Analysis of sleep apnea research with a special focus on the use of positron emission tomography as a study tool

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Conflicts of interest

The authors declare no conflicts of interest.

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SUMMARY

The quality of sleep plays a significant role in determining human well-being, and studying sleep and sleep disorders using various methods can aid in the prevention and treatment of diseases. Positron emission tomography (PET) is a noninvasive and highly sensitive medical imaging technique that has been widely adopted in the clinic. This review article provides data on research activity related to sleep and sleep apnea and discusses the use of PET in investigating sleep apnea and other sleep disorders. We conducted a statistical analysis of the number of original research articles published on sleep and sleep apnea between 1965 and 2021 and found that there has been a dramatic increase in publications since 1990. The distribution of contributing countries and regions has also undergone significant changes. Although there is an extensive body of literature on sleep research (256,399 original research articles during 1965–2021), PET has only been used in 54 of these published studies, indicating a largely untapped area of research. Nonetheless, PET is a useful tool for identifying connections between sleep disorders and pathological changes in various diseases, including neurological, metabolic, and cardiovascular disorders, as well as cancer. To facilitate the broader use of PET in sleep apnea research, further studies are needed in both clinical and preclinical settings.

Keywords

Metabolic activity, cardiovascular diseases, neurological diseases, positron emission tomography, radiopharmaceuticals, sleep apnea.

Abbreviations

[^{11}C]PIB	^{11}C-Labeled Pittsburgh compound B
[^{18}F]FBB	[^{18}F]Florbetaben
[^{18}F]FDG	2-Deoxy-2-[^{18}F]fluoroglucose
[^{11}C]DASB	[^{11}C]-3-amino-4-(2-dimethylaminomethyl-phenylsulfanyl)-benzonitrile

[^{11}C]DTBZ	[^{11}C]Dihydrotetrabenazine
AD	Alzheimer's disease
AHI	Apnea–Hypopnea Index
CPAP	Continuous positive airway pressure
CT	Computed tomography
IH	Intermittent hypoxemia
MRI	Magnetic resonance imaging
OSA	Obstructive sleep apnea
PET	Positron emission tomography
RBD	Rapid eye movement behavior disorder
ROI	Region of interest
SDB	Sleep-disordered breathing
SUV	Standardized uptake value
SUVmax	Maximum standardized uptake value
SUVmean	Mean standardized uptake value

1. Introduction

Human beings sleep for one-third of their lifetime, and the quality of sleep substantially determines the quality of life and socioeconomic status [1]. Owing to the utmost importance of sleep, it and its disorders, such as sleep apnea, are under active study. Sleep apnea affects one billion people worldwide [2]. It is characterized by breathing pauses during sleep, resulting in intermittent hypoxemia (IH) and sleep fragmentation. Although a narrow and collapsible upper airway is a prerequisite for sleep apnea, ineffective upper airway muscles, unstable ventilatory control (high loop gain), and low respiratory threshold markedly contribute to sleep apnea pathogenesis, allowing phenotyping of patients and finding potential therapeutic targets

[3]. Positron emission tomography (PET), a noninvasive and highly sensitive medical imaging technique, may provide deeper insights into morphological and functional changes in upper airway muscles, such as the pharyngeal dilator muscles [4] and genioglossus [5]. Furthermore, PET imaging provides thorough knowledge about the effects of continuous positive airway pressure (CPAP) and non-CPAP therapies.

Because intermittent hypoxia and inflammation affect all organs simultaneously, patients with sleep apnea are often multimorbid and suffer from multiorgan damage. This was recently confirmed by a Finnish register-based nationwide study, which is the largest investigation on multimorbidity in people with sleep apnea to date [6]. Population-based studies have shown clear links between sleep apnea and other diseases. For example, according to a study of 1.3 million people, patients with sleep apnea have a higher risk of developing dementia than a control population [7]. Among 23,035 men in a cohort study, sleep apnea was associated with an increased risk of male infertility [8]. In a nationwide study of 5.6 million people in the United States, certain cancers have significantly higher occurrences among patients with sleep apnea, including melanoma and pancreatic cancer [9], whereas in a European sleep apnea cohort, cardiovascular and metabolic diseases were highly prevalent [10]. Thus, sleep apnea is a major public health problem affecting the general population.

To manage sleep apnea in the population, disease mechanism studies are needed. Noninvasive whole-body imaging is an appropriate method to study disease mechanisms. PET is a noninvasive and extremely sensitive (femtomolar to picomolar) medical imaging technology. Being a quantitative and functional imaging modality, it is ideally suited for disease mechanism research. The PET technique is based on the detection of double γ-photons oppositely emitted from radiopharmaceuticals administered to patients, regardless of the location of the organ or tissue. Thus, PET imaging can simultaneously quantify functional changes in all organs and tissues of interest from a single, noninvasive scan. To perform PET

imaging, suitable radiopharmaceuticals are needed, and the radiopharmaceutical selected is based on the biological mechanism to be studied. For example, the glucose analog 2-deoxy-2-[^{18}F]fluoroglucose ([^{18}F]FDG) is a commonly used radiopharmaceutical in clinical PET imaging. Glucose is a universal compound that provides energy to cells, and [^{18}F]FDG is used to image energy consumption and metabolic activity in tissues. Over the past two decades, PET technology has made significant advancements in instrumentation and high-volume imaging data analysis. One notable development is the clinical application of total-body PET imaging systems, which has revolutionized the PET field. Conventional PET cameras can only image approximately 22 cm of the body at a time, making it impossible for whole-body pharmacokinetic studies with very short-lived radionuclides, such as oxygen-15. With total-body PET, all organs can be imaged simultaneously using low doses of radiopharmaceuticals and short-lived radionuclides. This technology is particularly useful for investigating complex diseases, including sleep disorders.

In this review article, we first provide an update on a 16-year-old historical overview of sleep and sleep apnea studies by Lavie [11]. Next, we focus on PET studies of sleep apnea and other sleep disorders. Compared with the large literature body of sleep apnea research in general, we found only 41 original research articles on human PET studies of sleep apnea and 10 original research articles on other sleep disorders. In addition, three articles were PET studies in animal models of sleep disorders. This review not only analyzes the current landscape of PET application in sleep apnea research but also pinpoints areas that warrant further investigation. PET research methodologies and results are summarized, and we aim to stimulate more research in this extremely exciting but, so far, less explored area of science and technology.

2. Methods

2.1. Literature search for sleep and sleep apnea

Following the example of Lavie [11], we conducted a literature search with the Web of Science database using two sets of search terms. First, we searched for publications that included the word *sleep* in the title, abstract, or as a keyword. Notably, the search parameter "author key word" was selected to represent keywords instead of the option "key word plus", which automatically generates keywords based on cited studies' titles. The second set of search terms included six terms: *sleep apnea, sleep apnoea, sleep disordered breathing, Pickwickian syndrome, upper airway occlusion during sleep,* and *snoring*. A publication was counted as a hit if it included any of these search terms (multiword terms surrounded with quotation marks) in its title, abstract, or keywords. The time of publication ranged from the January of 1965 to December of 2021. Database searches were conducted in September 2023.

2.2. Analysis of sleep apnea literature

Further investigation of the number of publications, contributing countries, and most cited sleep apnea studies was conducted following the analyses by Lavie [11]. These analyses were performed on research articles identified using the second set of search terms (*sleep apnea, sleep apnoea, sleep disordered breathing, Pickwickian syndrome, upper airway occlusion during sleep, snoring*). When reporting the countries with the most sleep apnea studies relative to the country population, we excluded countries with fewer than 10 sleep apnea studies to prevent them from appearing as top contributors entirely because of their small population size. When introducing the most cited studies, we manually excluded papers that did not focus on sleep apnea despite mentioning related terms and thus appearing among the detected publications in our Web of Science literature search.

2.3. Search and inclusion criteria for PET studies

PET-related articles searched from the Web of Science database were eligible if they met the following inclusion criteria: 1) was a peer-reviewed research article, 2) was written in English and published between 1992 and 2023, 3) investigated sleep apnea or its associations with different comorbidities, and 4) incorporated PET imaging. Fig. 1 summarizes the number of studies remaining after different filtering criteria.

Of the initial 128 articles, 50 remained after applying criteria 1-4, and four more were identified from their reference lists or other external sources. These 54 articles focused on PET studies of sleep apnea or other sleep-related phenomena. Among these 54 articles, 44 of them focused on sleep apnea study [4, 5, 12-53], among which three articles performed PET imaging studies in rodents subjected to experimental sleep apnea conditions [51-53]. Ten more articles [54-63] mimicking some of the features of sleep disorders or studying sleep duration and sleep quality were also included.

