabling development of personalized therapies for OSA.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Glossary of terms

AHI	Apnea hypopnea index
ASV	Adaptive servo ventilation
Auto-PAP	Auto-set positive airway pressure
BMI	Body mass index
COPD	Chronic obstructive pulmonary disease
CPAP	Continuous positive airway pressure
DNA	Deoxyribonucleic acid
DISE	Drug induced sleep endoscopy
ECG	Electrocardiogram

e-LFCnb	Elevated low frequency coupling in the narrow band as referred to in cardiopulmonary coupling
ESS	Epworth sleepiness scale
HFC	High frequency coupling as referred to in cardiopulmonary coupling
LFC	Low frequency coupling as referred to in cardiopulmonary coupling
MAD	Mandibular advancement device
mRNA	Messenger ribonucleic acid
miRNA	Mircro ribonucleic acid
NREM	Non-rapid eye movement
ODI	Oxygen desaturation index
OSA	Obstructive sleep apnea
P_{crit}	Passive critical closing pressure
PALM	Passive P_{crit}, Arousal threshold, Loop gain, and upper airway Muscle responsiveness.
REM	Rapid eye movement
RNA	Ribonucleic acid
TE-CSA	Treatment emergent central sleep apnea
SDB	Sleep disordered breathing
UAS	Upper airway neuro-stimulation
VLFC	Very low frequency coupling as referred to in cardiopulmonary coupling

Practice Points

1. OSA phenotype can be defined operationally as: “A category of patients with OSA distinguished from others by a single or combination of disease features, in relation to clinically meaningful attributes (symptoms, response to therapy, health outcomes, quality of life)
2. The AHI is insufficient to capture clinical heterogeneity of patients with OSA and should not be used in isolation for management of patients
3. Symptoms other than sleepiness (e.g., insomnia) should be considered during evaluation of OSA patients.
4. Elevated AHI (≥ 15 events per hour) during rapid eye movement sleep, even in those with overall AHI < 5, should prompt a discussion regarding risks and benefits of treatment
5. The “PALM” physiological framework approach is promising for identifying patients who may benefit from non-CPAP therapies, but further clinical validation is required
6. Although cephalometry captures craniofacial structural differences among OSA patients, current data does not support its use in clinical practice
7. Unsupervised phenotyping approaches (e.g., cluster analysis) are promising for identifying unique categories amongst patients with OSA

Research Agenda

1. Anchor clinical phenotypes to meaningful outcomes early during the phenotype identification process
2. Validate intermediate phenotypes (etiologic physiology, facial analysis, cardiopulmonary coupling measures) with clinical outcomes
3. Evaluate the putative phenotypes (and their features) using advanced analytic techniques (e.g. machine learning)
4. Assess temporal stability of identified phenotypes

