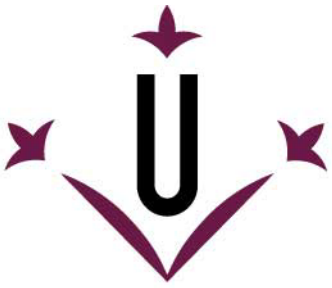
# Cuantificación, evaluación y gestión de la salud del sueño: hacia la incorporación del sueño como pilar de la salud

Iván David Benítez Iglesias



Universitat de Lleida

# TESIS DOCTORAL

# Cuantificación, evaluación y gestión de la salud del sueño: hacia la incorporación del sueño como pilar de la salud

Iván David Benítez Iglesias

Memoria presentada para optar al grado de Doctor por la Universidad de Lleida
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UNIVERSIDAD DE LLEIDA

# *Resumen*

Facultad de Medicina

Departamento de Ciencias Médicas Básicas

Doctor

**Cuantificación, evaluación y gestión de la salud del sueño: hacia la incorporación del sueño como pilar de la salud**

por Iván David BENÍTEZ IGLESIAS

La sociedad actual es plenamente consciente de la importancia de adoptar hábitos saludables para gozar de una buena salud. Así, la actividad física, una alimentación adecuada y el bienestar emocional son notablemente reconocidos como determinantes de la salud. Sin embargo, y a pesar de la creciente base de evidencia científica, el sueño sigue siendo poco reconocido como pilar de la salud. La presente tesis pretende contribuir al aumento de la comprensión sobre el impacto del sueño en la salud y la enfermedad, y para ello plantea hipótesis basadas en la medición, evaluación y gestión de la salud del sueño.

Primero, y dada la necesidad de contar con herramientas válidas para evaluar la salud del sueño, se llevó a cabo un estudio de traducción, adaptación y validación del cuestionario SATED, desarrollado por el Dr. Daniel Buysse. Los resultados de este proceso fueron muy satisfactorios a nivel psicométrico, lo que convierte a nuestra versión española del cuestionario SATED en la primera herramienta validada en español para medir la salud del sueño. Una vez lograda la validación del cuestionario, se realizó un estudio poblacional para evaluar la asociación de la salud del sueño con el estado general de salud de las personas. Además, se comparó la magnitud de la relación con la de otros aspectos relacionados con el estilo de vida como la dieta o la actividad física. Los resultados de este

estudio revelaron una asociación significativa entre la calidad del sueño y la percepción general de la salud, siendo la magnitud de la asociación comparable a la de otros hábitos saludables.

Segundo, en el ámbito de la gestión de la salud del sueño, esta tesis ha tratado la optimización de la gestión de patologías del sueño, usando como caso de estudio la gestión de la Apnea Obstructiva del Sueño (AOS). Así, se llevó a cabo un metaanálisis de datos individualizados de estudios que comparan modelos de gestión de la AOS basados en atención primaria con otros basados en unidades de sueño especializadas. Los resultados de este análisis demostraron que la gestión en atención primaria es una estrategia coste-efectiva en comparación con la gestión en unidades especializadas.

Por último, y dado el gran impacto que la pandemia de la COVID-19 ha tenido en nuestra sociedad, se evaluó su impacto en la calidad del sueño de la población, constatándose una disminución en la calidad del sueño que a su vez se relacionó estrechamente con el estado emocional de los individuos. En esta línea, también se realizó un análisis exhaustivo de la calidad del sueño en pacientes ingresados en unidades de cuidados intensivos por COVID-19. Los resultados revelaron una mala calidad del sueño en el 60.5% de los pacientes a los tres meses de seguimiento, que persistió en el 48.3% de los pacientes a los seis meses. Estos hallazgos subrayan la importancia de identificar y abordar las alteraciones del sueño en situaciones complejas a nivel poblacional e individual, como lo ha sido la pandemia de la COVID-19.

En conclusión, esta tesis defiende la importancia del sueño saludable en nuestras vidas, y postula la necesidad de promover estrategias que reconozcan su relevancia mediante la promoción de la higiene del sueño, y la gestión adecuada de las patologías que afectan su calidad.

UNIVERSITAT DE LLEIDA

# *Resum*

Facultat de Medicina

Departament de Ciències Mèdiques Bàsiques

Doctor

**Quantificació, avaluació i gestió de la salut de la son: cap a la incorporació de la son com a pilar de la salut**

per Iván David BENÍTEZ IGLESIAS

La societat actual és plenament conscient de la importància d'adoptar hàbits saludables per a gaudir d'una bona salut. Així, l'activitat física, una alimentació adequada i el benestar emocional són ben coneguts com a determinants de la salut. No obstant això, i malgrat la creixent base d'evidència científica, la son continua sent poc reconegut com a pilar de la salut. La present tesi pretén contribuir a augmentar la comprensió de l'impacte de la son en la salut i la malaltia, i per a això planteja hipòtesis basades en el mesurament, avaluació i gestió de la salut de la son.

Primer, i donat la necessitat de comptar amb eines vàlides per a avaluar la salut de la son, es va dur a terme un estudi de traducció, adaptació i validació del qüestionari SATED, desenvolupat pel Dr. Daniel Buysse. Els resultats d'aquest procés van ser molt satisfactoris a nivell psicomètric, la qual cosa converteix a la nostra versió espanyola del qüestionari SATED en la primera eina validada en espanyol per a mesurar la salut de la son. Una vegada aconseguida la validació del qüestionari, es va realitzar un estudi poblacional per a avaluar l'associació de la salut de la son amb l'estat general de salut de les persones. A més, es va comparar la magnitud de la relació amb la d'altres aspectes relacionats amb l'estil de vida com la dieta o l'activitat física. Els resultats d'aquest estudi van revelar una associació significativa entre la qualitat de la son i la percepció general de la salut,

sent la magnitud de l'associació comparable a la d'altres hàbits saludables.

Segon, en l'àmbit de la gestió de la salut de la son, aquesta tesi ha tractat l'optimització de la gestió de patologies de la son, utilitzant com a cas d'estudi la gestió de l'Apnea Obstructiva de la son (AOS). Així, es va dur a terme un metaanálisis de dades individualitzades d'estudis que comparen models de gestió de la AOS basats en atenció primària amb altres basats en unitats de la son especialitzades. Els resultats d'aquesta anàlisi van demostrar que la gestió en atenció primària és una estratègia cost-efectiva en comparació amb la gestió en unitats especialitzades.

Finalment, i donat el gran impacte que la pandèmia de la COVID-19 ha tingut en la nostra societat, es va avaluar el seu impacte en la qualitat de la son de la població, constatant-se una disminució en la qualitat de la son que al seu torn es va relacionar estretament amb l'estat emocional dels individus. En aquesta línia, també es va realitzar una anàlisi exhaustiva de la qualitat de la son en pacients ingressats en unitats de vigilància intensiva per COVID-19. Els resultats van revelar una mala qualitat de la son en el 60.5% dels pacients als tres mesos de seguiment, que va persistir en el 48.3% dels pacients als sis mesos. Aquestes troballes subratllen la importància d'identificar i abordar les alteracions de la son en situacions complexes a nivell poblacional i individual, com ho ha estat la pandèmia de la COVID-19.

En conclusió, aquesta tesi defensa la importància de la son saludable en les nostres vides, i postula la necessitat de promoure estratègies que reconeguin la rellevància de la son mitjançant la promoció de la higiene de la son, i la gestió adequada de les patologies que afecten la seva qualitat.

UNIVERSITY OF LLEIDA

# *Abstract*

Faculty of medicine

Department of Basic Medical Sciences

Doctor

**Quantification, evaluation, and management of sleep health: towards the inclusion of sleep as a pillar of health**

by Iván David BENÍTEZ IGLESIAS

The current society is fully aware of the importance of adopting healthy habits to enjoy good health. Thus, physical activity, proper nutrition, and emotional well-being are widely recognized as determinants of health. However, despite the growing scientific evidence base, sleep is still under-recognized as a cornerstone of health. This thesis aims to enhance the understanding of the impact of sleep on health and disease by proposing hypotheses based on the measurement, assessment, and management of sleep health.

First, and given the imperative need for valid tools to assess sleep health, a translation, adaptation, and validation study of the SATED questionnaire developed by Dr. Daniel Buysse was carried out. The results of this process were highly satisfactory at the psychometric level, making our Spanish version of the SATED questionnaire the first validated tool in Spanish for measuring sleep health. Once the validation of the questionnaire was achieved, a population-based study was conducted to assess the association between sleep health and the general health status of individuals. Furthermore, the magnitude of this relationship was compared to that of other lifestyle-related factors, such as diet or physical activity. The results of this study revealed a significant association between sleep

quality and the general perception of health, with the magnitude of the association comparable to that of other healthy habits.

Second, in the field of sleep health management, this thesis addressed the optimization of sleep disorder management, using the case study of Obstructive Sleep Apnea (OSA) as management. A meta-analysis of individualized data from studies comparing primary care-based management of OSA with specialized sleep unit-based management was conducted. The results of this analysis demonstrated that primary care management is a cost-effective strategy compared to that of specialized units.

Finally, given the significant impact of the COVID-19 pandemic on our society, its impact on the population's sleep quality was assessed, revealing a decrease in sleep quality that was closely related to emotional state of individuals. In this context, a comprehensive analysis of sleep quality in COVID-19 patients admitted to intensive care units was carried out. The findings revealed poor sleep quality in 60.5% of patients at three months of follow-up, persisting in 48.3% of patients at six months. These findings underscore the importance of identifying and addressing sleep disturbances in complex situations at both the population and individual levels, as has been the case with the COVID-19 pandemic.

In conclusion, this thesis advocates for the importance of healthy sleep in our lives and raises the need to promote strategies that recognize the relevance of sleep through the promotion of sleep hygiene and the appropriate management of conditions affecting its quality.

# *Agradecimientos*

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Gracias a mi hermano Raúl, quien ha sido un pilar fundamental en mi vida. Él me ha cuidado, enseñado y dirigido, además de ser el responsable de despertar en mí la pasión por la investigación que siento hoy en día. No tengo ninguna duda de que sin ti nada de esto hubiese ocurrido. Igualmente, es imposible no recordar a mis hermanitos, José Luís y Letizia. Gracias por quererme sin límites y hacerme sentir siempre protegido, os amo.

Dedicar unas palabras a mi madre es uno de los trabajos más gratos del final de este camino. Sin duda la persona más importante en mi vida, que me ha hecho sentir siempre tremendamente afortunado. Gracias mamá por ser una fuente de cariño ilimitada que me ha permitido aprender las cosas más fundamentales de la vida.

Por último, quiero agradecer a mis amores, mis hijos Hugo y Adriana, y mi mujer, Elsa. La paciencia infinita, el cariño incondicional y el apoyo continuo es parte esencial en la realización de esta tesis doctoral.

Gracias de corazón a todos.

Iván David Benítez Iglesias
22/09/2023

# *Índice*

# *Lista de abreviaciones*

| | |
|---|---|
| EEG | Electroencefalograma |
| AASM | American Academy of Sleep Medicine |
| SWS | Slow wave sleep |
| SHI | Sleep health index |
| OMS | Organización Mundial de la Salud |
| ESCA | Encuesta de salud pública de Catalunya |
| AUC | area under the ROC curve |
| AOS | Apnea obstructiva del sueño |
| IAH | Índice de apnea-hiponea |
| US | Unidad de sueño |
| CPAP | continuous positive airway pressure |
| SDRA | Síndrome de distrés respiratorio agudo |
| UCI | Unidad de cuidados intensivos |
| AFE | Análisis factorial exploratorio |
| AFC | Análisis factorial confirmatorio |
| SHS | Sleep health scale |
| PSQI | Índice de calidad del sueño de Pittsburgh |

*Para mi mamá,*
*ella es y será todo para mí.*

# *1. Introducción*

La conciencia social, en relación con la importancia de fomentar iniciativas que promuevan la salud del individuo, ha incrementado en consonancia al aumento del conocimiento de su impacto positivo sobre el estado de salud. Actualmente, es asumido que la actividad física, bienestar emocional y adquirir una correcta alimentación son determinantes para la salud (1). Igualmente, la creciente evidencia sobre la asociación del sueño con el estado de salud está posicionando la higiene del sueño como un pilar fundamental para la salud física y mental del individuo (2–6) (Figura 1). Sin embargo, en el entorno actual y las dinámicas de la sociedad dificultan el establecimiento de hábitos de sueño saludable, afectando directamente a su calidad, regularidad y duración (7–9). En este contexto, existe la necesidad de definir la salud del sueño y crear herramientas de medición cuantitativas que permitan seguir profundizando en la compresión de cómo un sueño saludable influye en el bienestar integral del individuo. Este conocimiento permitirá definir e impulsar estrategias en salud que promocionen el sueño como fuente de salud.