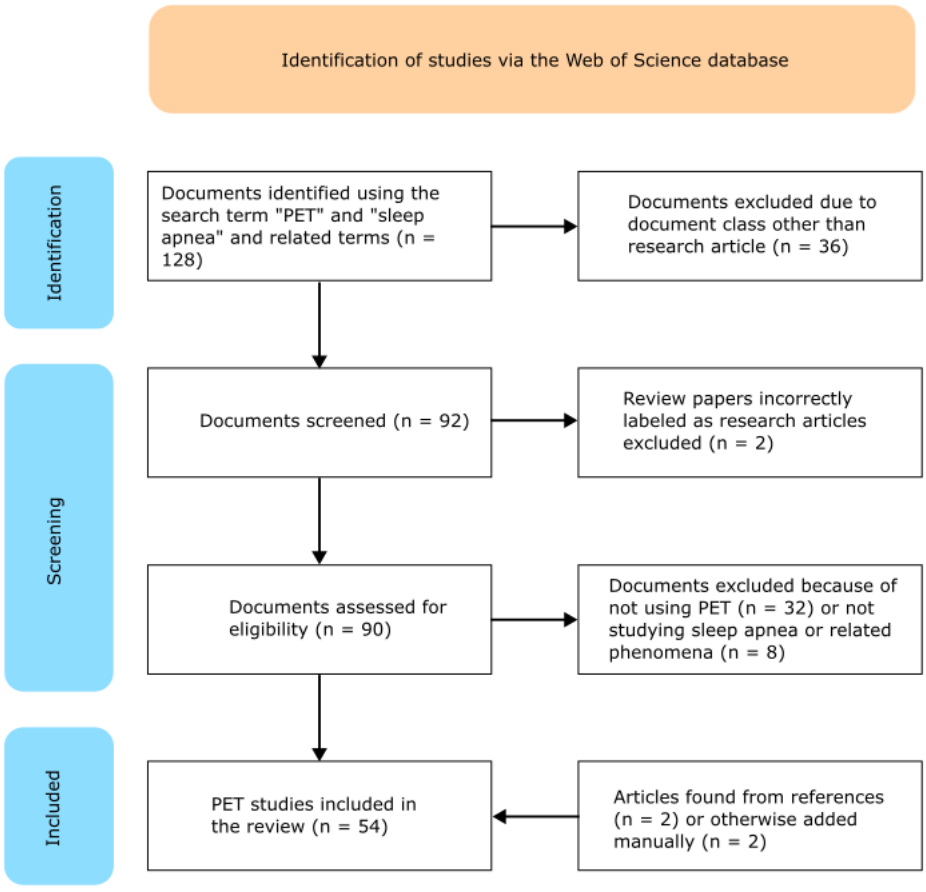

Fig. 1. Screening and selection process for relevant original articles included in this review.

3. Results

3.1. Development of sleep apnea literature

In 2008, Lavie published a thorough summary of past sleep apnea studies and the history of the disease. In our review, we evaluate how the literature has developed since Lavie's review [11]. Similarly, we performed a Web of Science article search using two sets of search terms. The first one included only the general word "sleep", but the second one contained multiple terms closely related to sleep apnea (see section 2.1 for further details). Unsurprisingly, the number of published papers has dramatically increased, and in particular, the proportion of review papers has grown with both search term sets (Table 1).

Table 1

Number of articles and proportions of different article types as searched from the Web of Science using two sets of search terms for the periods 1965–2006 and 1965–2021.

	"sleep"			"sleep apnea" and similar search terms		
	Lavie 2008 (1965–2006)	Current review (1965–2006)	(1965–2021)	Lavie 2008 (1965–2006)	Current review (1965–2006)	(1965–2021)
Number of hits	66,343	69,853	256,399	15,064	13,572	60,380
Article (%)	66.3	62.9	62.4	65.6	61.6	57.2
Review (%)	5.4	4.7	7.8	6.1	4.9	8.6
Editorial (%)	2.9	2.7	2.9	4.0	3.4	3.6
Letter (%)	3.0	2.8	2.0	5.6	5.3	3.7
Other (%)	21.8	27.0	24.9	18.8	24.8	26.8

Notably, in Lavie's study, the number of published research articles plateaus toward 2006 with both search term sets. However, this is likely caused by incomplete data due to slow publication processes because such phenomenon around 2006 is not visible in our searches conducted 15 years later (Fig. 2). Thus, the similar plateau of the number of sleep apnea studies

toward 2021 in our data is probably artificial. In Lavie's review, there is a sudden increase in the number of research articles related to the search term "sleep" right after 1990, and that seems not to be about slowly completing the database as the same jump is present in our data (Fig. 2). Despite our attempts to reproduce the literature search by Lavie [11], our results were slightly different (Table 1). This can be due to changes in the database or minor differences in the search parameters.

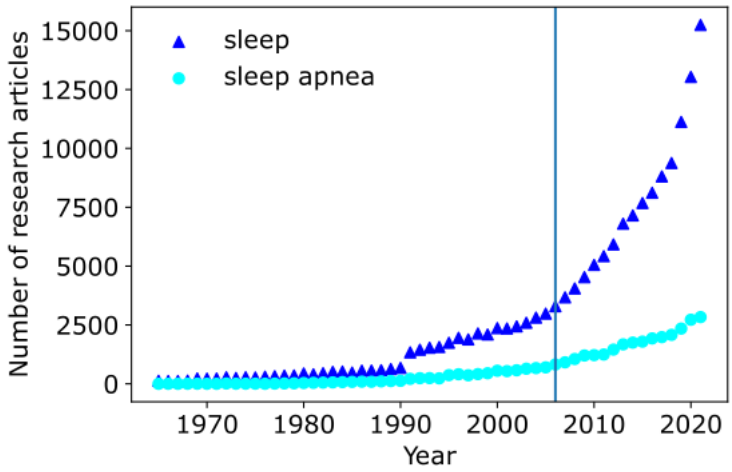

Fig. 2. Number of new research articles (y-axis) as a function of time (x-axis) with both search term sets according to the Web of Science.

The most notable change since 2006 in different countries' contribution to sleep apnea literature is that China is now the second biggest contributor to the total number of publications (Fig. 3A). In the review by Lavie covering publications until 2006, China was not among the countries with over 2% of the published research articles. Furthermore, Turkey, Brazil, South Korea, and Taiwan have become the top contributors, replacing Israel, Belgium, Finland, and Switzerland from the list of countries producing at least 2% of sleep apnea-related research articles. However, because investigating only the total number of publications favors countries with large populations, we also evaluated the number of sleep apnea-related research papers per million people (Fig. 3B). Countries with fewer than 10 sleep apnea publications were

excluded from the evaluation to avoid overrepresentation of countries with only a few publications and a small population size. Different European countries, the Nordics in particular, were well represented among the top contributors per million people, with Iceland, Finland, and Australia being the top three contributors. Australia, Canada, and Sweden were among the top contributing countries according to both metrics.

Fig. 3. A) Proportions and **B)** publications per million people of different countries' contributions to sleep apnea literature during 1965–2021, as reported in the Web of Science. Only countries with a proportion >2% are reported in **A)**, and the same number of top contributors is visualized in **B)**. Similar to [11], the proportions and publications per million people are calculated from research articles only, and no other article types are included.

Four of the ten most cited sleep apnea research articles were among the top 10 in the review by Lavie. Half of the six new papers in the list of the most cited studies were published after Lavie's review or shortly before it (Table 2). Notably, when investigating the most cited papers, article types other than original research were not considered. From the top 10 most cited papers list (Table 2) we removed three studies [64-66] only briefly mentioning sleep apnea or related term, but mainly focusing on other topics. We also excluded two guideline studies [67, 68] despite the Web of Science classifying them as original research, as well as an irrelevant paper [69] Investigating the average citations per year provides a less biased overview of the most impactful literature (Table 3), although most recently published studies are still at a disadvantage. Indeed, four of the ten articles with the top citations per year are not among the top 10 total citation studies, and all of those four have been published after 2015. From the list of top 10 citations per year articles (Table 3) we manually excluded five studies not focusing on sleep apnea or related phenomenon.

Table 2

Top 10 most cited sleep apnea studies according to the Web of Science database.