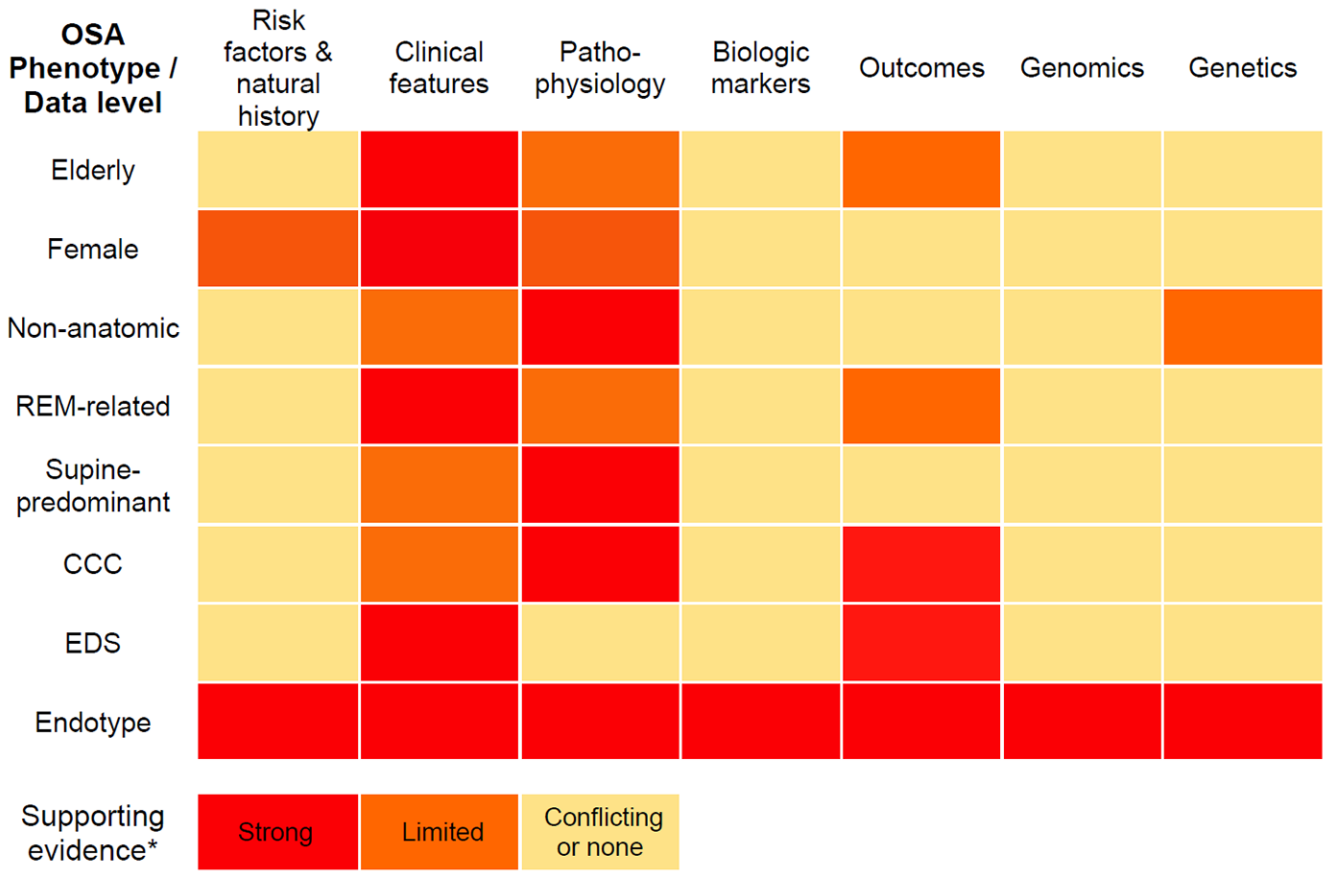

Figure 1. Heat map of key endotype and phenotype qualities illustrated through examples of possible phenotypes described in the literature

Phenotype illustrated above as having at least two data levels with strong supporting evidence (one must be "Outcomes"). Endotype illustrated above as having high degree of supporting evidence for each level (please see text for discussion).

CCC – Complete concentric palatal collapse, EDS – Excessive daytime sleepiness, Non-anatomic - (e.g. low arousal threshold or sensitive chemoreflex), OSA – Obstructive sleep apnea

* Degree of supporting evidence assigned by authors based on literature review (no formal definitions, for illustration purposes only).