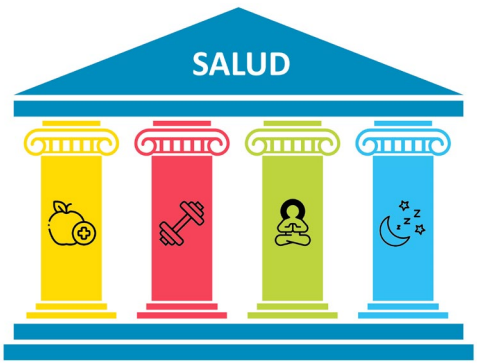


*Figura 1.* ***Representación de los pilares de salud.*** *Cada pilar representa un hábito que promociona la salud del individuo: alimentación saludable (amarillo), actividad física (rojo), bienestar emocional (verde), higiene del sueño (azul). Autoría propia.*

## *1.1. El sueño*

El sueño es un proceso fisiológico complejo que genera interés desde los principios de la civilización. Distintos profesionales como investigadores, médicos, psicólogos y filósofos han intentado entender este fenómeno, haciendo sus evaluaciones considerando diversas perspectivas como su función, características, funcionamiento o regulación (10). El estudio del sueño se realizaba únicamente por medio de observaciones del comportamiento del individuo hasta que, en 1924, experimentó un avance significativo mediante la electroencefalografía (EEG) (11). Esta herramienta permitió observar la presencia de ondas de distintos patrones que se correlacionaban con el comportamiento de los individuos. Actualmente, es conocido que el sueño se divide en fases definidas por diversas características como el patrón de ondas observadas en el EEG, la presencia o ausencia de tono muscular, la presencia de movimientos oculares rápidos y el patrón cardiorrespiratorio (12,13).

De acuerdo con la American Academy of Sleep Medicine (AASM), la arquitectura del sueño se divide en dos fases principales: el sueño sin movimientos oculares rápidos (NREM) y el sueño de movimientos oculares rápidos (REM) (14). La fase NREM contiene tres etapas, llamadas N1, N2 y N3. La primera se caracteriza por ondas de baja amplitud y frecuencia variada, además de una disminución del tono muscular respecto al estado de vigilia. La etapa N2 contiene igualmente ondas de baja amplitud y frecuencia variada, pero con la presencia de husos de sueño (secuencia de ondas distintas de alta frecuencia de 13-14 Hz y duración de ≥0,55 segundos) y complejos K (caracterizados por una onda negativa seguida inmediatamente de una onda positiva). Por último, la tercera etapa (N3) es conocida como sueño de ondas lentas (SWS, del inglés slow wave sleep) debido a la presencia de ondas de baja frecuencia

(0,5-2 Hz) y una amplitud en torno a los 75mV. En esta etapa habitualmente no se observan los movimientos rápidos de los ojos y el tono muscular es inferior al observado en la etapa N2. Contrariamente, la fase REM, se caracteriza por la presencia de ondas similares a las que se observan durante la vigilia (alta frecuencia y baja amplitud), pero con ausencia de tono muscular característica del periodo de sueño. Otra de las características principales de la fase REM es la presencia de movimientos oculares rápidos. La estructura del sueño incluye ciclos que constan de la ocurrencia de estas fases (N1, N2, N3 y REM), sucediendo entre cuatro y cinco veces en un episodio de sueño nocturno.

Gran parte de los estudios científicos que evalúan las características, el funcionamiento y la regulación del sueño tienen como objetivo entender mejor este complejo proceso con el propósito de mejorar la calidad de vida o prevenir eventos adversos asociados a una mala calidad del sueño (15). De hecho, en el periodo de sueño se experimentan diversos procesos fisiológicos que desempeñan un papel fundamental en la función cerebral y en el funcionamiento de los sistemas inmunológico, endocrino y cardiovascular (16,17). Estos procesos fisiológicos impactan sobre la conservación de energía (18), la restauración cerebral al disminuir la cantidad de moléculas tóxicas originadas de la actividad neuronal durante la vigilia (19,20) o la consolidación de la memoria (21,22). Actualmente, existen estudios científicos que demuestran que una disrupción del sueño tiene consecuencias sobre la salud a corto y largo plazo como un aumento del riesgo de padecer enfermedades como Alzheimer, Parkinson, enfermedades cardiovasculares, depresión o ansiedad (23).

Una encuesta conducida por la National Sleep Foundation en 2014 mostró que el 35% de los adultos estadounidenses reportaron una calidad del

sueño deficiente o insatisfactoria (24). Considerando factores previamente descritos y la elevada prevalencia de trastornos del sueño en la sociedad actual, es muy relevante promover estrategias para mejorar el sueño considerando diferentes perspectivas.

## *1.2. La salud del sueño*

Una correcta higiene del sueño es esencial para un desarrollo correcto de las capacidades físicas y psíquicas del ser humano (23). Tal y como sucede en otras disciplinas médicas, la medicina del sueño ha estado mayoritariamente centrada en la definición, identificación y tratamiento de los trastornos del sueño. Más allá de la importancia de las patologías del sueño, cabe destacar el papel crucial que puede tener la promoción de la salud del sueño como fuente de salud y calidad de vida (25).

Un comportamiento saludable es una acción del individuo que impacta positivamente sobre su estado de salud. A modo estructural, el comportamiento individual en relación al sueño se basa en tres componentes: la necesidad, la habilidad y la oportunidad del sueño (Figura 2). La **necesidad** de dormir es un requerimiento biológico basado en la necesidad del cuerpo de tener un descanso periódico (26). A pesar de que muchos estudios epidemiológicos han establecido un descanso diario entre seis y ocho [18], [19] horas como una duración saludable del sueño (27,28), la necesidad de descanso puede ser variable en función de las características del individuo, como la edad o el sexo (29). Por ejemplo, la AASM adaptó las recomendaciones en función del grupo de edad, siendo bebés, niños y adolescentes aquellos con mayor requerimiento de número de horas de sueño (28,30). Por otro lado, la **habilidad** para dormir está relacionada con la capacidad del individuo para conciliar y mantener el sueño en el periodo de descanso. Esta habilidad puede estar condicionada

por el estado mental, morbilidad y/o comportamiento social del individuo. La tercera componente es la **oportunidad** del sueño, siendo esta la cantidad del tiempo disponible del individuo para dormir. Esta componente se ve afectada principalmente por los hábitos diarios del individuo (16). El equilibrio entre estas tres componentes es clave para la promoción de la salud mediante el sueño. Por consiguiente, un comportamiento saludable del individuo en relación al sueño consiste en aplicar iniciativas que promuevan el ecosistema equilibrado entre estos tres pilares fundamentales (17).


*Figura 2.* ***Modelo de los procesos del sueño.*** *(adaptación de Sleep and Health (2019)* (31)*).*

La organización mundial de la salud, en el capítulo 1948, definió la salud como un estado de completo de bienestar físico, mental y social y no meramente la ausencia de enfermedad o dolencia (32). En estos términos, el Prof. Daniel Buysse (33) estableció una definición de la salud del sueño basada en cinco dimensiones del sueño asociadas con resultados en salud (satisfacción, alerta, horario, eficiencia y duración).

- **Satisfacción (Satisfaction)**: la satisfacción del sueño autopercibida es un buen indicador de la calidad de sueño.

Numerosos estudios han demostrado una asociación con el riesgo de mortalidad y patologías como síndrome metabólico, enfermedad coronaria (34,35), hipertensión (36,37) y depresión (38).

- **Alerta (Alertness)**: definida como la capacidad de mantenerse despierto en vigilia. Está fuertemente asociada con la calidad del sueño del día anterior. La somnolencia diurna es el síntoma principal tras un sueño no reparador influenciado por múltiples factores tales como su eficiencia, duración o estructura. Estudios longitudinales han mostrado una asociación entre el exceso de somnolencia y un mayor riesgo de enfermedad coronaria (39,40). Además, intervenciones sobre la reducción de la somnolencia han mostrado una mejora de resultados en salud (41).
- **Horario (Timing)**: considerado como el tramo del día en que ocurre el sueño del individuo. Es conocido que la noche es el periodo más saludable para dormir (42). El horario es importante debido a que, durante la evolución humana, varios procesos fisiológicos han evolucionado para ocurrir con ritmicidad y sincronización, entre ellos el sueño, para optimizar el gasto energético y otros procesos fisiológicos (43). Un gran número de estudios han demostrado que rutinas de sueño fuera del periodo nocturno producen una desincronización con otros procesos biológicos y, en consecuencia, promueven enfermedades, por ejemplo, metabólicas (44,45) o de deterioro cognitivo (46,47).
- **Eficiencia (Efficiency)**: entendida como la relación entre la habilidad del individuo para conciliar el sueño y la oportunidad ofrecida. Su medición se realiza mediante una ratio entre el tiempo total de sueño y el tiempo total en cama. Son numerosos los

estudios que han asociado la baja eficiencia del sueño con un aumento del riesgo de diabetes, incremento de mortalidad u otros problemas en salud (48–50).

- **Duración (Duration)**: es el número de horas diarias de sueño. Como ha sido descrito anteriormente, el ser humano requiere de un número de horas determinadas para obtener un sueño reparador. Esta necesidad puede ser variable en función de ciertas características del individuo. Una duración insuficiente ha sido asociada con mortalidad (51,52) y patologías crónicas cardiovasculares (53). Además, un meta-análisis de estudios prospectivos halló una asociación cuadrática entre la duración del sueño y resultados en salud, siendo los extremos de duración asociados con mortalidad (54,55), enfermedad cardiovascular (56), obesidad (57,58) o depresión (59).

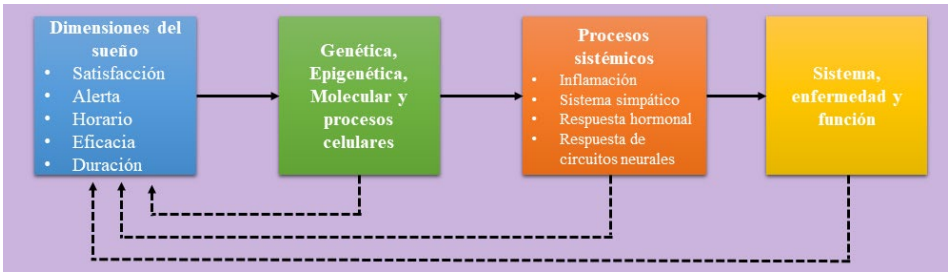


*Figura 3* ***Modelo conceptual de la salud del sueño*** *(adaptación de Buysse, 2014)* (33).

Esta definición del sueño está basada en un modelo conceptual que describe cómo puede afectar la función sueño-vigilia a funciones biológicas y a la salud global del individuo (Figura 3). El sueño promueve procesos intermedios que pueden incluir procesos epigenéticos, moleculares y celulares que a su vez afectan procesos a nivel de sistemas. Estos procesos, que van desde la inflamación hasta la función alterada de circuitos neurales, están más directamente relacionados con los resultados de salud. El modelo también reconoce que las relaciones entre la función

sueño-vigilia y los resultados a nivel molecular, celular, de sistemas y del organismo son recíprocas.

## *1.3. Medición de la salud del sueño*

La definición operativa de la salud del sueño conlleva la necesidad de herramientas que permitan cuantificar cada una de sus dimensiones previamente descritas (satisfacción, alerta, horario, eficacia y duración). En el ámbito de la investigación del sueño, se distinguen dos métodos de medición de parámetros del sueño: la medición objetiva y la medición subjetiva. La medición objetiva implica el uso de dispositivos de monitorización del sueño que registran la actividad cerebral y/o otros parámetros fisiológicos durante el sueño (60). Por otro lado, la medición subjetiva se basa en la información proporcionada por el individuo sobre sus propias percepciones y experiencias del sueño. Si bien la medición subjetiva puede ser menos precisa que la objetiva, proporciona información útil y complementaria sobre el sueño desde la perspectiva del individuo, incluyendo la calidad subjetiva del sueño y cualquier problema percibido con el sueño (60). A continuación, se presentan las principales herramientas para realizar una medición de parámetros del sueño.

***Polisomnografía***: consiste en la monitorización de diversas variables fisiológicas durante el sueño, incluyendo la actividad cerebral, la actividad muscular, la frecuencia cardíaca, la respiración y los movimientos oculares (61) (Figura 4). Esta prueba realiza una medición muy precisa de la arquitectura del sueño (cantidad de tiempo en las diferentes etapas del sueño durante el periodo de sueño), el tiempo despierto durante la noche o la cantidad de despertares. La polisomnografía es considerada la prueba de referencia para el diagnóstico de trastornos del sueño. En contra, son numerosas las limitaciones de esta prueba. Por ejemplo, la necesidad de

realizar esta prueba en un laboratorio de sueño aleja sus mediciones de un contexto real de sueño del usuario. Además, el registro de una única noche de sueño puede ser poco representativo del sueño global del individuo (62). Por último, tiene un alto coste económico debido a la necesidad de personal especializado para la realización e interpretación de la prueba (63).