First author	Title of article	Year	Citations	Previous list*	Ref.
T Young	The Occurrence of Sleep-Disordered Breathing among Middle-Aged Adults	1993	7,297	Yes	[70]
PE Peppard	Prospective study of the association between sleep-disordered breathing and hypertension	2000	3,432	Yes	[71]
JM Marin	Long-term cardiovascular outcomes in men with obstructive sleep apnea-hypopnoea with or without treatment with continuous positive airway pressure: an observational study	2005	3,289	No	[72]
PE Peppard	Increased Prevalence of Sleep-Disordered Breathing in Adults	2013	2,702	No	[73]
FJ Nieto	Association of sleep-disordered breathing, sleep apnea, and hypertension in a large community-based study	2000	2,292	Yes	[74]
E Shahar	Sleep-disordered breathing and cardiovascular disease: cross-sectional results of the Sleep Heart Health Study	2001	2,092	No	[75]
HK Yaggi	Obstructive Sleep Apnea as a Risk Factor for Stroke and Death	2005	2,075	No	[76]
NC Netzer	Using the Berlin Questionnaire to identify patients at risk for the sleep apnea syndrome	1999	1,920	No	[77]
CE Sullivan	Reversal of obstructive sleep apnoea by continuous positive airway pressure applied through the nares	1981	1,885	Yes	[78]
VK Somers	Sympathetic neural mechanisms in obstructive sleep apnea	1995	1,783	No	[79]

*****The list published by Lavie [11].

Table 3

Top 10 most cited sleep apnea studies per year according to the Web of Science database.

First author	Name	Year	Citations per year	Citations	Ref.
AV Benjafield	Estimation of the global prevalence and burden of obstructive sleep apnoea: a literature-based analysis	2019	255	1,276	[1]
PE Peppard	Increased Prevalence of Sleep-Disordered Breathing in Adults	2013	245	2,693	[73]
T Young	The Occurrence of Sleep-Disordered Breathing among Middle-Aged Adults	1993	235	7,290	[70]
JM Marin	Long-term cardiovascular outcomes in men with obstructive sleep apnea-hypopnoea with or without treatment with continuous positive airway pressure: an observational study	2005	173	3,284	[72]
R Heinzer	Prevalence of sleep-disordered breathing in the general population: the HypnoLaus study	2015	158	1,424	[80]
RD McEvoy	CPAP for Prevention of Cardiovascular Events in Obstructive Sleep Apnea	2016	149	1,191	[81]

PE Peppard	Prospective study of the association between sleep-disordered breathing and hypertension	2000	143	3,425	[71]
B Cariou	Phenotypic characteristics and prognosis of inpatients with COVID-19 and diabetes: the CORONADO study	2020	139	555	[82]
HK Yaggi	Obstructive Sleep Apnea as a Risk Factor for Stroke and Death	2005	109	2,075	[76]
FJ Nieto	Association of sleep-disordered breathing, sleep apnea, and hypertension in a large community-based study	2000	96	2,292	[74]

3.2. PET studies

We found 54 original research articles on PET studies of sleep apnea, other types of sleep disorders and experimental sleep disorders, which were published in peer-reviewed international scientific journals (Table 4). There were 41 articles regarding PET studies in patients with sleep apnea, seven articles about different sleep disorders, and six dealing with experimental studies in humans or animal. In these studies, some patients had comorbidities of neurological, cardiovascular, metabolic diseases, or cancer. Some study subjects were healthy and were subjected to experimental conditions mimicking sleep disorders. The sample sizes ranged from 1 to 1,639 (Fig. 4). In most cases, [^{18}F]FDG was used to monitor the alteration of metabolic activity in the tissues or organs of interest. Studies on Alzheimer's disease, amyloid burden, and their relationship to hypoxia and sleep apnea usually employed radiotracers such as [^{11}C]PIB and [^{18}F]florbetapir. Carbon-11 (^{11}C)-labeled acetic acid ([^{11}C]acetate) was used to measure myocardial energetics. Perfusion studies were conducted using radiolabeled water ([^{15}O]H_2O) and [^{13}N]ammonia. In addition, several other radiopharmaceuticals have occasionally been used for targeted PET imaging of certain receptors. In the above-mentioned studies, PET was used in combination with other imaging techniques, including magnetic resonance imaging (MRI) and computed tomography (CT). MRI and CT facilitate the localization of radioactivity uptake in exact anatomical structures, thus being very useful. Radioactivity uptake in a region of interest (ROI) can be expressed as the standardized uptake value (SUV). SUV enables researchers and clinicians to compare radiotracer uptake across

different patients or over time, making it useful for monitoring disease progression or treatment response. SUV calculation uses the mean standardized uptake value (SUVmean) and the maximum standardized uptake value (SUVmax). SUVmean is the average uptake activity in ROI, whereas SUVmax represents the pixel with the highest radiotracer uptake activity in the same ROI. In many cases, the term SUV indicates SUVmean if not otherwise specified.

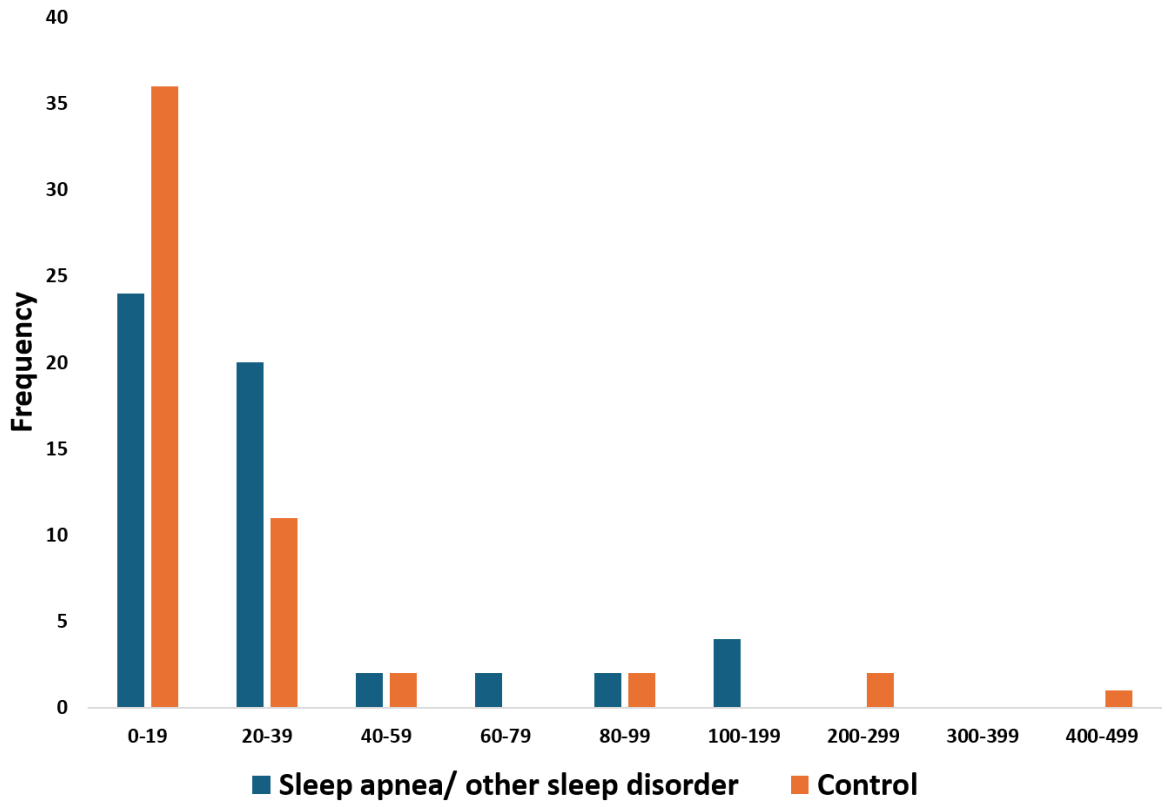

Fig. 4. Sample sizes of patients with sleep apnea/other sleep disorders and controls. Sample sizes range from 1 (case study) to 487 (cohort study); the sample sizes of most studies are less than 40.

Table 4

Summary of PET studies on sleep apnea and other sleep disorders.