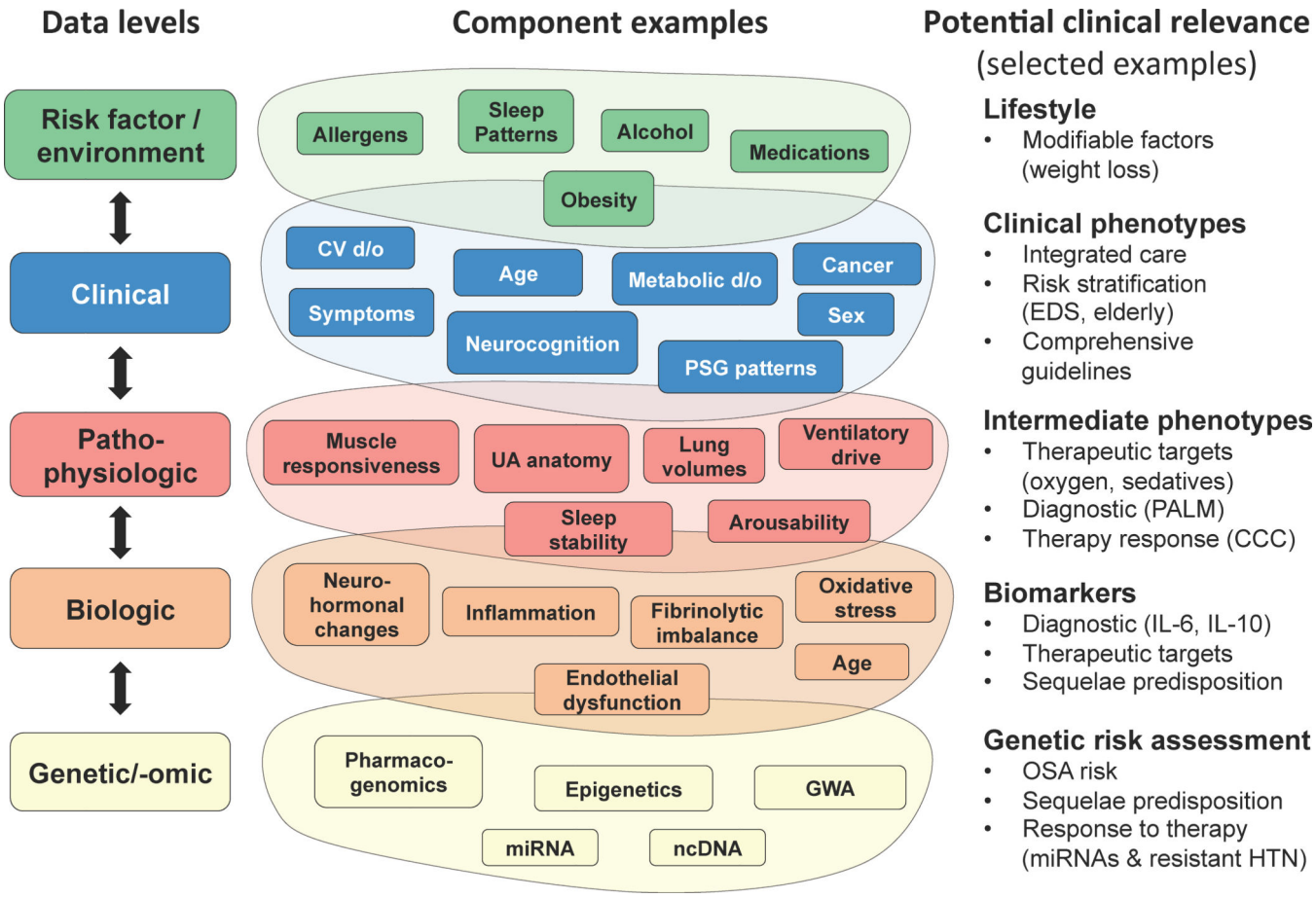

Figure 2. Data levels in obstructive sleep apnea (OSA) phenotyping and the potential benefits

Illustration of phenotyping data levels (risk factor/environment, clinical, pathophysiologic, biological, gen-etic/omic) in OSA and the potential benefits (right-hand column). Each level shows only some examples of the potential components (not intended to be comprehensive). Arrows signify integration of the levels to better understand their relationship in OSA. CCC – complete concentric palatal collapse, CV d/o – cardiovascular disorders, EDS – excessive daytime sleepiness, GWA – genome-wide associations, HTN – hypertension, IL – interleukin, miRNA – microRNA, ncDNA – non-coding DNA, PALM - Passive $\underline{P}_{crit}$, Arousal threshold, Loop gain, and upper airway Muscle responsiveness model, PSG – polysomnographic, UA – upper airway. Structure adapted with permission from Agusti et al., 2011 [115], with permission of the American Thoracic Society. Copyright © 2016 American Thoracic Society.