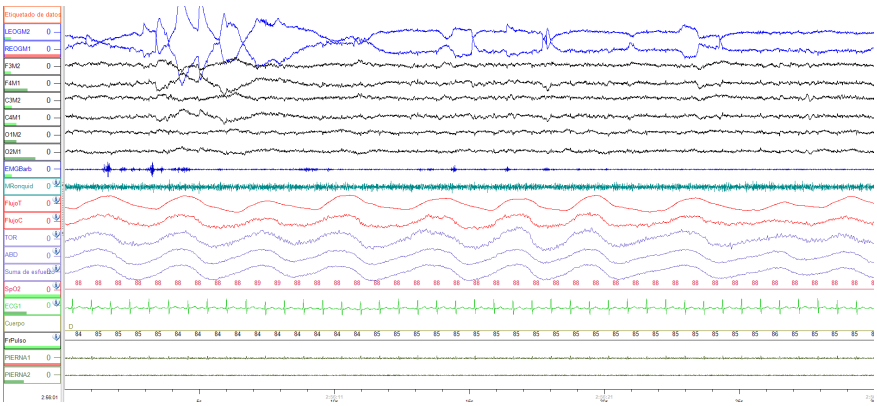


*Figura 4. Registro de parámetros polisomnográficos. Autoría propia.*

***Actigrafía***: otra alternativa para medir los parámetros del sueño de manera objetiva es por medio del uso de actígrafos (64), pulseras inteligentes que contienen acelerómetros y con ello, pueden estimar periodos de sueño por la cantidad de movimiento del individuo. Estos dispositivos permiten la medición objetiva de la duración del sueño, la eficiencia, latencia y sus patrones de sueño-vigilia. El registro de estos parámetros del sueño mientras el individuo está en su casa representa un contexto de rutina habitual del sueño. Además, los actígrafos permiten el registro continuo de varios días, lo que permite capturar la variabilidad diaria en la rutina de sueño del individuo y obtener una caracterización más precisa de su patrón de sueño-vigilia global. Aunque los actígrafos son una herramienta útil para la medición objetiva de la calidad del sueño (65), no están exentos de importantes limitaciones. Por ejemplo, los actígrafos realizan una

estimación indirecta de los parámetros del sueño a través de la medición del movimiento del individuo, lo que puede generar mediciones imprecisas. Además, los resultados son sensibles a la calibración del dispositivo y a la depuración de los datos procesados, requiriendo la intervención de personal especializado.

***Mobile Health**:* actualmente existen otros dispositivos inteligentes capaces de realizar estudios del sueño como la tecnología de Mobile Health (66). Los dispositivos portátiles, como los relojes inteligentes, pueden medir la cantidad de sueño, la calidad del sueño y estimar la duración de cada fase del sueño, todo ello en tiempo real. Estos dispositivos utilizan una variedad de sensores, como acelerómetros y micrófonos, para detectar los movimientos corporales y los patrones respiratorios que indican el periodo de sueño. La principal limitación de estos dispositivos es que frecuentemente no disponen de validación clínica para poder evaluar su correcta estimación y precisión de los parámetros del sueño (67,68).

***Cuestionarios o diarios de sueño:*** estas herramientas se basan en la autoevaluación de los patrones de sueño y la percepción subjetiva de la calidad del sueño por parte del individuo, lo que les convierte en instrumentos potencialmente efectivos para la caracterización del sueño (69). Son numerables las fortalezas del cuestionario como herramienta para medir la salud del sueño. En primer lugar, los cuestionarios son relativamente fáciles de administrar, lo que los hace accesibles para estudios de evaluación poblacional. Además, los cuestionarios pueden ser administrados de forma remota, lo que permite la recopilación de datos a distancia y la realización de estudios a gran escala. Otra ventaja importante del cuestionario es su capacidad para evaluar diferentes aspectos de la salud del sueño, como la somnolencia diurna, la calidad del sueño, la

duración del sueño y los trastornos del sueño, lo que lo convierte en una herramienta versátil para la evaluación de la salud del sueño. Sin embargo, estas herramientas tampoco están exentas de limitaciones. En primer lugar, están limitadas por la subjetividad por parte del usuario y pueden realizar estimaciones sesgadas del sueño del individuo. Por otra parte, los cuestionarios pueden necesitar personal encargado de administrar la encuesta para asegurar la claridad y mantener la neutralidad interpretativa del encuestado. Debido a la accesibilidad y versatilidad de los cuestionarios para evaluar diferentes aspectos del sueño, se consideran una buena opción para una evaluación poblacional en estudios epidemiológicos.

Existen diversas alternativas para la medición mediante cuestionario de la salud del sueño. Por ejemplo, la National Sleep Foundation de EEUU propone un cuestionario, llamado Sleep Health Index (SHI) (70), en el que incluyen catorce preguntas relativas a tres dimensiones del sueño: la duración, la calidad y los trastornos. Además, las propiedades psicométricas del cuestionario fueron validadas en población norteamericana (70). Por otro lado, Buysse (2014) (33) propuso un cuestionario de autoevaluación basado en las cinco dimensiones incluidas en su propia definición de salud del sueño. Este cuestionario, llamado SATED por sus siglas en inglés (Satisfaction with sleep; Alertness during waking hours; Timing of sleep; sleep Efficiency; and sleep Duration), incluye las dimensiones del sueño que han sido consistentemente asociadas con resultados en salud (Figura 5).

CUESTIONARIO SATED

| | Nunca/Muy pocas veces (0) | Algunas veces (1) | A menudo/Siempre (2) |
|---|---|---|---|
| 1. ¿Está satisfecho/a con su sueño? | | | |
| 2. ¿Permanece despierto/a el día sin quedarse dormido? | | | |
| 3. ¿Duerme ( o intenta dormir) entre las 2 y las 4 de la madrugada? | | | |
| 4. Por la noche, ¿pasa menos de 30 minutos despierto? (Incluye el tiempo que pasa para quedarse dormido y los despertares nocturnos) | | | |
| 5. ¿Duerme entre 6 y 8 horas al día ? | | | |

0 = Mala calidad del sueño — Buena calidad del sueño = 10

*Figura 5.* ***Adaptación al español del cuestionario de salud del sueño SATED.*** *Autoría propia.*

El cuestionario SATED presenta múltiples ventajas en comparación con otros cuestionarios que miden criterios similares a los incluidos en la definición de salud del sueño. En primer lugar, destaca su concisión, ya que incluye todas las dimensiones del sueño asociadas con resultados en salud en cinco preguntas cortas. Este formato facilita su comprensión, además de su traducción y aplicación en diversos idiomas y culturas. Sin embargo, es importante destacar que el cuestionario SATED no ha sido validado clínicamente, lo que implica la necesidad de realizar una adaptación cultural a la población objetivo y testear sus características psicométricas, como fiabilidad, validez, sensibilidad y factibilidad. La inclusión de las dimensiones consideradas relevantes por expertos es importante, pero no suficiente para certificar su correcta medición y sensibilidad a los cambios de interés en la población objetivo.

## *1.4. El sueño como pilar de salud*

Es bien conocido que la adopción de estilos de vida saludables puede reducir el riesgo de padecer enfermedades no transmisibles (71). En esta línea, la Organización Mundial de la Salud (OMS) ha propuesto en su informe sobre enfermedades no transmisibles la importancia de reducir el consumo de alcohol, sal/sodio, y tabaco, y aumentar la actividad física,

como hábitos saludables que contribuyen a reducir el riesgo de enfermedades como hipertensión, diabetes y obesidad (72). A pesar de que se cuenta con información respecto al impacto del sueño sobre la salud del individuo (73), las recomendaciones generales acerca de hábitos saludables no incluyen la promoción de la higiene del sueño.

Por el contrario, la importancia de dormir bien es conocida desde la antigüedad. Por ejemplo, Arnau de Vilanova, prominente médico del siglo XIII, incluyó en su obra "*Regimen Sanitatis ad regem Aragonum*" una sección sobre el sueño y su importancia para la salud (74). En ella recomendaba que se durmiera lo suficiente; que se mantuviera un horario regular de sueño; que se evitara el sueño durante el día, ya que esto podría afectar negativamente el patrón de sueño nocturno; que se durmiera en un lugar tranquilo y bien ventilado; y, que se evitara la ingesta de alimentos y bebidas pesados antes de dormir.

El sueño es un fenómeno humano que impacta diariamente sobre la salud de las personas. Por lo tanto, es de gran interés científico conocer a nivel poblacional parámetros relacionados con la salud del sueño. Debido a las complejidades inherentes de llevar a cabo mediciones objetivas del sueño a escala poblacional, la estimación de parámetros de sueño es habitualmente realizada mediante cuestionarios aplicados a muestras representativas de la población. La duración del sueño ha sido el parámetro de interés más utilizado en la mayoría de los estudios poblacionales sobre el sueño. Por ejemplo, el Behavioral Risk Factor Surveillance System de los Estados Unidos (75) estima la duración del sueño mediante la siguiente pregunta por encuesta telefónica: *en promedio, ¿cuántas horas duerme en un período de 24 horas?* En otras encuestas de salud pública, suele incluirse alguna pregunta relacionada con la duración del sueño para obtener información sobre los patrones de sueño de la población. La

medición de la duración del sueño en muestras representativas de la población tiene como principal propósito estimar la prevalencia de sueño insuficiente. Este indicador es de gran interés para la salud pública, ya que se ha demostrado que la falta de sueño adecuado se asocia con una amplia variedad de patologías físicas y mentales (76). Aunque existe un debate en curso sobre la cantidad mínima de tiempo de sueño necesario para considerarlo suficiente, la mayoría de las investigaciones indican que se necesita al menos seis o siete horas de sueño por noche para garantizar una buena salud (77,78). Debido al impacto del sueño sobre la salud, no es suficiente valorar su estado únicamente a través de la medición de su duración sino de mediciones que incluyan las dimensiones que la componen.

En un estudio previo realizado por nuestro grupo de investigación [43], se evaluó la salud de sueño en la población de Catalunya (79). Para llevar a cabo esta evaluación, se incluyó el cuestionario SATED en la encuesta de salud pública de Catalunya (ESCA) de 2015. La muestra es extraída mediante un muestreo probabilístico polietápico representativo de la población no institucionalizada mayor de 14 años, estratificado por edad, sexo y tamaño del municipio. En los análisis se incluyeron un total de 4.385 encuestas tras la exclusión de los trabajadores del turno de noche. En términos generales, se observó que un porcentaje significativo de la población experimentaba problemas en al menos una de las dimensiones evaluadas por el cuestionario SATED, siendo la eficiencia y la alerta las más afectadas. Además, los resultados del estudio indicaron que la salud del sueño disminuía en función de la edad y era peor en el sexo femenino. Adicionalmente, se evaluó la asociación de la puntuación total de SATED con el estado de salud autopercibida por el individuo. Se encontró una fuerte asociación entre estos factores, mostrando un alto poder

discriminatorio entre los individuos con correcto o deficiente estado de salud global. Esta discriminación fue superior a la medición habitual del sueño como es la duración (AUC de 0.56 vs 0.798; p-value<0.001 en test de DeLong). Concretamente, se observó que la satisfacción y la alerta eran las dimensiones con mayor asociación con la percepción global del estado de salud del individuo. Por último, se identificaron factores clínicos y sociodemográficos asociados a la salud del sueño. El modelo multivariante final mostró que educación, empleo, salud autopercibida, calidad de vida, enfermedades crónicas, tratamientos farmacológicos, actividad física y número de visitas al médico son factores asociados con la salud del sueño (Figura 6).

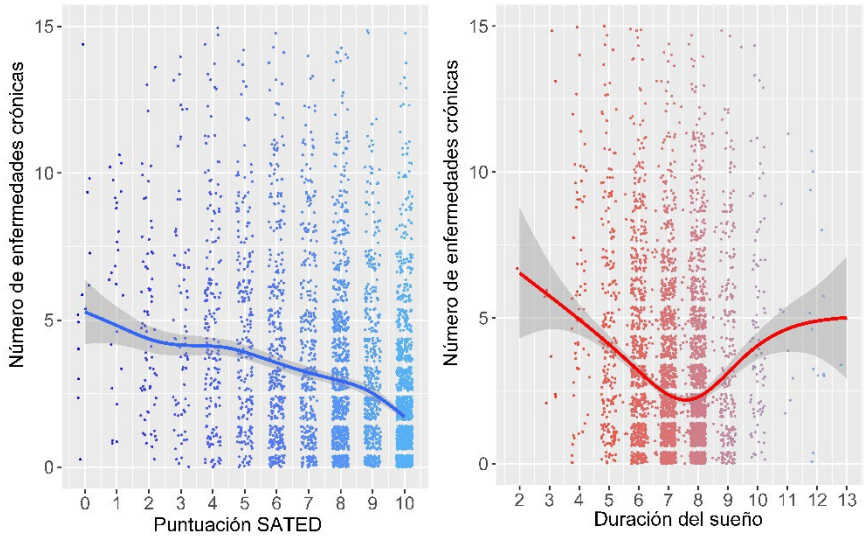


*Figura 6.* ***Salud y duración del sueño en función del número de enfermedades crónicas del individuo****. Adaptación de Dalmases M, Benítez I et al.* (79)*. Las líneas representan un suavizado no paramétrico del número de enfermedades crónicas en relación al puntaje SATED y la duración del sueño. Las áreas grises corresponden a intervalos de confianza del 95%. Autoría propia.*

La importancia de estos hallazgos reside en la caracterización de la situación actual de la salud del sueño en la población estudiada y la posibilidad de desarrollar estrategias efectivas de promoción de la higiene del sueño. Por otra parte, los resultados respaldan la importancia de medir

parámetros multidimensionales del sueño y no únicamente su duración. Consecuentemente, el diseño de encuestas de salud pública debería considerar un cambio en el enfoque de la evaluación del sueño de la población. Esta caracterización de la salud del sueño de la población es esencial para enfocar estrategias efectivas en la mejora de su salud general.