	Sleep disorder	Comorbidity	Radiopharmaceutical	Imaging modality	ROI	Sample size	Key results	Reference
		Sleep apnea in patients						
1	OSA	N.D.	[^{18}F]FDG	PET	brain	2	Assess local cerebral glucose metabolic rate.	Mohsenifar 1994 [12]
2	OSA	unclear persistent sleepiness	[^{18}F]FDG	PET	brain	7	Patients with unclear persistent sleepiness after CPAP was found with abnormal metabolism in the frontal brain areas.	Antczak 2007 [13]
3	OSA	N.D.	[^{18}F]FDG	PET, MRI	brain	16	Significant cerebral metabolic changes were observed in SA patients compared with healthy controls, hypometabolism in the right hemisphere and prefrontal cortex.	Yaouhi 2009 [14]
4	OSA	obesity	[^{18}F]FDG	PET, MRI	tongue	72	Increased tongue size and adiposity contribute positively to OSA development.	Kim 2014 [5]
5	OSA	N.D.	[^{18}F]FDG	PET, MRI	upper airway	5	Upper airway inflammation.	Cohen 2022 [15]
6	OSA	obesity	[^{18}F]FDG, [^{15}O]H_2O	PET	whole body	15	OSA was associated with insulin resistance.	Koh 2022 [16]
7	OSA	N.D.	[^{18}F]FDG	PET, MRI	visceral adipose	16	The severity of OSA was positively associated with [^{18}F]FDG uptake in visceral adipose tissue after adjusting for age and body mass index.	Kundel 2021 [18]
8	OSA	atherosclerosis	[^{18}F]FDG	PET, MRI	cardiovasculature	5	Change of [^{18}F]FDG uptake in atherosclerotic plaques were observed before and after CPAP therapy.	Kundel 2018 [17]
9	OSA	tumor	[^{18}F]FDG	PET, CT	upper aerodigestive tract	9	Aerodigestive tract tumors led to airway blockage and further caused OSA.	Zhu 2014 [19]
10	OSA	Alzheimer's disease	[^{18}F]FBB [^{18}F]AV1451	PET	brain	119	Significant differences in amyloid burden, quantified by [^{18}F]AV-1451 uptake, were identified OSA and non-OSA patients.	Elias 2018 [20]
11	OSA	heart failure	[^{11}C]acetate	PET, CT	left ventricle	7	Cardiac efficiency of OSA patients improves after long-term CPAP therapy, as quantified by [^{11}C]acetate uptake.	Yoshinaga 2007 [21]
12	OSA	heart failure	[^{11}C]acetate [^{11}C]hydroxyephedrine	PET	heart	23	Short-term CPAP therapy might improve myocardial sympathetic neuron function but only exert limited effects on overall improvement in energetics.	Hall 2014 [22]
13	OSA	N.D.	[^{11}C]PIB	PET	brain	111	[^{11}C]PIB uptake increased in cognitively normal patients as OSA progress.	Sharma 2018 [23]

14	OSA	N.D.	[^{11}C]PIB	PET	brain	34	OSA was associated with markers of increased amyloid burden over the 2-year follow-up.	Jackson 2020 [24]
15	OSA	N.D.	[^{18}F]florbetapir [^{18}F]FDG	PET	brain	20	Over the course of the 2-year follow-up, increased amyloid accumulation was associated with OSA.	Mendes 2018 [25]
16	OSA	N.D.	[^{13}N]ammonia	PET	heart	23	No evidence was found that a short-term CPAP withdrawal leads to cardiovascular, renal or dermal microvascular impairment.	Schwarz 2016 [26]
17	OSA/short sleep duration	atherosclerosis	[^{18}F]FDG	PET, MRI	cardiovasculature	18	Vascular inflammation (TBR>1.6) is more prevalent in people with short sleep duration (<6h) compared with people sleep more (>6h), although not statistically significant. Additionally, sleep fragmentation contributes positively to carotid wall thickness.	Kundel 2021 [27]
18	OSA	N.D.	[^{18}F]FDG	PET, MRI	brain	13	After CPAP treatment, significant hypometabolism was observed in OSA patients' brains, including bilateral prefrontal areas, left cuneus and left cingulate cortex.	Ju 2012 [28]
19	OSA	Parkinson's disease	[^{11}C]DASB [^{11}C]DTBZ	PET, MRI	brain	39	Neither serotonin degeneration nor dopamine in the brain correlates with SDB development in PD patients.	Lelieveld 2012 [4]
20	OSA and non-OSA	Alzheimer's disease	[^{18}F]FDG [^{18}F]florbetapir	PET, MRI, CT	brain	96	[^{18}F]florbetapir PET images of cognitively unimpaired elderly individuals demonstrate that OSA/SDB patients displayed higher levels of Aβ-deposition, perfusion, and glucose uptake than healthy controls.	André 2020 [29]
21	OSA and non-OSA	N.D.	[^{18}F]FDG	PET	brain	22	Hypometabolism was observed in multiple areas in the right hemisphere and prefrontal cortex of the OSA patients.	Osorio 2014 [30]0/0/0000 0:00:00 AM
22	OSA	none, mild cognitive impairment, or Alzheimer's disease	[^{18}F]florbetapir	PET, MRI	brain	29	In cognitively normal and mild cognitive impairment groups, OSA subjects experienced faster annual increase in florbetapir uptake and decrease in CSF Aβ42 levels; as well as increases in CSF T-tau, and P-ta; compared with non-OSA participants. No significant variations in the biomarker changes over time were seen in the Alzheimer's disease group.	Bubu 2019 [31]

23	OSA	none, mild cognitive impairment	[^{18}F]florbetapir	PET, MRI	brain	31	$OSA^{+}/A\beta^{+}$ participants were more likely to progress from cognitively normal to mild cognitive impairment and from mild cognitive impairment to Alzheimer's disease, and progressed earlier, compared to other participants combined.	Bubu 2020 [32]
24	OSA	N.D.	[^{82}Rb]-chloride	PET, CT	cardiac	178	OSA is associated with myocardial perfusion abnormalities that suggest prior subclinical myocardial scarring or infarction.	Vaccarino 2022 [33]
25	OSA	Atherosclerosis	[^{18}F]FDG	PET, MRI	carotid arteries	11	Despite a trend toward a higher carotid wall thickness in OSA vs. non-OSA participants, no independent association between OSA and carotid plaque inflammation was found.	Shah 2023 [34]
26	OSA	N.D.	[^{11}C]PIB	PET, CT	brain	14	The OSA severity alone may not predict Aβ deposition in OSA patients with normal cognition.	Handa 2019 [35]
27	OSA	periodic limb movement disorder	[^{18}F]FDG	PET	brain	20	Sleep dysregulation and nocturnal hypoxia present in OSA patients, more than sleep fragmentation in periodic limb movement disorder patients, were associated with the alteration in cerebrospinal fluid and Alzheimer's disease biomarkers.	Fernandes 2022 [36]
28	OSA	multiple-system atrophy	[^{11}C]DTBZ	PET, SPECT	brain	13	Decreased pontine cholinergic projections may contribute to OSA in multiple-system atrophy.	Gilman 2003 [37]
29	OSA	N.D.	[^{11}C]PIB	PET, MRI	brain	19	The OSA group showed a higher PiB uptake in the right posterior cingulate gyrus and right temporal cortex as compared to non-OSA group.	Yun 2017 [38]
30	OSA	Parkinson's disease	[^{18}F]FP-CIT	PET, CT, MRI	brain	40	Dopamine availability in the caudate nucleus of the OSA group was significantly lower than that of the non-OSA group. On subgroup analysis, such association was found in female but not in male patients.	Oh 2023 [39]
31	OSA	N.D.	[^{82}Rb]-chloride	PET, CT	cardiac	32	Coronary endothelial vasoreactivity is impaired in insufficiently treated OSA patients compared to well-treated patients and controls.	Dunet 2016 [40]

32	OSA	N.D.	[^{18}F]FDG	PET, CT	brain	34	Cognitive impairment, reduced cerebral glucose consumption, and alterations in cerebrospinal fluid biomarkers were observed in OSA patients. Notably, cognition and brain glucose consumption improved after beneficial CPAP treatment.	Fernandes 2022 [41]
33	OSA	N.D.	[^{18}F]FDG	PET, MRI	neck	38	CPAP therapy reduces metabolic activity within the upper airway of adults with OSA. Furthermore, upper airway metabolic activity correlate with a noninvasive marker of inflammation.	Cohen 2023 [42]
34	OSA	N.D.	[^{18}F]FDG	PET, CT	carotid arteries, aorta, spleen, bone marrow	34	Patients with severe OSA are characterized by decreased baroreflex sensitivity and increased splenic activity.	Kaiser 2022 [43]
35	OSA	N.D	[^{11}C]PIB	PET, CT, MRI	brain	19	Severe OSA was associated with decreased gray matter−white matter contrast in amyloid tracer uptake, with significant correlation with clinical parameters of smoking and AHI.	Ylä-Herttuala 2022 [44]
36	OSA	N.D.	[^{11}C]PIB	PET	brain	19	Increased [^{11}C]-PiB uptake was seen in middle-aged cognitively intact patients with severe OSA. The changes in cortical Aβ uptake suggest that severe OSA itself may predispose to alterations related to AD already in middle age.	Ylä-Herttuala 2021 [45]
37	OSA	N.D	[^{18}F]NAV4694	PET	brain	34	Nocturnal hypoxemia was related to brain Aβ burden in OSA participants. Aβ burden and hypoxemia had differential impacts on cognition.	Cavuoto 2023 [46]
38	OSA	N.D.	[^{18}F]FDG	PET, MRI	brain	23	In sedentary patients with moderate to severe OSA, exercise training is associated with improvement in exercise capacity and OSA severity, but also increased CMRgl, attention/executive functioning.	Ueno-Pardi 2022 [47]