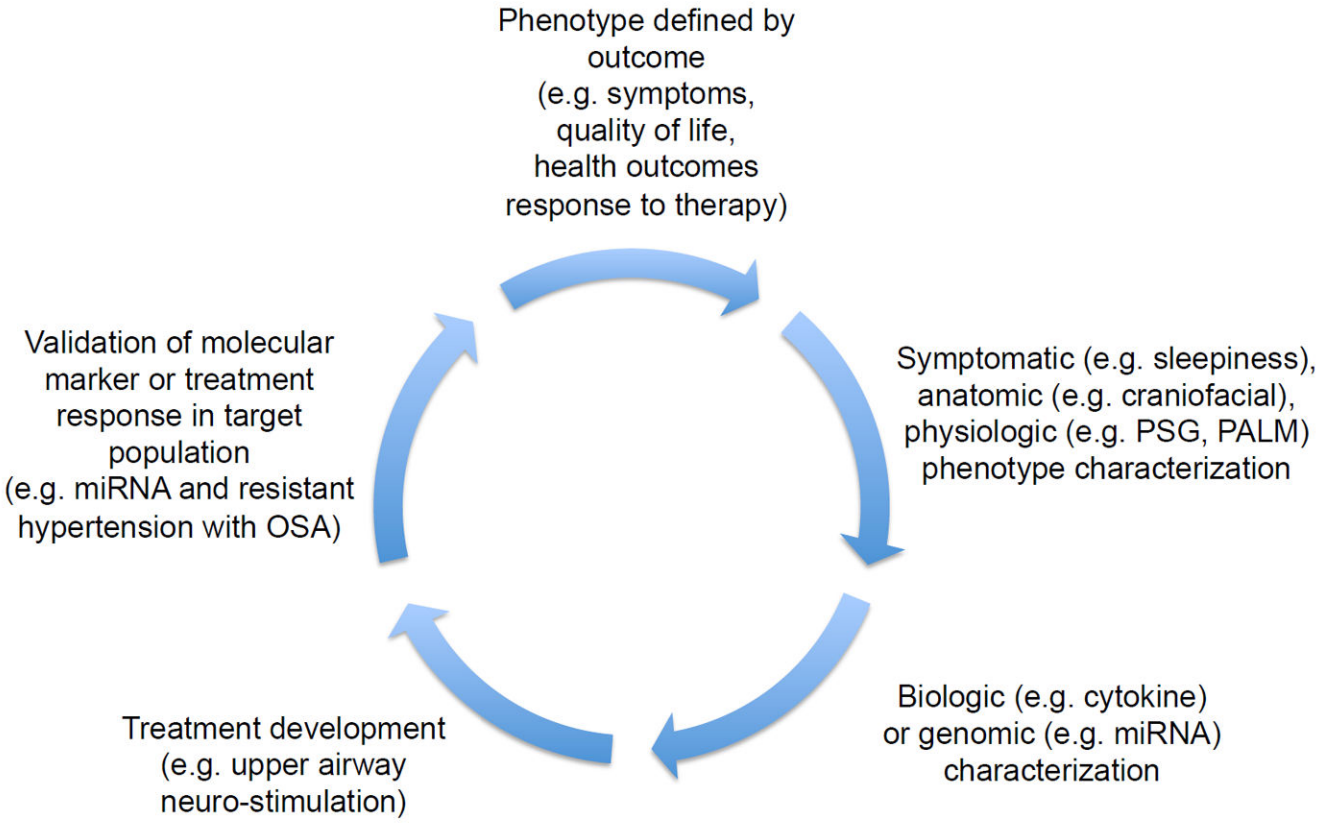

Figure 3. Iterative process of phenotype identification and validation in obstructive sleep apnea (OSA)

Multiple points of entry into the process are possible. For example, phenotyping process may begin by differentiation of patient group based on a biomarker, later validated by similar clinical prognosis or response to treatment within that subgroup. Alternatively, patient groups may be identified by similar clinical outcomes potentially suggesting a physiologic target for focused treatment. Adapted from Han et al., 2010 [23], with permission of the American Thoracic Society. Copyright © 2016 American Thoracic Society.

Table 1

Phenotyping approaches*, associated analytic methods and examples of potential clinical phenotypes identified

Approach	Features	Analysis method examples	Phenotyping examples
Supervised	Single	• t-tests • Analysis of variance • Regression • Survival analysis	• Excessive daytime sleepiness OSA • REM related OSA • OSA in elderly • Complete concentric palatal collapse OSA
	Multiple	• See above and • Classification and regression trees • Random forest modeling • Neural networks	• Anatomic vs. non-anatomic (elevated loop gain, low arousal threshold, low upper airway muscle responsiveness) OSA • Chemoreflex activated and poor sleep quality (elevated low frequency narrow band coupling and low high frequency coupling) • Facial photographic phenotypes (Mandibular length, maxillary- mandibular relationship, etc.)
Unsupervised	Multiple	• Hierarchical or K-means clustering • Self organizing maps • Network analysis	• Excessive daytime sleepiness, disturbed sleep and asymptomatic • Younger female, insomnia and comorbid OSA • Elderly male, symptomatic, comorbid OSA • Moderate and severe OSA without comorbidities

See references [16, 26-29] for details on methodology.

OSA – obstructive sleep apnea, REM – rapid eye movement.