Una vez definida la salud del sueño y establecida su medición, el siguiente paso natural es determinar su impacto en la salud individual. Es habitual referir al ejercicio físico y/o una alimentación saludable como hábitos recomendados para mantener un buen estado de salud. Sin embargo, cada vez más ha sido reconocida la importancia de la salud del sueño como uno de los principales comportamientos modificables para la promoción de salud (73). Dada la creciente evidencia de la relación entre el sueño y la salud, se requiere de nuevas investigaciones que establezcan el impacto de hábitos saludables relacionados con el sueño sobre la salud global del individuo.

## *1.5. Trastornos respiratorios durante el sueño*

Existen diversos factores que pueden tener un impacto directo sobre la salud del sueño, entre ellos, diferentes estilos de vida, patologías y síndromes. Además, ciertas características sociales como la cohesión social, la seguridad y la densidad poblacional también pueden influir en la calidad del sueño de las personas (80–82). Por otro lado, la adopción de hábitos sedentarios (83) y una mala nutrición (84,85) son comportamientos individuales que se han relacionado con un mayor riesgo de trastornos del sueño. Desde el punto de vista clínico, existen múltiples problemas de salud que pueden afectar el sueño, siendo el insomnio y los trastornos respiratorios durante el sueño las patologías más prevalentes en la sociedad occidental (86,87). Los trastornos respiratorios durante el sueño impactan

sobre la calidad del sueño, generando desequilibrios en la estructura natural del sueño, con fragmentaciones del sueño y desaturaciones de oxígeno.

El trastorno respiratorio nocturno más prevalente en la sociedad es la Apnea Obstructiva del Sueño (AOS). La AOS se caracteriza por episodios repetidos de obstrucción de la vía aérea superior durante el sueño, provocando una reducción del flujo aéreo parcial o total, que ocasiona las hipopneas y apneas, respectivamente (88).

La apnea se caracteriza por la reducción de más del 90% del flujo respiratorio durante más de diez segundos. Son clasificadas como obstructivas si vienen acompañadas de un esfuerzo respiratorio, centrales si no existe esfuerzo respiratorio o mixtas si el esfuerzo aparece en la fase final de la apnea (89). La hipopnea se define como una reducción del flujo respiratorio de entre el 30-90%, con una duración de más de diez segundos acompañada de una desaturación de oxigeno superior a 3% y/o un microdespertar medible en el EEG. Las apneas/hipopneas obstructivas provocan sueño fragmentado por microdespertares, presiones intratorácicas negativas, episodios intermitentes de hipoxia y activación simpática, que desencadenan mecanismos intermedios como estrés oxidativo e inflamación, que son los que median el daño en diferentes órganos y explican la patología asociada a la AOS (90).

Un diagnóstico simplificado de AOS se establece ante en la presencia de un índice de apnea-hipopnea (IAH, número de apneas y/o hipopneas por hora) superior a 5 eventos/h y la presencia de síntomas clínicos o ante un IAH > 15 eventos/h independientemente de los síntomas (91).

Estudios epidemiológicos han situado la prevalencia de la AOS entre el 9%

y el 38% en estudios realizados en población adulta (88,92–94). Debido a esta alta prevalencia, la AOS es considerada uno de los trastornos del sueño más prevalentes en población general. El riesgo de padecer AOS está estrechamente relacionado con la edad, el sexo y el índice de masa corporal del individuo (95). Dado el aumento de la tasa de obesidad y el envejecimiento de la población en población occidental, se espera que la prevalencia de la AOS siga aumentando en el futuro.

El manejo integral del paciente con AOS se realiza en unidades del sueño especializadas (US), incluyendo el diagnóstico, tratamiento y seguimiento del paciente. El método de diagnóstico de referencia de la AOS es la polisomnografía convencional realizada en una unidad de sueño (ver sección 1.2). Debido a su alto coste y baja accesibilidad, se han desarrollado otros métodos de diagnóstico más económicos y con mayor accesibilidad, como la poligrafía respiratoria, que habitualmente se realiza en domicilio. Este método diagnóstico ha mostrado ser de utilidad para el diagnóstico en pacientes sin patología compleja asociada ni sospecha de otros trastornos del sueño y es de gran utilidad en el día a día de las unidades del sueño (96). La poligrafía presenta la limitación que, dado que no se conoce el tiempo de sueño, puede infravalorar el IAH en sujetos que duerman poco. El tratamiento de los pacientes con AOS incluye fundamentalmente tratamiento conservador, tratamiento postural, dispositivo de avance mandibular, cirugía o tratamiento con presión positiva continua en las vías respiratorias (CPAP por sus siglas en inglés) (97). El tratamiento postural se utiliza en pacientes que tienen AOS mayoritariamente en decúbito supino. La cirugía otorrinolaringológica, maxilofacial o bariátrica se reserva para casos concretos con hipertrofia amigdalar, anomalías craneofaciales o grandes obesos, respectivamente. El tratamiento conservador consiste en medidas

higiénico-dietéticas (dormir horas suficientes y en un horario regular, perder peso si el paciente tiene sobrepeso u obesidad, abstinencia de tabaco y alcohol, y realización de ejercicio físico) y se indica en todos los pacientes independientemente de la gravedad (98). En los casos graves, el tratamiento que ha demostrado ser más efectivo es el tratamiento con CPAP (99).

La alta prevalencia (100) y la cronicidad de la AOS, junto con el alto coste del manejo del paciente (101), hacen que sea poco viable manejar a los pacientes únicamente en US. Además, este enfoque de gestión puede llevar a un infradiagnóstico (102), siendo especialmente preocupante en patologías de alta prevalencia. El diagnóstico, tratamiento y seguimiento del paciente con AOS requieren de estrategias que involucren a otros profesionales de la salud para lograr una gestión adecuada.

En este contexto, han surgido nuevas propuestas de gestión coordinada con la atención primaria. La atención primaria puede ser un recurso fundamental para la identificación, diagnóstico y tratamiento de pacientes con AOS debido a su contacto transversal con la sociedad y su experiencia en el manejo de otras patologías altamente prevalentes (103,104). Se han llevado a cabo varios ensayos clínicos para evaluar la eficacia y la relación coste-efectividad del manejo de la AOS en atención primaria. Estos ensayos han sido diseñados para demostrar que el manejo de pacientes con sospecha de AOS en atención primaria es al menos igual de eficaz que en US, pero a un coste inferior. Es por esta razón que todos los ensayos plantearon un contraste de hipótesis de no inferioridad sobre el resultado primario en salud. Un primer ensayo clínico llevado a cabo por un equipo de investigación australiano [53] comparó la eficacia del manejo de AOS en US versus atención primaria (105). El estudio mostró que la eficacia del

manejo de pacientes con AOS no fue inferior a la que se obtiene en unidades especializadas, en términos de reducción de somnolencia diurna. Además, el manejo en primaria mostró ser una estrategia coste-efectiva.

El interés creciente en este tema ha promovido la realización de nuevos ensayos clínicos (106–108), de los cuales dos han sido liderados por nuestro grupo de investigación y han demostrado resultados similares al ensayo pionero (105). Aunque todos los ensayos han evidenciado una eficacia no inferior del manejo del paciente en atención primaria en comparación con la unidad especializada, se ha observado cierta heterogeneidad en las estimaciones del efecto, probablemente debido a diferencias en los diseños de los estudios, incluyendo el método diagnóstico y la preparación del equipo médico. Además, es importante destacar que los tamaños muestrales de los ensayos citados se calcularon con el propósito de demostrar la no inferioridad en el resultado primario (somnolencia diurna medida mediante la escala de somnolencia Epworth (109)). Por consiguiente, no se pudo llevar a cabo un análisis de subgrupos ni una evaluación de los resultados secundarios con la potencia estadística adecuada. Esto resalta la necesidad de continuar realizando estudios que proporcionen mayor evidencia sobre la eficacia global y por subgrupos del manejo del paciente con AOS en atención primaria.

## *1.6. Impacto de la COVID-19 sobre la salud del sueño*

La realización de esta tesis coincidió temporalmente con la emergencia del SARS-CoV-2, el cual se propagó rápidamente (110), desencadenando una pandemia a nivel global. Además de tener impactos significativos en la sociedad de diversas formas, este contexto afectó a la salud del sueño de la población, dando lugar a desequilibrios en sus aspectos fundamentales: la necesidad, la capacidad y la oportunidad relacionada con el sueño

(detalladas en la sección 1.2). Además, un gran número de individuos infectados por SARS-CoV-2 que desarrollaron la enfermedad conocida como COVID-19, reportaron trastornos de sueño durante y tras superar la fase aguda de la enfermedad. Debido a la crucial importancia que adquirió el estudio del sueño durante la pandemia, se tomó la decisión de enfocar la presente tesis en la ampliación de conocimiento en relación a la asociación entre el sueño y el contexto de la COVID-19, así como en las posibles repercusiones que esta enfermedad pueda tener en los patrones de sueño.

El sueño es un proceso relevante desde varias perspectivas. Dada su compleja relación con la función inmune, el sueño puede modular tanto la susceptibilidad como la recuperación relacionada con una infección viral (111). Asimismo, las medidas de restricciones de movilidad para controlar la tasa de infección por SARS-CoV-2 medió un cambio de hábitos que afectaron a la vida diaria de los individuos, incrementando la presencia de factores de riesgo de la disrupción del sueño como son la ansiedad y depresión (112). Por otro lado, cabe destacar que el 14% de los pacientes de COVID-19 han requerido ingreso hospitalario (113), lo que representa un factor de riesgo añadido para la disrupción de los ritmos circadianos y las alteraciones del sueño (114). De acuerdo con la descripción previa, se decidió enfocar los estudios subsecuentes en dos principales líneas: i) El impacto de la pandemia sobre la calidad de sueño poblacional y ii) las alteraciones del sueño en pacientes críticos por COVID-19.

### *1.6.1. Impacto de la pandemia sobre el sueño poblacional*

La calidad del sueño es altamente susceptible a contextos de cambios emocionales y de restricciones sociales. La pandemia podría afectar al sueño de los individuos por distintas razones: i) aumento de ansiedad y

depresión por la incertidumbre asociada a este contexto; ii) aumento del estrés por las restricciones sociales, confinamiento, contexto económico; iii) aumento en el uso de medios digitales; iv) reducción de la exposición a la luz solar; v) limitación del nivel de actividad por las restricciones y/o confinamiento.

Respecto a la ansiedad y depresión, diversos estudios indican una compleja relación entre estos factores y el sueño. De hecho, la calidad del sueño está estrechamente relacionada con el estado de ánimo, que cambia durante el tiempo con restricciones de movilidad. Huang y colaboradores (2020) observaron una alta prevalencia (35%) del trastorno de ansiedad generalizada, aumentando en aquellos pacientes más preocupados por la pandemia (115). Además, en un estudio realizado durante la etapa incipiente de la pandemia en China, el 54% de los participantes calificaron el impacto psicológico como moderado o severo y aproximadamente un tercio reportó ansiedad moderada a severa (116).

Por otro lado, el contexto social en el periodo de pandemia provocó un aumento del uso de medios digitales. El abuso del uso de estos medios genera un aumento de exposición a la luz artificial, que puede impactar sobre la higiene de sueño del usuario. De hecho, estudios científicos mostraron un retraso en el horario de inicio y final del sueño durante el confinamiento, posiblemente influenciados por el aumento del uso de dispositivos electrónicos cerca de la hora de dormir entre otros factores (117).

Existen otros factores asociados al periodo de pandemia que pueden afectar al sueño, tales como la reducción de la exposición a la luz solar, la limitación de la actividad durante el día y las alteraciones en los horarios de las comidas. Estos factores pueden llevar a la disrupción de los ritmos

circadianos afectando directamente la calidad del sueño del individuo (118,119).