39	sleep disordered breathing	N.D.	[^{18}F]florbetapir	PET, MRI	brain	122	A higher sleep apnea severity was related to lower medial temporal lobe subregion volumes, but only in amyloid-positive individuals. In the whole cohort, lower whole hippocampal and CA1 volumes at baseline were associated with worse episodic memory performance at follow-up.	Andre 2023 [48]
40	sleep disordered breathing	mild cognitive impairment	[^{11}C]PIB	PET, MRI	brain	13	Among older adults with mild cognitive impairment, greater sleep-disordered breathing severity is associated with greater Aβ deposition. There were no significant associations between sleep-disordered breathing and Aβ deposition among cognitively normal participants.	Spira 2014 [49]
41	witnessed apnea	N.D.	[^{18}F]AV1451 [^{11}C]PIB	PET	brain	43	A significant association between witnessed apneas in cognitively unimpaired elderly and elevated tau-PET signal in tau-susceptible brain regions was identified.	Carvalho 2020 [50]
		Other sleep disorders in patients						
42	narcolepsy	N.D.	[^{18}F]FDG	PET	brain	71	Narcoleptic patients.	Huang 2016 [54]
43	rapid eye movement sleep disorder	multiple system atrophy	[^{18}F]FDG	PET	brain	1	A female senior patient with early-stage multiple system atropy showed decreased metabolism in the cerebellum and pons.	Takaya 2016 [55]
44	sleep–wake disruption	N.D.	[^{11}C]PIB	PET	brain	32	Sleep condition was associated with Aβ plaque accumulation across subsequent years in cognitively normal older adults.	Winer 2020 [56]
45	inadequate sleep	N.D.	[^{11}C]PIB	PET	brain	98	Greater amyloid accumulation, indicated as PiB distribution volume ratio, was observed in AD-sensitive brain regions in the cognitively healthy middle-aged adults with poorer sleep condition, including less adequate sleep, more sleep problems, and more sleepiness.	Sprecher 2015 [57]
46	excessive daytime sleepiness*	N.D.	[^{11}C]PIB	PET	brain	30	Aβ accumulation changes in 123 normal elderly individuals with different sleep conditions proved that poorer sleep leads to greater Aβ accumulation.	Spira 2018 [58]

47	rapid eye movement sleep disorder	depression	[^{18}F]FDG	PET, CT, MRI	brain	1	Case report highlighting REM sleep behavior disorder's potential interaction with depression and cognitive impairment, producing early dementia alike symptoms.	Clarke 2000 [59]
48	several self-reported sleep measures	N.D.	[^{18}F]florbetapir	PET, CT	brain	143	Study did not confirm the association between amyloid-PET burden and poor sleep quantity/quality in elderly population.	Gabelle 2019 [60]
		Experimental sleep disorders in human						
49	isocapnic hypoxia	N.D.	[^{15}O]H_2O	PET	gray matter	5	Various regions of the brain exhibited diverse patterns of blood flow changes in response to hypoxia.	Binks 2008 [62]
50	mouth breathing	N.D.	[^{18}F]FDG	PET, MRI	brain	10	Mouth breathing was found to correlate with abnormal cerebral metabolism.	Park 2021 [61]
51	acute sleep deprivation	N.D.	[^{18}F]FBB	PET, MRI	brain	20	Amyloid accumulation was observed in hippocampus and thalamus after acute one-might deprivation in both genders. For adults well rested, longer sleep hour is negatively related to amyloid accumulation.	Shokri-Kojori 2018 [63]
		Experimental sleep disorders in animal models						
52	OSA	lung carcinoma	[^{18}F]FDG	PET, CT	tumor	24	Mice exposed to IH had larger tumors with increased glucose uptake than in the control group.	Zhang 2019 [51]
53	hypoxia	N.D	[^{18}F]FDG	PET, CT	brain	30	Several brain regions had altered metabolism after the hypoxemia days, but recovered with five days in normal condition.	Mun 2022 [52]
54	hypoxia	N.D.	[^{18}F]FDG	PET, MRI	brown adipose tissue	NA	The brown adipose tissue exposed to hypoxia showed browning, but also increased tissue specific and systemic insulin resistance.	Dahan 2022 [53]

N.D., not defined. *Participants reported excessive daytime sleepiness and napping but no diagnosed sleep disorder.

3.3. Sleep apnea in patients

3.3.1. PET imaging with [^{18}F]FDG

Among the 41 articles on sleep apnea in patients (Table 4, Entry 1-41), [^{18}F]FDG was used in the research in 20 articles. [^{18}F]FDG-PET in combination with CT/MRI has wide application in neuropsychology and clinical assessments of cerebral structure and function. [^{18}F]FDG uptake can provide insights into brain metabolic activity, as a clinical tool for evaluating neurological changes in the brain. One of the pioneering studies was to use [^{18}F]FDG to assess local cerebral glucose metabolic rate in a case study of two patients with or without global oxygen supply dependency [12]. In 2007, Antczak et al. reported a [^{18}F]FDG-PET study in seven patients with unclear persistent sleepiness [13]. In their study, there were 167 patients with OSA, all of whom were treated with CPAP. Among them, 13 patients had persistent sleepiness, and the causes were not determined by routine clinical measurements. Eventually, seven patients underwent PET imaging, and abnormal [^{18}F]FDG uptake in the brain was observed in five patients, either hypometabolic or hypermetabolic, mainly in frontal brain areas. This study provided the earliest clinical evidence that [^{18}F]FDG-PET could be used to image brain injury in patients with OSA. Similarly, [^{18}F]FDG-PET was used to monitor the CPAP treatment effect by quantification of cerebral glucose uptake [28]. The research conducted by Fernandes et al. [41] expanded on the impact of CPAP therapy on glucose consumption in the brain and cognitive function. They additionally utilized [^{18}F]FDG-PET to investigate the effects of OSA and periodic limb movement disorder on cerebral glucose consumption and cerebrospinal fluid biomarkers for Alzheimer's disease. Their findings indicate that OSA patients, in particular, exhibit altered levels of Aβ42 and reduced cerebral glucose metabolism in the temporal regions [36]. In another study [14], [^{18}F]FDG-PET was used for brain imaging in 16 patients with newly diagnosed sleep apnea compared with 14 healthy controls. In these

patients, only minor clinical symptoms in terms of memory and motor impairments were observed. However, with [^{18}F]FDG-PET, significant cerebral metabolic changes were observed. Hypometabolism was found in multiple areas in the right hemisphere and prefrontal cortex of the patients. Reduced glucose metabolism was observed in the brains of cognitively normal elderly patients with OSA/SDB [31]. The impact of exercise training on the severity of OSA and various cognitive functions has been investigated, showcasing the versatility of [^{18}F]FDG-PET applications. As demonstrated by Ueno-Pardi and coworkers, exercise training has a favorable influence on exercise capacity, a reduction in the AHI, oxygen desaturation, and arousal index; enhancement of attention and executive functioning, and a rise in cerebral metabolic glucose rate in the right frontal lobe [47].

Previous studies have reported that increased tongue size and adiposity are associated with a higher risk of OSA [5]. Obesity often leads to enlarged upper airway soft tissue and further leads to OSA. The functions of the tongue and upper airway muscles are critical to breathing, and it is essential to understand the changes in their function in OSA. Accordingly, [^{18}F]FDG-PET has been used to quantify metabolic activity in tongue and upper airway tissues. In the study of 72 patients with OSA and obesity, reduced [^{18}F]FDG metabolism was observed in the tongue compared with the control group of 30 obese subjects without OSA [5]. The decreased metabolic activity was interpreted to be the result of denervation–reinnervation of the muscle fibers and independent of the fat content in the tongue or body mass index. This is an excellent example of the use of PET techniques for studying disease mechanisms in sleep disorders. On the other hand, Cohen et al. used [^{18}F]FDG-PET to show that CPAP treatment reduces metabolic activity of the pharyngeal mucosa of OSA patients. In addition, they demonstrated using nasal lavage proteomics that the [^{18}F]FDG-based measures correlated with inflammation [42]. In a recent study, five patients with OSA underwent [^{18}F]FDG PET/MRI to assess upper airway inflammation [15]. The upper airway is often a target for OSA therapy, and the PET

imaging and data analysis methods described in this study may be useful for monitoring the treatment response. Clinical evidence indicates that OSA is associated with obesity and type 2 diabetes. Using [^{18}F]FDG-PET imaging, Koh et al. demonstrated that OSA was associated with insulin resistance [16]. This is another excellent example of how PET techniques contribute to the study of disease mechanisms, in addition to their roles in medical diagnosis.

Visceral adipose tissue is an indicator of cardiovascular risk in patients with OSA. In a recent study including 16 patients with OSA, the severity of OSA was positively associated with [^{18}F]FDG uptake in visceral adipose tissue after adjusting for age and body mass index [17], whereas no significant association was found between OSA and visceral adipose volume. Compared with the mild OSA group, [^{18}F]FDG uptake in visceral adipose tissue in the moderate-to-severe OSA group was significantly higher. In addition, CPAP adherence was inversely correlated with visceral adipose volume. Therefore, PET can be a useful approach in patient stratification for further treatment planning of OSA. Furthermore, inflamed atherosclerotic plaques may rupture and cause severe cardiovascular events. Thus, monitoring the status of atherosclerotic plaques is sometimes required. In a study including five patients with OSA, [^{18}F]FDG-PET imaging was performed before and after CPAP therapy, and the differences in [^{18}F]FDG uptake in atherosclerotic plaques were observed. These results indicate that plaque inflammation in patients with OSA can be mitigated by CPAP treatment, and CPAP presented a similar effectiveness as statin therapy alone on non-OSA patients [18]. [^{18}F]FDG-PET imaging has also been employed to evaluate the effect of sleep duration on atherosclerosis and vascular inflammation by measuring metabolic activity within the arterial wall and in atherosclerotic plaques. Kaiser and colleagues investigated the relationship between OSA and cardiovascular disease by examining whether OSA severity is associated with a number of factors, such as hematopoietic activity of the spleen and bone marrow, and arterial inflammation. The results of the [^{18}F]FDG-PET scan showed an increase in splenic activity in

patients with severe OSA [43]. In 2021, Kundel et al. [19] compared the risks of atherosclerosis in individuals (48 out of 58 patients had OSA) with different sleep durations. The [^{18}F]FDG-PET images indicated that people with chronic short sleep duration (less than 6 hours) had increased [^{18}F]FDG uptake in the lesions and significantly higher atherosclerosis prevalence than those who slept more than 6 hours. Moreover, the study found that sleep fragmentation is related to increased carotid wall thickness. Similarly, in 2023 Shah et al. reported differences in carotid wall thickness of OSA patients and non-OSA participants, yet their [^{18}F]FDG investigation did not reveal significant differences in target-to-background ratios, indicating lack of carotid wall inflammation [34]. In rare cases, tumor growth blocks the airway and causes OSA. A study in China reported nine rare cases of patients with OSA and aerodigestive tract tumors [20]. At least in one case, a notable increase in [^{18}F]FDG uptake was observed in both palatine tonsils, suggesting malignancy.

3.3.2. PET imaging with other radiopharmaceuticals

Carbon-11 (^{11}C) is a positron-emitting radionuclide with a physical half-life of 20 minutes. ^{11}C-labeled compounds have the same elemental compositions and molecular structures as the corresponding non-radiolabeled compounds, and the biological functions of the radiolabeled compounds remain the same. One of the commonly used ^{11}C-labeled natural compounds is [^{11}C]acetate. Acetate has multiple biological functions, including protein acetylation and cellular metabolism. In 2007, Yoshinaga et al. [22] reported the use of [^{11}C]acetate for PET imaging of myocardial energetics in patients with OSA and heart failure. Patients were treated with CPAP, and myocardial energetics were quantified using [^{11}C]acetate uptake data. On the basis of these measurements, the authors concluded that longer-term CPAP therapy was beneficial for improving cardiac efficiency. Later, [^{11}C]acetate PET was used to measure myocardial efficiency in another study of patients with OSA and heart failure [23]. Among the 45 patients, 22 were treated with CPAP for 6–8 weeks and 23 remained without CPAP

treatment. In the same study, another radiopharmaceutical [^{11}C]hydroxyephedrine was used to measure the distribution of cardiac sympathetic neurons. Taken together, the results showed that short-term CPAP might improve myocardial sympathetic neuron function but only exert limited effects on overall improvement in energetics. [^{11}C]PIB is a small organic radioligand that binds to amyloid proteins and is commonly used for clinical PET imaging of neurological diseases, including Alzheimer's disease (AD). [^{11}C]PIB was used in a longitudinal study in people aged 55–90 years with normal cognition but OSA [24]. During the two-year follow up, increased [^{11}C]PIB signals were observed along with OSA progression. Thus, OSA was considered to be a contributing factor in amyloid deposition in cognitively normal subjects, and early intervention may be useful in these patients. However, in another study on the correlation between multimorbidity and amyloid deposition using [^{18}F]florbetafir PET imaging, there was no obvious correlation [26]. [^{13}N]Ammonia PET imaging is a well-established method for clinical measurement of myocardial blood flow, which can be used to monitor the relevant treatment in a quantitative manner. Similar to [^{11}C]acetate, [^{13}N]ammonia is isotopically radiolabeled, which enables the preservation of its biological function as the natural compound ammonia. [^{13}N]Ammonia is a good radiopharmaceutical for tissue perfusion. On the basis of [^{13}N]ammonia PET measurements, the authors [27] observed that short-term CPAP withdrawal had no effect on myocardial function. [^{82}Rb]-chloride is another radiotracer that is commonly used to evaluate myocardial perfusion. For example, it has been used by Dunet et al. to assess myocardial perfusion before and after CPAP treatment for OSA patients. Their findings emphasized the significance of effective CPAP treatment, as coronary endothelial vasoreactivity was found to be altered in insufficiently treated OSA patients compared to those who received proper treatment and controls [40]. Additionally, Vaccarino et al. utilized [^{82}Rb]-chloride to investigate the relationship between myocardial perfusion abnormalities and OSA. Their study involved twins and found that the risk of abnormal

perfusion was highest when both twins had OSA, although evolved AHI was also a risk factor on its own [33].

There are two beta-amyloid specific radiotracers that are frequently used in neurological disease studies, such as Alzheimer's disease, before or after the onset: [^{11}C]PIB and [^{18}F]florbetapir. The primary difference between these two radiotracers is that ^{18}F has a longer physical half-life. Bubu and colleagues utilized [^{18}F]florbetapir to investigate whether self-reported OSA diagnosis affects brain amyloid burden over time in cognitively normal, mildly cognitively impaired, or Alzheimer's disease elderly individuals. Additionally, several biomarkers from cerebrospinal fluid were measured. The study concluded that among elderly participants with no or mild cognitive impairment, OSA diagnosis was associated with a greater increase in amyloid burden over time compared to the non-OSA group. However, this phenomenon was not observed in AD patients [31]. In 2021, Bubu et al. continued their research using [^{18}F]florbetapir PET, demonstrating that individuals with both OSA and beta-amyloid burden have a synergistic risk. These results in elderly individuals with both conditions progressing faster to mild cognitive impairment or AD compared to other groups [32]. Additionally, Andre et al. studied the synergy between sleep-disordered breathing (SDB) and amyloid burden measured with [^{18}F]florbetapir, targeting different brain regions in cognitively intact elderly. They observed that in amyloid-positive participants, SDB severity was linked to lower medial temporal lobe subregion volumes [48]. In 2020, Andre et al. [30] examined [^{18}F]florbetapir PET/MRI images of 127 cognitively unimpaired elderly individuals and found that individuals with OSA/SDB displayed higher levels of Aβ-deposition, perfusion, and glucose uptake than healthy controls. Specifically, patients with OSA/SDB experiencing hypoxia were associated with increased Aβ-deposition. However, in a different study on the relationship between multimorbidity and amyloid deposition using [^{18}F]florbetafir PET imaging, there was no clear relationship, but OSA alone was associated with amyloid burden

[25]. The [^{11}C]PIB studies regarding the connection between OSA and beta-amyloid accumulation are somewhat contradictory. In one study, Ylä-Herttuala et al. observed increased [^{11}C]PIB uptake in cognitively normal middle-aged participants with OSA, indicating increased amyloid burden [45]. They later continued their study to determine if the typical contrast between [^{11}C]PIB uptake in gray matter and white matter was decreased in participants with severe OSA. Their findings were consistent with their previous study, as several OSA patients showed significantly decreased gray matter-white matter contrast. Additionally, smoking and AHI were found to significantly correlate with the contrast [44]. Yun et al. discovered that OSA patients exhibited increased [^{11}C]PIB uptake in the right posterior cingulate gyrus and right temporal cortex compared to the control participants [38]. In a longitudinal study conducted on individuals aged 55–90 with normal cognitive function but OSA, [11C]PIB was used. During the two-year follow-up, increased signals were observed alongside the progression of OSA. As a result, OSA was deemed a contributing factor in amyloid deposition in cognitively normal subjects, and early intervention may be beneficial for these patients. On the other hand, Handa et al. found increased [^{11}C]PIB cortical uptake in only one out of the 14 OSA patients examined [35]. Similarly, Spira et al. did not report any correlation between beta-amyloid accumulation and [^{11}C]PIB in cognitively normal adults. Among mildly cognitively impaired participants, higher AHI was related to greater amyloid deposition [49].