Teniendo en cuenta el aumento de estos factores de riesgo de alteraciones del sueño, es razonable creer que existe un empeoramiento de la calidad del sueño a nivel poblacional en periodo de pandemia. Estudios científicos con medidas del estado del sueño previo y durante la pandemia son necesarios para evidenciar y cuantificar el verdadero impacto de la pandemia sobre la salud del sueño.

### *1.6.2. Calidad del sueño tras enfermedad crítica por COVID-19*

Más allá de la influencia del contexto anímico y social sobre la calidad de sueño, la infección por SARS-CoV-2 en sí misma podría ser otro factor de riesgo sobre la disrupción del sueño (120). Por otro lado, cabe destacar que un alto porcentaje de personas infectadas acaban desarrollando una enfermedad grave de COVID-19, requiriendo así cuidados hospitalarios (121). Entre estos pacientes hospitalizados, una proporción significativa pueden desarrollar una enfermedad crítica, que resulta en síndrome de distrés respiratorio agudo (SDRA) (122,123), siendo necesario el ingreso del paciente en una unidad de cuidados intensivos (UCI).

Los pacientes que requieren un ingreso en UCI experimentan secuelas multidimensionales tras el alta hospitalaria, siendo frecuentes los problemas de sueño durante un largo periodo de tiempo (124). El síndrome de cuidados intensivos (PICS, por sus siglas en inglés de Post-intensive Care Syndrome) es una condición clínica bien reconocida que describe el deterioro en la salud física, cognitiva y psicológica que se produce después de la hospitalización en una UCI.

La prevalencia de alteraciones del sueño en pacientes que han ingresado

en la UCI se estima en un rango del 20% al 67%, y puede variar según factores como el sexo, la edad, la presencia de enfermedades crónicas, especialmente respiratorias, y la calidad del sueño previa a la enfermedad (124). Los posibles factores de riesgo para las alteraciones de sueño asociados con la estancia en UCI incluyen la exposición excesiva y desincronizada con la luz artificial, junto con una insuficiente exposición a la luz natural, horarios de alimentación poco habituales, e intervenciones constantes para el cuidado del paciente durante la noche (125–127). Además, otros eventos relacionados con enfermedades agudas, como la presencia de síntomas de dolor, procesos inflamatorios, medicación, restricciones físicas o el uso de ventilación mecánica invasiva pueden ser factores relevantes en la alteración del sueño tras el alta hospitalaria (128). Por otro lado, es común la presencia de depresión y ansiedad en pacientes que han superado una enfermedad crítica, las cuales pueden tener un impacto significativo en la calidad del sueño del individuo (129).

Un equipo de investigadores australianos lideró un estudio sobre la persistencia de alteraciones del sueño en pacientes críticos tras el alta hospitalaria (130). Los resultados del estudio indicaron que la calidad del sueño se vio afectada en las primeras fases de recuperación. La persistencia de estos trastornos estuvo presente a medio plazo, aunque algunos de estos pacientes afectados recuperaron los niveles de calidad previos a la enfermedad a los seis meses tras el alta hospitalaria. Estos hallazgos son prometedores, pero es importante investigar la validez externa de estos hallazgos tanto en pacientes con COVID-19 como pacientes residentes en otra área geográfica.

Por otra parte, a pesar de la creciente evidencia del impacto del ingreso en UCI sobre alteraciones del sueño de los pacientes, la Conferencia

Internacional de Consenso sobre Predicción e Identificación de Deficiencias a Largo Plazo Después de Enfermedades Críticas no incluyó las alteraciones del sueño como una de las secuelas persistentes en estos pacientes (131). Considerando la evidencia existente sobre el impacto de enfermedades críticas en las alteraciones del sueño, es necesario llevar a cabo nuevos estudios para responder a cuestiones que aún no se han abordado tales como: ¿es distinto el impacto de la enfermedad crítica por COVID-19 sobre las alteraciones del sueño respecto a las otras enfermedades críticas? ¿Existe alguna información clínica durante la hospitalización que se asocie con el riesgo de padecer alteraciones del sueño tras el alta hospitalaria? ¿Son precisos y/o replicables los tiempos de recuperación de las alteraciones del sueño reportados anteriormente? ¿Está la alteración del sueño principalmente asociada al insomnio condicionado o a la disrupción de los ritmos circadianos? ¿Está la alteración del sueño asociada a las otras secuelas de una enfermedad crítica?

Es necesario un mayor conocimiento sobre estos puntos para diseñar estrategias en salud adecuadas a la mejora de la calidad del sueño en esta población específica.

# *2. Hipótesis*

La presente tesis plantea hipótesis basadas en la promoción, identificación, gestión y tratamiento de la salud del sueño del individuo. A continuación, se presentan las hipótesis específicas para cada perspectiva de investigación incluida.

1. Sobre la medición e importancia de la salud del sueño:
   - H.1.1 El cuestionario SATED es una herramienta útil para la medición de la salud del sueño.
   - H.1.2 La salud del sueño es uno de los principales comportamientos modificables del individuo que impacta sobre su estado de salud general.
2. Respecto al manejo del paciente con AOS:
   - H.2.1 La integración de atención primaria en el manejo del paciente con sospecha de AOS es una estrategia coste-efectiva.
3. En cuanto al impacto de la COVID-19 sobre la salud del sueño:
   - H.3.1 El periodo de pandemia impactó sobre el estado de la salud del sueño del individuo.
   - H.3.2 Existe un alto riesgo de que el paciente COVID-19 ingresado en unidad de cuidados intensivos experimente alteraciones del sueño a los tres meses del alta hospitalaria.
   - H.3.3 Existe un alto riesgo de que las alteraciones del sueño en pacientes COVID-19 ingresado en unidad de cuidados intensivos persista a los seis meses tras el alta hospitalaria.

Estas hipótesis son contrastadas mediante los objetivos y estudios que se detallan en las siguientes secciones.

# *3. Objetivos*

La tesis plantea objetivos de acuerdo con las hipótesis presentadas en la sección anterior (sección 2). A continuación, se presentan los objetivos incluidos en la presente tesis.

O.1.1 Adaptar el cuestionario de la salud del sueño SATED para la evaluación de población de habla hispana y evaluar sus propiedades psicométricas.

O.1.2 Evaluar el impacto de la salud del sueño sobre el estado general de salud del individuo; y, comparar la magnitud de su asociación respecto a otros estilos de vida como la dieta, la actividad física, el tabaquismo, y el consumo de alcohol.

O.2.1 Evaluar la coste-efectividad del manejo del paciente con sospecha de AOS en atención primaria en comparación con el manejo del paciente en una unidad especializada en sueño.

O.3.1 Evaluar el cambio de la calidad del sueño relacionado al periodo de pandemia en población general.

O.3.2 Evaluar la calidad del sueño a los 3 meses del alta hospitalaria en pacientes ingresados en unidades de cuidados intensivos por COVID-19.

O.3.3 Evaluar la calidad del sueño a los 6 meses del alta hospitalaria en pacientes ingresados en unidades de cuidados intensivos por COVID-19.

A continuación, se presenta la tabla 1 que muestra la relación entre hipótesis, objetivos y artículos científicos derivados de la presente tesis.

*Tabla 1. Relación entre los objetivos de la tesis con sus hipótesis y artículos científicos asociados*

| Objetivo | Hipótesis | Artículo científico |
|---|---|---|
| O.1.1 | El cuestionario SATED es una herramienta útil para la medición de la salud del sueño | Validation of the Satisfaction, Alertness, Timing, Efficiency and Duration (SATED) Questionnaire for Sleep Health Measurement (Resultados O.1.1) |
| O.1.2 | La salud del sueño es uno de los principales comportamientos modificables del individuo que impacta sobre su estado de salud general | Impact of sleep health on self-perceived health status (Resultados O.1.2) |
| O.2.1 | La integración de atención primaria en el manejo del paciente con sospecha de AOS es una estrategia coste-efectiva | Primary versus Specialist Care for Obstructive Sleep Apnea: A Systematic Review and Individual-Participant Data-Level Meta-Analysis (Resultados O.2.1) |
| O.3.1 | El periodo de pandemia impactó sobre el estado de la salud del sueño del individuo | Decrease in sleep quality during COVID-19 outbreak (Resultados O.3.1) |
| O.3.2 | Existe un alto riesgo de que el paciente COVID-19 ingresado en unidad de cuidados intensivos experimente alteraciones del sueño a los tres meses del alta hospitalaria | Sleep and Circadian Health of Critical COVID-19 Survivors 3 Months After Hospital Discharge (Resultados O.3.2) |
| O.3.3 | Existe un alto riesgo las alteraciones del sueño en pacientes COVID-19 ingresado en unidad de cuidados intensivos persista a los seis meses tras el alta hospitalaria | Sleep and circadian health 6 months after critical COVID-19 disease (Resultados O.3.3) |

# *4. Metodología*

Esta sección presenta un resumen general del diseño de los estudios realizados, que dan respuesta a los objetivos de la tesis. La descripción detallada de la metodología ha sido incluida en los artículos científicos asociados a cada uno de los objetivos (ver sección 3).

Para la adaptación cultural del cuestionario SATED y la evaluación de sus propiedades psicométricas (objetivo 1.1) se diseñó un estudio de traducción y validación de cuestionarios. El diseño del estudio fue basado en guías de recomendaciones metodológicas para estudios de traducción y validación (132,133) (ver Tabla 2). Respecto a la comparativa de los diferentes hábitos saludables (incluido el sueño) con la percepción global de la salud del individuo (objetivo 1.2) se llevó a cabo un estudio epidemiológico transversal con un muestreo representativo de la población de Catalunya mediante la encuesta de salud pública ESCA (134) (ver Tabla 3). Otro estudio fue diseñado para la evaluación de la coste-efectividad del manejo del paciente con sospecha de AOS en atención primaria comparado con US (objetivo 2.1) basado en una revisión sistemática y meta-análisis con datos individualizados. El estudio fue registrado en PROSPERO (CRD42020154688) (135) y se realizó de acuerdo con la lista de verificación PRISMA (136) (ver Tabla 4). En relación a la evaluación del impacto de la pandemia por COVID-19 sobre la calidad del sueño (objetivo 3.1) se diseñó un estudio observacional retrospectivo en población general que comparó el estado de la calidad del sueño de los participantes pre y pos inicio de la pandemia (ver Tabla 5). Por último, se diseñó un estudio observacional prospectivo con seguimiento tras el alta hospitalaria para evaluar las secuelas en el sueño de pacientes ingresados en unidades de cuidados intensivos por COVID-19 a los tres meses (objetivo 3.2) y seis meses (objetivo 3.3) de seguimiento (ver Tabla 6 y 7,

respectivamente).

*Tabla 2. Características del estudio asociado al objetivo O.1.1.*

| | **Estudio O.1.1** |
|---|---|
| Objetivo | Adaptación cultural del cuestionario SATED y la evaluación de sus propiedades psicométricas |
| Diseño de estudio | Estudio observacional, transversal de traducción y validación de cuestionario |
| Población | Población general |
| Grupos de estudio | Población con alta y baja calidad del sueño basado en la puntuación del cuestionario SATED |
| Tamaño muestral | n = 4385 para medidas psicométricas<br>n=200 para validez de criterio<br>n = 21 para fiabilidad test-retest |
| Resultados primarios | Estado de salud general autopercibida |
| Características | |
| Edad, años (mean (DE)) | - |
| Sexo (femenino) | - |

*Tabla 3. Características del estudio asociado al objetivo O.1.2.*

| | **Estudio O.1.2** |
|---|---|
| Objetivo | Comparar la magnitud de la asociación de los hábitos saludables (incluido el sueño) con el estado de salud |
| Diseño de estudio | Estudio epidemiológico transversal con un muestreo representativo de la población de Catalunya mediante la encuesta de salud pública ESCA (134) |
| Población | Población general |
| Grupos de estudio | Población con alta y baja calidad del sueño basado en la puntuación del cuestionario SATED |
| Tamaño muestral | n = 4385 |
| Resultados primarios | Estado de salud general autopercibida |
| Características | |
| Edad, años (mean (DE)) | 47 (19.0) |
| Sexo (femenino) | 51% |

*Tabla 4. Características del estudio asociado al objetivo O.2.1.*

| | **Estudio O.2.1** |
|---|---|
| Objetivo | Evaluar la coste-efectividad del manejo del paciente con sospecha de AOS en atención primaria |
| Diseño de estudio | Revisión sistemática y meta-análisis con datos individualizados. El estudio fue registrado en PROSPERO (CRD42020154688) (135) y se realizó de acuerdo con la lista de verificación PRISMA IPD (136) |
| Población | Población con sospecha de AOS |
| Grupos de estudio | Pacientes con manejo en unidad de sueño o atención primaria |
| Tamaño muestral | n = 970 |
| Resultados primarios | Somnolencia diurna medida por la escala de somnolencia de Epworth (109) |
| Características | |
| Edad, años (mean (DE)) | 54 (11.5) |
| Sexo (femenino) | 26% |