In addition to [^{18}F]florbetapir and [^{11}C]PIB, other radiopharmaceuticals have been employed to investigate the potential association between OSA and the development of AD. For instance, [^{18}F]NAV-4694 is a more recent tracer for beta-amyloid plaques that exhibits imaging characteristics similar to [^{11}C]PIB [83]. Cavuoto et al. administered it to assess the effects of hypoxemia and disrupted slow-wave sleep on amyloid burden and cognitive function. They observed a connection between OSA and increased amyloid deposits but discovered that

hypoxemia and amyloid burden impact distinct cognitive functions [46]. Besides beta-amyloid, tau protein is another hallmark of AD. [^{18}F]AV-1451, also referred to as [^{18}F]flortaucipir, is a radiotracer that targets tau protein. Carvalho and colleagues used [^{18}F]AV-1451 to explore whether apneas reported by bed partners are correlated with increased tau accumulation in cognitively normal elderly individuals. They found that participants with high [^{11}C]PIB uptake (i.e., amyloid burden) in the enthinal cortex and inferior temporal cortex had higher tau levels when experiencing apnea-related events. If the status of amyloid positivity was not taken into account, only the increase in tau levels in the inferior temporal cortex was found to be significant [50]. In a separate study, Elias et al. utilized [^{18}F]AV-1451 to examine tau levels in participants with and without OSA. However, they did not identify any significant differences between the two groups. Instead, their findings revealed a relationship between amyloid burden, OSA, and the moderating effects of BMI and the apolipoprotein E ε4 allele [20]. The ^{11}C-labeled radiotracers [^{11}C]DASB and [^{11}C]DTBZ are highly specific ligands for the serotonin transporter and vesicular monoamine transporter type 2. They are gaining more popularity in cell mechanism studies because they can be used to measure the distribution and integrity of these transporters based on their binding. In 2012, Lelieveld et al. investigated the cause of upper airway dysfunction of OSA/SDB observed in patients with Parkinson's disease [4]. [^{11}C]DASB and [^{11}C]DTBZ PET images showed that caudal brainstem and striatal dopaminergic activity did not correlate with OSA/SDB severity, indicating that they were not the cause of SDB observed in patients with Parkinson's disease. In 2003, Gilman and his team utilized [^{11}C]DTBZ PET to explore the basis of OSA in multiple-system atrophy. However, their findings did not show a correlation between OSA severity and [^{11}C]DTBZ binding. Instead, their other experiments suggested that decreased pontine cholinergic projections could be linked to OSA in multiple-system atrophy patients [37]. The difference in the availability of striatal dopamine between Parkinson's disease patients with and without OSA has been

investigated. In a study conducted by Oh et al., it was demonstrated that the OSA patients had significantly lower dopamine levels in the right caudate nucleus, but not in other regions [39].

3.4. Other sleep disorders in patients

In addition to OSA, [^{18}F]FDG-PET was used to measure glucose metabolic activities in other sleep disorders. The case report [34] published in 2016 described [^{18}F]FDG and [^{11}C]PIB PET scans of a 66-year-old female patient with both RBD and sleep apnea. Decreased uptake of [^{18}F]FDG was observed, showing decreased metabolism in the cerebellum and pons. A previous case study from the year 2000 documented a case of a patient with Rapid Eye Movement Behavior Disorder (RBD). The patient was a 74-year-old man with a history of depression and was later diagnosed with OSA. The results of the [^{18}F]FDG-PET scan were normal, while the MRI scan showed mild cortical atrophy and slight enlargement of the brain's ventricles. This case underscores the significance of accurately diagnosing RBD since its symptoms and potential interactions with depression and cognitive impairment can resemble early dementia. [^{18}F]Florbetapir and [^{18}F]florbetaben ([^{18}F]FBB) are other ^{18}F-labeled tracers that have been clinically used to measure β-amyloid plaques in the brain. [^{18}F]Florbetapir biodistribution also reflects brain perfusion. Gabelle and colleagues employed [^{18}F]florbetapir to examine the impact of various sleep measures and disorders on amyloid burden in different cortical regions. They gathered self-reported data on nighttime sleep duration, daytime nap duration, risk of sleep disorders like OSA, RBD, restless legs syndrome, insomnia, and use of sleep medication, but none of these factors demonstrated a significant connection to amyloid burden in their study [60]. [^{11}C]PIB PET imaging also provides valuable insight to Aβ accumulation changes in cognitively normal elderly individuals with different sleep conditions [37]. In 2015, Sprecher et al. investigated adults suffering from chronic inadequate sleep and sleepiness and found that they tended to have higher PIB uptake (higher Aβ accumulation) in AD-sensitive brain regions [38]. Similarly, in 2018, a longitudinal study conducted by Spira et

al. [39] compared Aβ accumulation changes in 123 normal elderly individuals with different sleep conditions, and their results are consistent with the observations of Sprecher et al. [^{11}C]PIB PET images taken at baseline and 15-year follow-up showed higher PIB uptake in elderly individuals with worse sleep efficiency than people with proper sleeping, which indicates that older individuals with poor sleep quality are predicted to be more prone to the Aβ accumulation over time [39].

3.5 Experimental sleep disorder in humans

Water (H_2O) is a molecule of life and a critical medium for cell survival. The transportation of water in tissues reflects the biological activity of the tissues. Accordingly, PET imaging with radiolabeled water [^{15}O]H_2O is one way to visualize and quantify tissue function in health and disease. Binks et al. [32] applied this technique to measure gray matter blood flow in five healthy individuals who had been subjected to hypoxic conditions in a laboratory environment. Upon hypoxia, changes in blood flow occurred in different patterns across the brain, indicating large heterogeneity of the brain regions in response to hypoxia. Additionally, mouth breathing, considered as a factor that can contribute to sleep disorders, is also found to correlate with abnormal cerebral metabolism. In 2020, Park and coworkers [35] compared the metabolic differences between people in individuals with varying dominant breathing patterns. The research revealed that individuals who predominantly breathed through their mouths exhibited reduced [^{18}F]FDG uptake in cerebral areas compared to those who predominantly breathed through their noses.[^{18}F]FBB is another ^{18}F-labeled tracer that has been clinically used to measure β-amyloid plaques in the brain. In 2018, Shokri-Kojori et al. [36] used [^{18}F]FBB-PET imaging to study the effects of acute sleep deprivation in β-amyloid accumulation in human brains. They observed that even after one night of sleep deprivation [^{18}F]FBB uptake increased in AD-sensitive regions, namely the hippocampus and thalamus.

3.6 Experimental sleep disorder in animals

Animal models offer a chance for disease mechanism investigations. Unfortunately, our search only yielded three preclinical studies in the context of sleep research. In each of these three studies, the same radiotracer [^{18}F]FDG was employed. In addition to neurological, metabolic, and cardiovascular diseases, population-based statistics have shown that certain types of cancers have a higher prevalence among patients with OSA. However, it is not clear whether OSA causes the formation of cancer or whether cancer is a comorbidity with OSA. In the preclinical setting, it is a challenging task to generate a disease model in animals to mimic the spontaneous cancer formation induced by OSA. Instead, it is feasible to first establish the tumor in animals, apply conditions mimicking OSA, and observe tumor growth compared with the control groups. In a preclinical study reported by Zhang et al. in 2019 [29], the researchers used a mouse model to mimic individuals with OSA and Lewis lung cancer subjected to IH. The findings showed that mice exposed to IH had larger tumors with increased glucose uptake than in the control group. However, after endostatin administration, both the control and IH groups exhibited reduced glucose uptake in their tumors. Dahan and his team utilized mice to investigate the influence of intermittent hypoxia (IH) on brown adipose tissue. The mice were divided into two groups, with one group experiencing reduced oxygen levels during sleep and the other group serving as a control with normal oxygen levels. The researchers then employed [^{18}F]FDG PET scans to analyze the brown adipose tissue and found that the hypoxia group exhibited decreased glucose uptake compared to the control group. Interestingly, a similar trend was observed in the skeletal muscle [53]. Mun and colleagues explored the impact of hypoxia on brain metabolism by dividing rats into groups that were exposed to hypoxia for different durations in a chamber. After five days of hypoxia exposure and five days of recovery, all rats underwent [^{18}F]FDG scans. The study revealed that most brain regions were affected by the hypoxia treatment, but the differences between the hypoxia and control groups were no longer

statistically significant after five days of recovery [52]. However, the small sample size may have impacted the conclusions drawn from this study.