*Tabla 5. Características del estudio asociado al objetivo O.3.1.*

| | **Estudio O.3.1** |
|---|---|
| Objetivo | Evaluar el cambio de la calidad del sueño en periodo de pandemia |
| Diseño de estudio | Estudio observacional retrospectivo con evaluación del sueño pre e intra pandemia |
| Población | Población general. |
| Grupos de estudio | - |
| Tamaño muestral | n = 71 |
| Resultados primarios | Cambio de calidad del sueño pre e intra pandemia medido por cuestionario Pittsburgh (137) |
| Características | |
| Edad, años (mean (DE)) | 40.7 (11.9) |
| Sexo (femenino) | 75% |

*Tabla 6. Características del estudio asociado al objetivo O.3.2.*

| | **Estudio O.3.2** |
|---|---|
| Objetivo | Evaluar la calidad del sueño en pacientes COVID-19 críticos a los tres meses tras el alta hospitalaria |
| Diseño de estudio | Estudio observacional prospectivo con seguimiento tras alta hospitalaria |
| Población | Pacientes supervivientes a COVID-19 ingresados en unidades de cuidados intensivos |
| Grupos de estudio | - |
| Tamaño muestral | n = 172 |
| Resultados primarios | Calidad del sueño a los tres meses tras el alta hospitalaria medido por cuestionario Pittsburgh (137) |
| Características | |
| Edad, años (mean (DE)) | 61 (14.2) |
| Sexo (femenino) | 32.6% |

*Tabla 7. Características del estudio asociado al objetivo O.3.3.*

| | **Estudio O.3.3** |
|---|---|
| Objetivo | Evaluar la calidad del sueño en pacientes COVID-19 críticos a los seis meses tras alta hospitalaria |
| Diseño de estudio | Estudio observacional prospectivo con seguimiento tras alta hospitalaria |
| Población | Pacientes supervivientes a COVID-19 ingresados en unidades de cuidados intensivos |
| Grupos de estudio | - |
| Tamaño muestral | n = 145 |
| Resultados primarios | Calidad del sueño a los seis meses tras el alta hospitalaria medido por cuestionario Pittsburgh (137) |
| Características | |
| Edad, años (mean (DE)) | 60.9 (0.34) |
| Sexo (femenino) | 32,10% |

# *5. Resultados*

El presente capítulo presenta los resultados obtenidos en los estudios incluidos en la tesis que dan respuesta a las hipótesis planteadas. En la tabla 8 se relaciona el objetivo planteado en la tesis con la sección correspondiente al detalle de los resultados.

*Tabla 8. Relación entre los objetivos de la tesis y las secciones donde se presentan los resultados.*

| | **Objetivo** | **Sección** |
|---|---|---|
| O.1.1 | Adaptar el cuestionario de la salud del sueño SATED para la evaluación de población de habla hispana y evaluar sus propiedades psicométricas | Sección 5.1 |
| O.1.2 | Evaluar el impacto de la salud del sueño sobre el estado general de salud del individuo; y, comparar la magnitud de su asociación respecto a otros estilos de vida como la dieta, la actividad física, el tabaquismo, y el consumo de alcohol | Sección 5.2 |
| O.2.1 | Evaluar la coste-efectividad del manejo del paciente con sospecha de AOS en atención primaria en comparación con el manejo del paciente en una unidad especializada en sueño | Sección 5.3 |
| O.3.1 | Evaluar el cambio de la calidad del sueño relacionado al periodo de pandemia en población general | Sección 5.4 |
| O.3.2 | Evaluar la calidad del sueño a los tres meses del alta hospitalaria en pacientes ingresados en unidades de cuidados intensivos por COVID-19 | Sección 5.5 |
| O.3.3 | Evaluar la calidad del sueño a los 6 meses del alta hospitalaria en pacientes ingresados en unidades de cuidados intensivos por COVID-19 | Sección 5.6 |

## *5.1. Resultados del objetivo O.1.1*

**Título:** Validation of the Satisfaction, Alertness, Timing, Efficiency and Duration (SATED) Questionnaire for Sleep Health Measurement

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# Validation of the Satisfaction Alertness Timing Efficiency and Duration (SATED) Questionnaire for Sleep Health Measurement

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**Key Words:** Public Health; Sleep Hygiene; Surveys and Questionnaires.

**Abstract**

**Rationale:** Sleep constitutes a fundamental pillar of health in individuals and is an indicator of the health of a population.

**Objectives:** Aiming to develop an easy-to-use tool to measure sleep health, we translated into Spanish, adapted and validated the Satisfaction Alertness Timing Efficiency Duration (SATED) questionnaire.

**Methods**: The reliability of the questionnaire was evaluated using a sample of 4385 participants from the 2015 Catalan Health Survey. Criterion validity, construct validity and feasibility were assessed in an independent sample of 200 subjects who completed the Epworth Sleepiness Scale, Pittsburgh Sleep Quality Index, anxiety scale of the State-Trait Anxiety Inventory, mood scale of the Profile of Mood States and a one-week sleep diary.

**Results**: The SATED questionnaire obtained adequate internal consistency (Cronbach's $\alpha = 0.77$); statistically significant correlations of its five items with the total score (rho = 0.55-0.69); and a suitable goodness of fit in the confirmatory factor analysis ($\chi 2 = 30.93$, df = 5, $p < 0.001$, RMSEA = 0.049, CFI = 0.99, SRMR = 0.043). The criterion and construct validity were adequate, with correlations in the expected directions. The feasibility of the questionnaire was satisfactory, being easy and intelligible, and requiring approximately one minute to be completed.

**Conclusions**: This questionnaire is reliable and valid for measuring sleep health in the general population. Encouraging the use of SATED is expected to raise awareness that sleep, like diet and physical activity, is a key modifiable factor for promoting health.

## Introduction

Sleep constitutes a fundamental pillar of health in individuals and is an indicator of the health of a population [1,2]. Nonetheless, the definition of what constitutes healthy sleep is not well established. The World Health Organization (WHO) considers health as a state of physical, mental and social well-being, rather than the mere absence of disease [3]. The WHO definition permits health to be measured and quantified. By extension, healthy sleep is not simply an absence of sleep pathologies, but can be defined as a multidimensional sleep-wake pattern that adapts to individual, social and environmental requirements, thereby promoting the physical, mental and social well-being of an individual [4].

Consistent with WHO's definition of health, there have been several initiatives to measure and quantify health sleep. The Satisfaction, Alertness, Timing, Efficiency and Duration (SATED) questionnaire was introduced in 2014 [4]. Subsequently, two additional tools were developed or adapted. The Sleep Health Index (SHI) of the National Sleep Foundation [5] measures three dimensions of sleep health, namely duration, quality and disorders, through 14 questions, and has been validated in the North American population. The Sleep Health Scale (SHS), based on a version of SATED that included another dimension (regularity), has been validated in the Portuguese population [6].

Our goal was to test the psychometric properties of a Spanish version of the SATED scale[4]. Specifically, we describe the processes related to the translation, adaptation, and psychometric evaluation of the SATED questionnaire for use in the Spanish language. However, the psychometric properties of the original SATED scale have not yet been assessed.

## Methods

### *SATED Questionnaire*

SATED is a self-administered questionnaire evaluating five dimensions of sleep health shown to be associated with various health outcomes: (i) subjective satisfaction; (ii) alertness during waking hours; (iii) appropriate timing; (iv) efficiency; and (v) adequate duration. The original questionnaire consists of five questions, each related to the frequency of meeting one dimension of sleep health. Each item is rated from 0 to 2, with 0 for "never" or "rarely", 1 for "sometimes", and 2 for "usually" or "always". The total score ranges 0 to 10 points, with 0 and 10 points representing the worst and best sleep health, respectively. Except for sleep satisfaction, which is a subjective parameter, quantitative criteria for every dimension can be objectively measured. The process involved in adapting and validating the Spanish version of the SATED questionnaire is summarized in Figure 1.

### *Translation to Spanish*

A sleep expert and three professional translators, all native-Spanish speakers with a high level of English proficiency, independently developed four different translations. The translators and research team checked and compared the four translations. A team of four clinical and research experts in sleep medicine, who are all members of the Spanish Sleep Society, created the final version of the translated questionnaire. A native English-speaking translator, experienced in medical publications, back-translated the final version. The professionals involved in the translation, consolidation and back-translation processes evaluated the final version of the questionnaire.

*Population*

Psychometric analysis of the questionnaire was conducted in two different populations. The first phase involved 4385 participants older than 14 years of age from the Catalan Health Survey (ESCA) 2015 [7]. ESCA includes a representative sample of the non-institutionalized population of Catalonia, stratified by age, gender and health region, and obtained by a multiple-stage probabilistic sampling. A qualified interviewer visits the homes of selected subjects and asks approximately 500 questions. In its 2015 version, the ESCA included questions from the SATED questionnaire. The ESCA is an official statistic of the Catalan Government, approved by the Advisory Commission for the Treatment of Confidential Information (CATIC) form the Health Department of Catalonia. The ESCA fulfills with the Spanish regulatory framework and follows the guidelines of the Declaration of Helsinki. All participants in the ESCA are appropriately informed and provide their consent to participate in the survey. Detailed descriptions of the content, methodology and results related to sleep from the ESCA 2015 have been published[2].

A second phase was conducted using an independent sample of 200 subjects older than 18 years of age, who were physically and mentally able to participate in this study. To be more representative of the population, the sample was stratified by sex, age, educational and social level, as well as sleep habits and pathologies, through proportional allocation. All subjects completed a one-week sleep diary, as well as the SATED, Epworth Sleepiness Scale (ESS) [8], Pittsburgh Sleep Quality Index (PSQI) [9], the State-Trait Anxiety Inventory (STAI) [10] and the Profile of Mood States (POMS) questionnaires [11]. Test-retest reliability for SATED was assessed in a random subsample of 21 subjects who completed the questionnaire twice one-week apart. The studies in this second phase were approved by

the Clinical Research Ethics Committee (CEIC) of the Arnau de Vilanova University Hospital in Lleida (CEIC-1694), and all the participants signed an informed consent.

*Validation of the SATED Questionnaire*

The reliability of the questionnaire was evaluated by internal consistency through the estimation of Cronbach's Alpha and item-total correlations. The Cronbach's Alpha coefficient was estimated assuming ordinal scale [12] and a value greater than 0.70 was considered as adequate [13,14]. The sample extracted from ESCA was randomly divided into two independent groups in order to perform an exploratory factor analysis (EFA) and a confirmatory factor analysis (CFA). In both samples, Kaiser-Meyer-Olkin (KMO) and Bartlett's sphericity tests were performed to determine the suitability of the samples for factor analysis. Once the nature and distribution of the score of each item was evaluated, a polychoric correlation matrix was used to perform the EFA. The method of ordinary least squares was applied for the factor estimation. The number of factors was determined with Kaiser criterion and parallel analysis methods [15].

Ultimately, the oblique rotation method was applied. The same adjustment parameters were applied to the CFA. Goodness of fit for CFA was assessed using standard criteria and measures: p value $< 0.05$ for the $X^2$ adjustment statistics of the model, values $\leq 0.06$ for the Root Mean Square Error of Approximation (RMSEA), values $\geq 0.95$ for the Comparative Fit Index (CFI) and values $\leq 0.08$ for the Standardized Root Mean Residual (SRMR)[16]. The criterion concurrent validation of the Duration, Efficiency and Timing items was estimated through correlation with sleep diary measures. The Alertness and Satisfaction items were evaluated by correlation with the ESS items and the first item of the PSQI, respectively.

In order to assess construct validity, SATED was correlated with the degree of anxiety measured by the STAI and POMS questionnaires. All correlations were evaluated using Spearman rank correlation coefficient.

Test-retest reliability was calculated using a Pearson correlation in the subgroup that completed the scale twice (one-week time interval); values ≥ 0.7 indicate adequate test-retest reliability. [17] Finally, to analyze the feasibility of the questionnaire, a survey regarding the time of completion, clarity, easiness and intelligibility was conducted.

## Results

*Phase 1: Translation*

The initial Spanish translation process generated four very similar versions. During the consolidation phase of the different translations, we decided to incorporate the clarification "including napping" to question 5: "Do you sleep between 6 and 8 hours a day, including napping?". The subsequent back-translation process found no semantic or conceptual discrepancies with respect to the original English questionnaire except for the aforementioned clarification. The experts participating in the processes of translation, consolidation and back- translation concluded that the final questionnaire was clear and easy to understand, could be answered in a short period, and would be understandable to individuals older than 12 years old. The final SATED questions in Spanish and Catalan can be found in the Online Supplement.

*Phase 2: Internal Consistency and Factor Analysis*

As previously published, the sample consisted of 4385 subjects. Mean body mass index (SD) was 25.6 (4.5) kg/m$^{2)}$, 51% were women, 20% were older than 65 years of age, and 82% rated their health status as good [2].

SATED questionnaire results are presented in Table E1 of the Online Supplement.

The questionnaire exhibited adequate internal consistency (Cronbach's α = 0.77). The Cronbach's α of the questionnaire. Every individual score of the SATED items correlated significantly with the total score. The correlation ranged from *rho* = 0.69 with the item Satisfaction, to *rho* = 0.55 with the item Alertness (Table 1).

The adequacy of the sample for factor analysis was verified by EFA (KMO = 0.71, Bartlett: $\chi^2$ = 1499.12, df = 10, p <0.001) and CFA population (KMO = 0.7, Bartlett: $\chi^2$ = 1433.23, df = 10, p <0.001). In the EFA, the Kaiser criterion and parallel analysis determined a single- factor underlying structure with high loading for each of the five items. The unifactorial structure estimated in the CFA showed similar loads to those reported by the EFA (Table2).

Moreover, the goodness-of-fit indices of the model showed adequate values ($\chi^2$ = 30.93, df = 5, p <0.001, RMSEA = 0.049, CFI = 0.99, SRMR = 0.043).

*Phase 3: Criterion and Construct Validation*

A total of 200 participants (median (IQR) age of 44 years (30-57), median weight 64.5 kg (57- 75), a median BMI of 23 (20-25), 62% women) were included, see Table E2 in the Online Supplement. Participants reported a SATED scale mean (SD) of 7.20 (2.04), with 1 and 10 being the minimum and maximum reported values, respectively.

Table 3 shows the Spearman rank correlation coefficients of the individual score of the SATED items with sleep diary measurements, ESS score and the PSQI sleep quality index.

Duration and Efficiency items from SATED correlated significantly and in the expected theoretical direction with the diary sleep diary measurements. However, the Timing item from SATED correlated only with Latency. As expected, the Alertness correlated negatively with ESS score. The Satisfaction showed significantly correlation (rho = -0.57) with the first component of PSQI (subjective sleep quality). The SATED score showed a significant correlation with every sleep diary measurement except for the number of awakenings.

The sleep quality construct measured by the SATED questionnaire was evaluated through its association with the degree of anxiety (STAI questionnaire) and mood profile (POMS questionnaire). Table 4 shows that the results of the construct validation were consistent with the expected theoretical directions, with higher SATED scores associated with lower anxiety and more positive ratings on the mood profile.

The mean time (SD) for completion of the questionnaire was 0.9 (0.55) minutes per participant. A majority (94.5%) of the participants expressed not needing assistance to answer the questionnaire. In general, participants described the questionnaire as clear, easy and intelligible. However, 104 (52%) participants stated that they could have responded with more than one answer for some questions of the questionnaire.

Test-retest reliability assessed using Pearson correlation on 21 subjects over a one-week period was 0.93 (p value < 0.001), greater than typical cut-off of 0.7 for test-retest reliability [17].

## Discussion

In the present study, a Spanish-language version of the SATED questionnaire was adapted and validated for use as a tool for measuring sleep health at the population level. An initial translation and adaptation phase led to the creation of the final version proposed in this work. The second phase evaluated the reliability of the tool, demonstrating an acceptable internal consistency measured by Cronbach's α, and significant item-total correlations for all individual SATED items. An EFA showed the single-factor underlying structure of the questionnaire.

Suitable goodness of fit in confirmatory factor analysis confirmed its structure in an independent sample. This is the first time that the internal consistency and the underlying structure of the SATED questionnaire was evaluated in a broad and representative sample of a general population.

Criterion validity, construct validity and feasibility were evaluated in an independent sample of 200 subjects, stratified by sex, age, educational level, social level, sleep habits and pathologies by proportional allocation. Criterion validity was assessed with the ESS sleepiness scale, the PSQI sleep quality index and a one-week sleep diary, finding satisfactory correlations all in the expected directions. Construct validity was assessed with the STAI anxiety scale and POMS mood scale, finding also satisfactory correlations. The test-retest reliability showed high correlation between the answers to the test and its repetition one week later. Finally, the feasibility of the questionnaire was favorable, being easy, intelligible and requiring approximately one minute for completion. Thus, this SATED validation has demonstrated satisfactory psychometric properties, constituting the first validated tool in Spanish for sleep health measurement.

To date, only two studies have attempted to validate a tool for measuring sleep health, namely the Sleep Health Scale (SHS) and Sleep Health Index (SHI). Comparison with the SHS [6], also based on SATED and validated in the Portuguese population, reveals two significant differences. Firstly, SHS included the dimension of Regularity and found that the Efficiency dimension did not load on the single latent factor; and secondly, it uses a score of 0 to 5 for each item instead of a score of 0 to 2. Although the psychometric properties of both tools are similar in terms of reliability, this version in the present study exhibits better correlation with the Pittsburgh Sleep Quality Index, which was the only assessment of criterion/construct validity in the Becker study. In addition, in the SHS study, the sample selected was based on convenience, which could potentially affect generalization of the results at a population level. Finally, given that the dimension of Regularity was not considered in the current validation and the psychometric properties of the current validation were at least as good as those of the SHS, it cannot be confirmed nor denied that Regularity could be a 6$^{th}$ dimension of the sleep health construct.

Similar to our instrument, the SHI of the National Sleep Foundation[5] demonstrated a high reliability. However, in terms of criterion validity and construct validity, SHI was not compared with other tools, such as ESS, PSQI, STAI, POMS, or sleep diaries, but only with general questions about health status, stress or life satisfaction, with correlations close to 0.35. Thus, despite being longer and more complex, the SHI does not necessarily have superior psychometric characteristics compared to the present version of the SATED questionnaire. Moreover, SATED could be a better choice when time for completing the questionnaire is an important factor.

Healthy sleep can be defined as the sleep-wake pattern that best adapts to individual, social and environmental requirements, and optimizes the

physical, mental and social well- being of the individual [4]. Considering the adverse health outcomes associated with poor sleep health or sleep deficiency, it is essential to understand what questionnaires like SATED are measuring and how generalizable are data from population sleep health [4]. In a previous work, SATED scores have been shown to correlate with general health indicators, such as the self- perceived health status and total number of comorbidities [2]. The present work reveals that the most important psychological complaints in the general population, anxiety [18,19] and mood [20,21], correlate significantly with the SATED measure of sleep health. Published studies have linked individual sleep characteristics with indices of labor productivity, and healthy sleep with the social health of an individual [22–24]. Existing literature confirms the importance of measuring the sleep health at both the individual and population levels and is consistent with the idea that healthy sleep is a fundamental pillar of health.

The present adaptation and validation of the SATED questionnaire for its use in Spanish has several strengths. First, it used a large population sample to evaluate the reliability of the tool. Second, the questionnaire has been compared to a large number of tools, including ESS, PSQI, STAI, POMS and sleep diaries. Finally, it has been demonstrated to be simple and easy to use. Both Spanish and Catalan are Romance languages and there is a close relationship between the two; hence, language is not expected to have any substantial impact on the psychometric characteristics of the SATED. Finally, the absence of objective measures of sleep, specifically regarding sleep duration and efficiency, must be considered as a potential limitation of the current study and encouraged in upcoming validation studies.

In conclusion, we have described the process of developing, adapting, and validating the SATED questionnaire into the Spanish language. SATED

has been proven to be sufficiently reliable and valid for use to measure sleep health in the general population. Given the relevance of sleep health in an individual and at the population level, encouraging the use of SATED is expected to raise awareness that sleep, like diet and physical activity, is a key modifiable factor for promoting health.

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**Table 1.** Correlation between individual score of the SATED items and the total score.

| | Correlation SATED score | Correlation between items | | | | |
|---|---|---|---|---|---|---|
| | Total | Satisfaction | Alertness | Timing | Efficiency | Duration |
| Satisfaction | 0.69 | - | 0.14 | 0.31 | 0.27 | 0.55 |
| Alertness | 0.55 | | - | 0.17 | 0.17 | 0.14 |
| Timing | 0.60 | | | - | 0.24 | 0.34 |
| Efficiency | 0.64 | | | | - | 0.25 |
| Duration | 0.68 | | | | | - |

The table shows Spearman rank correlation coefficients. SATED: Satisfaction Alertness Timing Efficiency Duration.

**Table 2.** Saturations of the items in the rotated factor of the exploratory and confirmatory factor analysis.

| | EFA Factor 1 *(Std. loadings)* | CFA Factor 1 *(Std. loadings)* |
|---|---|---|
| Satisfaction | 0.803 | 0.795 |
| Alertness | 0.346 | 0.349 |
| Timing | 0.659 | 0.672 |
| Efficiency | 0.564 | 0.492 |
| Duration | 0.866 | 0.868 |

EFA: Exploratory Factor Analysis; CFA: Confirmatory Factor Analysis.

**Table 3.** Correlation between individual score of the SATED items and sleep diary measurements, ESS score and the PSQI sleep quality index.

| | Sleep Diary | | | | Questionnaires | |
|---|---|---|---|---|---|---|
| | Efficiency | TST | Awakenings | Latency | ESS | PSQI |
| Satisfaction | **0.32** | **0.23** | **-0.17** | **-0.24** | -0.14 | **-0.52** |
| Alertness | 0.10 | 0.09 | 0.07 | -0.13 | **-0.31** | **-0.28** |
| Timing | 0.05 | 0.06 | 0.03 | **-0.14** | 0.06 | -0.05 |
| Efficiency | **0.42** | 0.09 | **-0.19** | **-0.42** | -0.02 | **-0.45** |
| Duration | **0.18** | **0.27** | 0.09 | **-0.12** | -0.01 | **-0.38** |
| Total Score | **0.40** | **0.32** | -0.06 | **-0.38** | -0.15 | **-0.56** |

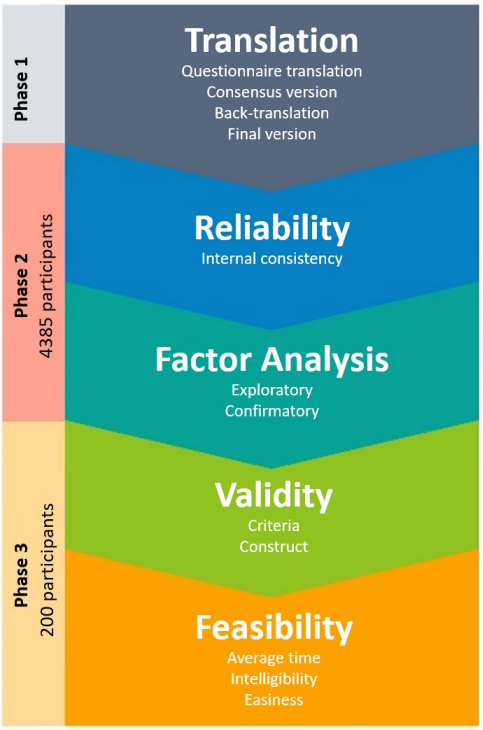
P-values below 0.05 appear in bold. TST: Total Sleep Time; ESS: Epworth Sleepiness Scale; PSQI: Pittsburgh Sleep Quality Index.

**Table 4.** Correlation between individual score of the SATED items and the degree of anxiety and mood profiles.

| | STAI | | | POMS | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Sum of positive items | Sum of negative items | Degree of anxiety | Tension | Depression | Anger | Vigor | Fatigue | Sum of positive items | Sum of negative items | Total Score |
| Satisfaction | **-0.29** | **0.31** | **-0.26** | **-0.34** | **-0.28** | **-0.24** | **0.18** | **-0.23** | **-0.33** | **0.18** | **-0.37** |
| Alertness | -0.15 | **0.26** | **-0.22** | **-0.17** | **-0.21** | **-0.13** | **0.18** | **-0.26** | **-0.23** | 0.18 | **-0.27** |
| Timing | 0.00 | 0.04 | -0.04 | -0.01 | -0.02 | 0.05 | -0.05 | -0.09 | -0.03 | -0.05 | 0.01 |
| Efficiency | **-0.25** | **0.24** | **-0.22** | **-0.25** | **-0.35** | **-0.20** | **0.17** | **-0.21** | **-0.30** | **0.17** | **-0.32** |
| Duration | **-0.14** | **0.17** | **-0.19** | **-0.24** | **-0.15** | **-0.15** | 0.04 | **-0.20** | **-0.22** | 0.04 | **-0.21** |
| Total | **-0.27** | **0.30** | **-0.29** | **-0.30** | **-0.32** | **-0.23** | **0.18** | **-0.26** | **-0.35** | **0.18** | **-0.37** |

P-values below 0.05 appear in bold. STAI: State-Trait Anxiety Inventory; POMS: Profile of Mood States.

Figure 1. Adaptation and validation of the SATED questionnaire.