4. Discussion

This review provides a literature analysis of the publications regarding sleep and sleep apnea research during 1965–2021, with an analytical methodology similar to that published in Lavie's study investigating the period 1965–2006. This approach allowed us to compare the data and determine the development trends during different periods. We observed that while the number of published sleep apnea studies has kept increasing, the number of general sleep-related papers has exploded, particularly in the last three years of the investigated period. In 1990, there was a sudden increase in the published sleep studies visible both in Lavie's study and here, but the reason for this remains unclear. Our results show that the biggest change since Lavie's study in the contributing countries is the rise of different Asian countries, although if scaled by population size, Europe and the Nordics in particular are best represented among the top contributors. High scientific output combined with very small population results in the large proportion of Iceland depicted in Fig. 3. Notably, the number of sleep apnea studies published during 1965–2006 was slightly different in our search and in the search by Lavie despite the use of the same search criteria and database. Surprisingly, our search revealed fewer published studies, although the decrease was less than 10%. This decrease could be because of either changes in the database itself or a different definition of the search field "key word". The Web of Science has two keyword-related search options called "key word plus" and "author key word", we do not know which definition was used in the study by Lavie. Here "author key word" was used.

The emergence of AI tools has facilitated the discovery of new strategies for academic literature research. While these tools are capable of delivering extensive and relevant articles, their results are not always reproducible. Moreover, they typically require a distinct set of

search terms, which may differ from the more conventional search methods that use structured 'IF' and 'AND' statements for different parts of the papers. In this study, we briefly experimented with two AI search methods, Paper Digest and Semantic Scholar, using our search terms (PET and six sleep apnea related terms). However, the results showed that sleep apnea dominated the search results, while PET imaging was largely overlooked. While it would be beneficial for these tools to have a smaller set of search terms, using different keywords in different search tools can make the review process confusing. Many literature search guidelines, such as PRISMA, emphasize the importance of clearly describing the search process. However, not utilizing tools that can be practical and useful is a significant sacrifice. Therefore, it is worth considering whether the guidelines should be updated to better accommodate the use of new AI tools. Despite the substantial surge in research on various aspects of sleep apnea, the use of PET imaging in sleep apnea and other sleep disorders remains extremely limited, with only 54 original research articles compared with 60,380 articles about sleep apnea research. Throughout the 20^{th} century, only a few clinical PET imaging studies, including those of patients with sleep disorders, have been published. Most studies appeared only after 2010. This may be attributed to several reasons. First, compared with sleep apnea research, the clinical PET technique has a much shorter history. Although the first evidence of the medical use of positron emission was published in 1951, the first human PET tomograph was published in 1974, and PET cameras have become increasingly available since the 1990s. Second, to produce positron-emitting radionuclides (e.g., ^{18}F and ^{11}C) for routine clinical use, sophisticated instrumentation, such as medical cyclotrons, is required. The setup and maintenance of a radionuclide production facility is costly and time consuming. Third, similar to radionuclide production, the manufacturing of radiopharmaceuticals (e.g., [^{18}F]FDG) requires large investment and skilled personnel with appropriate training for radiation work. Finally yet importantly, in clinical practice, it is not a conventional procedure to send patients

for PET imaging only because they have sleep disorders, as PET imaging is not an essential tool for the diagnosis of sleep disorders per se.

In addition to instrumentation, the availability of suitable radiopharmaceuticals is critical to advance PET applications in the clinic. [^{18}F]FDG, [^{11}C]acetate, and [^{15}O]H_2O are among the first radiopharmaceuticals that have become available for clinical PET imaging in general. Thus, it is understandable that they were the first radiopharmaceuticals used in PET research of sleep apnea and other sleep disorders. With time, an increasing number of PET radiopharmaceuticals have become available, which enable the specific targeting of different types of receptors, biological pathways, and mechanisms. For example, [^{11}C]PIB, [^{18}F]florbetapir, and [^{18}F]FBB are useful imaging agents that bind amyloid proteins. Similarly, [^{18}F]AV1451 is also intended for binding pathological insoluble protein formation in the brain, and its target is tau proteins. [^{11}C]DASB is a ligand targeting the serotoninergic system, and [^{11}C]DTBZ targets the striatal dopaminergic system. [^{11}C]Hydroxyephedrine has been used to map the distribution pattern of cardiac sympathetic neurons. In addition, [^{13}N]ammonia was used in one study of patients with OSA based on its utility in tissue perfusion measurement.

Sleep apnea and other sleep disorders affect multiple organs and tissues. As listed in Table 4, in most of the PET studies, the research targets were the brain, heart, upper airway tissues, and adipose tissues. Thus far, the studies mainly provide evidence of links between sleep disorders and tissue functional changes with PET techniques and methodologies in the data analysis, which is definitely valuable. In the future, it will be beneficial to conduct in-depth disease mechanism studies at the cellular and molecular level using PET techniques. Therefore, it may be helpful to use relevant disease models in animals to mimic clinical observations. Surprisingly, only very few PET studies using animal models of sleep disorders have been reported. Our literature review uncovered only three preclinical studies focusing on PET imaging in sleep disorders or simulated OSA conditions. It is important to note that these

studies varied greatly in their applications, yet they all employed the same radiopharmaceutical, [^{18}F]FDG. Consequently, the extent of animal research in this area remains largely untapped. With animal experiments, it is feasible to collect the tissues of interest in larger quantities and perform in-depth histological and molecular analyses, and to correlate radiopharmaceutical uptake with cell subpopulations, gene expression, and protein expression. These approaches may enhance our understanding of the molecular basis of sleep disorder-induced tissue functional changes. In addition, with animal studies, it is possible to increase the sample sizes when justified. In general, the clinical studies listed in Table 4 have relatively small sample sizes for various reasons. One of the reasons may be the limited availability of patients with clinically similar indications and physiological parameters, such as age, gender, genetic background, and comorbidity, which can be conveniently modeled with animals.

Sleep disorders, such as OSA, insomnia disorder, and restless legs syndrome, pose a significant challenge to healthcare systems and their limited resources. It is vital to identify patients with the highest risk of comorbidity or who will derive the most benefit from treatments. Recently, there has been considerable interest and discussion on the various clinical and physiological phenotypes of OSA, as well as to a lesser extent, other sleep disorders. However, the results have been controversial, and several unresolved issues remain. Further insight is needed, especially regarding how sleep disorders and their various phenotypes impact cardiometabolic and cognitive health. In the field of OSA, researchers are moving beyond traditional measures such as AHI and exploring PET studies as a potential tool. While PET imaging is likely to be a powerful tool for studying the mechanisms of sleep disorders, its use requires specialized skills and infrastructure. As a result, PET studies are unlikely to be included in standard clinical operating procedures, not at least in the near future.

In the context of sleep research, both clinical and preclinical PET studies have shown great potential in identifying the relationships between disease phenotypes, tissue functional changes,

and biomarker expression. PET's strength lies in its ability to perform functional imaging, allowing it to quantify functional changes in all tissues with a single non-invasive scan. This makes it particularly useful for studying the intricate mechanisms of diseases, as demonstrated in the large volume of oncological research. As clinical researchers increasingly recognize the value of PET, it is likely that it will be more widely adopted in sleep clinics and other clinical settings. However, the need for specialized skills and infrastructure remains a barrier to broader use. Nonetheless, the rapid expansion of PET facilities in countries and regions around the world in recent years should facilitate the adoption of PET for a wider range of applications.

5. Conclusion

During the last 30 years or so, there has been a dramatic increase in the number of articles in sleep research in general, and the landscape of contributing countries has changed significantly. Regarding the study of sleep apnea, 73,952 articles have been found in the period from 1965 to 2021, which has steadily increased with time. In contrast to the large body of literature on sleep and sleep apnea research, PET imaging was described in only 54 original research articles. Nevertheless, extremely interesting findings have been presented in several medical indications, including neurological, cardiovascular, and metabolic diseases, and cancer. These results indicate that PET is indeed a suitable technique for the identification of pathological changes in a sensitive and noninvasive manner in patients with sleep disorders. Thus far, PET studies have mainly focused on clinical use to identify the links between sleep disorders and pathological changes. In the future, it will be equally important to study the underlying mechanisms using PET. To perform in-depth research at the molecular level with relatively large sample sizes, it would make sense to use disease models in animals as well. We hope that this review article will encourage further collaboration in sleep apnea research among experts in disease modeling, PET imaging, radiopharmaceutical chemistry, and biomedicine.

Practice points

- The number of sleep research articles has dramatically increased since 1990.
- PET was used in only 54 original research articles on sleep apnea, other sleep disorders, or on experimental sleep disorder conditions in humans or animals.
- PET is useful for identifying the link between sleep apnea and pathological changes.
- Only a few PET studies have been conducted in animal models of sleep apnea.

Research agenda

- More clinical evidence of PET imaging in patients with sleep disorders and/or multimorbidities is required. PET imaging may provide an early detection of pathological changes that may not be discovered by conventional diagnostic methods for sleep apnea.
- PET techniques should be incorporated into disease mechanism studies in clinical and preclinical settings. This will eventually facilitate the use of PET in the clinic for the benefit of patients.

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