# Validation of the Satisfaction Alertness Timing Efficiency and Duration (SATED) questionnaire for sleep health measurement

Ivan Benítez, Núria Roure, Lucía Pinilla, Esther Sapiña-Beltran, Daniel J Buysse, Ferran Barbé, Jordi de Batlle

**Online Supplement**

SATED Spanish translation:

| Cuestionario de salud del sueño SATED | | | | | |
|---|---|---|---|---|---|
| **Con qué frecuencia usted....** | | | | | |
| | Nunca | Muy pocas veces | Algunas veces | A menudo | Siempre |
| **1**. ¿Está satisfecho/a con su sueño? | ☐ | ☐ | ☐ | ☐ | ☐ |
| **2**. ¿Permanece despierto/a todo el día sin quedarse dormido/a? (no incluye la siesta) | ☐ | ☐ | ☐ | ☐ | ☐ |
| **3**. ¿Duerme (o intenta dormir) entre las 2 y las 4 de la madrugada)? | ☐ | ☐ | ☐ | ☐ | ☐ |
| **4**. Por la noche, ¿pasa menos de 30 minutos despierto? (incluye el tiempo que pasa para quedarse dormido y los despertares nocturnos) | ☐ | ☐ | ☐ | ☐ | ☐ |
| **5**. ¿Duerme entre 6 y 8 horas al día? (incluye la siesta) | ☐ | ☐ | ☐ | ☐ | ☐ |

Cada ítem del cuestionario tiene una puntuación de 0 a 2 puntos, siendo 0 para "nunca" o "muy pocas veces", 1 para "algunas veces", y 2 para "a menudo" o "siempre". La puntuación total se obtiene sumando la puntuación de los 5 ítems del cuestionario. La puntuación total del cuestionario va de 0 a 10 puntos, siendo 0 la peor salud del sueño y 10 la mejor salud del sueño.

**SATED Catalan translation:**

| Qüestionari de salut del son SATED | | | | | |
|---|---|---|---|---|---|
| **Amb quina freqüència vostè....** | | | | | |
| | Mai | Molt poques vegades | Algunes vegades | Sovint | Sempre |
| **1**. Està satisfet/a amb el seu son? | ☐ | ☐ | ☐ | ☐ | ☐ |
| **2**. Es manté despert/a tot el dia sense quedar-se adormit/da? (no inclou la migdiada) | ☐ | ☐ | ☐ | ☐ | ☐ |
| **3**. Dorm (o intenta dormir) entre les 2 i les 4 de la matinada? | ☐ | ☐ | ☐ | ☐ | ☐ |
| **4**. Durant la nit, passa menys de 30 minuts despert/a? (inclou el temps que passa per quedar-se adormit/da i les interrupcions del son) | ☐ | ☐ | ☐ | ☐ | ☐ |
| **5**. Dorm entre 6 i 8 hores al dia? ( inclou la migdiada) | ☐ | ☐ | ☐ | ☐ | ☐ |

Cada ítem del qüestionari te una puntuació de 0 a 2 punts, coresponent una puntuació de 0 per "mai" o "molt poques vegades", 1 per "algunes vegades", i 2 per "sovint" o "sempre". La puntuació total s'obté sumant la puntuació dels 5 ítems del qüestionari. La puntuación total del qüestionari va de 0 a 10 punts, essent 0 la pitjor salut del son i 10 la millor salut del son.

Table E1. Results of the SATED questionnaire for the 4385 participants of the ESCA 2015.

| | Never | Rarely | Sometimes | Usually | Always | Total Score |
|---|---|---|---|---|---|---|
| Satisfaction | 114 (2.60%) | 368 (8.39%) | 755 (17.2%) | 1369 (31.2%) | 1779 (40.6%) | 1.61 (0.68) |
| Alertness | 486 (11.1%) | 350 (7.98%) | 703 (16.0%) | 868 (19.8%) | 1978 (45.1%) | 1.46 (0.79) |
| Timing | 122 (2.78%) | 161 (3.67%) | 639 (14.6%) | 900 (20.5%) | 2563 (58.4%) | 1.73 (0.57) |
| Efficiency | 442 (10.1%) | 418 (9.53%) | 857 (19.5%) | 982 (22.4%) | 1686 (38.4%) | 1.41 (0.80) |
| Duration | 133 (3.03%) | 244 (5.56%) | 370 (8.44%) | 1036 (23.6%) | 2602 (59.3%) | 1.74 (0.60) |

SATED: Satisfaction Alertness Timing Efficiency Duration; ESCA: Health Survey of Catalonia.

Table E2. Main characteristics of the subjects in phase 3 (n=200)

| | |
|---|---|
| Sex: Men | 76 (38%) |
| Age (years) | 44 (30-57) |
| BMI | 23 (20-25) |
| Social class (education) | |
| Primary | 32 (16%) |
| Secondary | 53 (26.5%) |
| University | 104 (52%) |
| NA | 11 (5.5%) |
| At least one chronic disorder | 60 (30%) |

Proportion or median [P25-P75], as appropriate.

## *5.2. Resultados del objetivo O.1.2*

**Título:** Impact of sleep health on self-perceived health status

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SCIENTIFIC REPORTS

OPEN

# Impact of sleep health on self-perceived health status

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**Although sleep habits have long been recognized as a promoter of health, the World Health Organization 2014 report on non-communicable diseases (NCDs) only listed smoking, alcohol intake, diet and physical activity (PA) as key modifiable risk factors that could enhance health and prevent NCDs. Cross-sectional data on 4385 surveys from the 2015 Catalan Health Survey, representative of the 2015 non-institutionalized Catalan population over age 14, were used to assess and compare the independent associations of low PA (International Physical Activity Questionnaire (IPAQ): low activity); poor diet (PREvención con DIeta MEDiterránea questionnaire (PREDIMED): low-adherent); poor sleep health (Satisfaction, Alertness, Timing, Efficiency and Duration scale (SATED): <8); smoking status; and, alcohol intake (high-risk drinker based on standard drink units) with having a poor self-perceived health status. Logistic regression models adjusted by age, gender, education level and number of comorbidities showed that poor sleep health had the strongest independent association with poor self-perceived health status (OR = 1.70; 95%CI: 1.37–2.12), followed by poor diet (OR = 1.37; 95%CI: 1.10–1.72) and low PA (OR = 1.31; 95%CI: 1.01–1.69). This suggests that sleep habits should be included among the important modifiable health risk factors and be considered a key component of a healthy lifestyle.**

Having a healthy lifestyle is key to enjoying good health and avoiding non-communicable diseases (NCDs). In this sense, the World Health Organization (WHO) 2014 report on NCDs cited reduction in alcohol, salt/sodium and tobacco use; increased physical activity (PA); and, halting the rise of the hypertension, diabetes and obesity as some of the global targets for the control of NCDs[1]. Similarly, Ezzati and Riboli listed smoking, alcohol consumption, excess weight and obesity, diet and nutrition, and PA in their summary of behavioural and dietary risk factors for non-communicable diseases published in 2013[2]. Interestingly neither the 280-page long WHO report nor the highly cited article referred to sleep health or sleep habits as a potentially modifiable factor that could enhance health and prevent NCDs.

The interest in healthy sleep as a promoter of health has been documented since the origins of medicine, through the Middle Ages and up to the present. Short sleep duration has specifically been associated with hypertension[3,4], cerebrovascular diseases[5], coronary heart diseases[6,7], cancer[5,8], obesity[9], diabetes[10], and all-cause mortality[11,12]. Similarly, long sleep duration has been associated with adverse health outcomes[10,11,13]. Growing evidence suggests that sleep habits beyond sleep duration, such as changes in sleep timing due to shift work[14,15] or even subjective sleep quality[16,17], could be associated with NCDs, quality of life and overall health status.

In this context, it is reasonable to ask whether sleep health is a neglected pillar of health. Using data from the 2015 Catalan Health Survey (ESCA)[18], the authors aimed to assess and compare the relative weights of diet, PA, smoking, alcohol consumption and sleep in relation to self-perceived health status.

## Methods

**Design, population and data collection.** This is an observational cross-sectional study based on the ESCA 2015 survey[18]. The study population and sampling methodology have been described elsewhere[19]. Briefly, a multistage probability sampling method was used to obtain a representative sample of the non-institutionalized population in Catalonia in 2015. Up to 5598 surveys were obtained in two waves using computer-assisted

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interviews. Full details on the interviewing methodology have been described elsewhere[19]. For the purpose of this manuscript analyses a total of 4385 surveys corresponding to people above 14 years-old and not working night shift were considered.

The survey consisted on almost 500 questions including sociodemographic variables; health status & health-related quality of life; chronic diseases; unintentional injuries; pharmacological treatment; daily life limitations and disability; preventive practices; social support; mental wellbeing; dietary habits; PA and mobility; tobacco; alcohol; cannabis; use of healthcare resources during last 15 days and last year; material deprivation; and, sleep health. A full description of the ESCA 2015 questionnaire can be found elsewhere[19] and the complete survey, in Catalan or Spanish, is publicly available from the Catalan Government web site (http://salutweb.gencat.cat/ca/el_departament/estadistiques_sanitaries/enquestes/esca/ [Accessed: August 20th, 2018]).

Sleep health was assessed using the SATED scale (Satisfaction, Alertness, Timing, Efficiency and Duration)[20]. Briefly, SATED is the result of a comprehensive review of the literature on sleep dimensions and their association with specific health outcomes in an attempt to create a tool capable of quantifying sleep health. SATED assesses 5 dimensions of sleep health by means of 5 questions: sleep Satisfaction ("Are you satisfied with your sleep?"); Alertness during waking hours ("Do you stay awake all day without dozing?"); Timing of sleep ("Are you asleep, or trying to sleep, between 2:00 a.m. and 4:00 a.m.?"); sleep Efficiency ("Do you spend less than 30 minutes awake at night? This includes the time it takes to fall asleep and awakenings from sleep"); and sleep Duration ("Do you sleep between 6 and 8 hours per day?"). Respondents indicate the frequency with which they experience or engage in each dimension, with answers ranging from 0 to 2 points (0 = "never" or "very rarely"; 1 = "sometimes"; 2 = "often" or "always"). Items on the SATED scale can be totalled to produce a single summary score, ranging from 0 (very poor sleep health) to 10 (excellent sleep health). For the purpose of this study having a SATED score $<8$ was considered as poor sleep health; this threshold corresponds to the median for this population as published elsewhere[19].

The *PREvención con DIeta MEDiterránea* (PREDIMED) questionnaire[21,22], measuring adherence to Mediterranean diet, was used as a measure of the healthiness of participants' diet. Any score below 9 out of 14 questions was considered as a poor adherence to Mediterranean diet and thus poor diet, whereas scores of 9 or more were considered as a healthy diet. PA was measured using the International Physical Activity Questionnaire (IPAQ)[23,24], that classifies subjects' PA in low, moderate or vigorous. For the purpose of the analyses, we considered moderate and vigorous PA as a healthy PA and low PA as a poor PA. Smoking was assessed by a question on smoking status (never, former, current). Finally, an estimation of each subject's risk of abusing alcohol was defined based on consumed standard drink units. Any weekly alcohol intake up to 28 standard drinks ("standard drinks" = 10 grams of pure alcohol) for men and 17 for women in the last 12 months was considered as low risk. Intake above these levels was considered high risk. Subjects without any alcohol intake in the last 12 months were considered as non-drinkers[25].

Self-rated health status was assessed with the question: "In general, how would you rate your health" with the possible choices being "excellent", "very good", "good", "fair", or "poor". For the current analyses, excellent, very good and good ratings were considered as good self-rated health status while fair and poor as a poor self-rated health status.

The ESCA survey is an official statistic of the Catalan Government. It was approved by the Consultants' Committee of Confidential Information Management (CATIC) from the Catalan Health Department. ESCA was conducted in accordance to the Catalan and Spanish regulatory framework, in agreement with the year 2000 revision of the Helsinki Declaration. All participants in the ESCA survey were adequately informed and provided consent to participate. Data analysed in this study are included in this published article (Supplementary Information Files).

**Statistical analysis.** Appropriate weighting adjustment was applied to achieve representative frequencies, as less populated territories were oversampled. Continuous variables were summarized as the mean (standard deviation) and categorical variables as percentages. Diet, PA, smoking, alcohol consumption and sleep health were assessed, individually and jointly, as determinants of poor self-rated health using a survey-weighted logistic model[26] adjusted for age, gender, education level and number of comorbidities. A modelling of the effect of the number of risk categories on self-perceived health status was used to assess the additive effect of having multiple poor health behaviours. The conferred risks were estimated using odds ratios (OR) and 95% confidence intervals (CI). Differences in the classification accuracy of the models were assessed by comparing the area under the receiver operating characteristic curve (AUC). Goodness of fit was assessed using the Hosmer-Lemeshow calibration test. R statistical software, version 3.4.1, was used for all the analyses. All tests were two tailed, and p-values $< 0.05$ were considered statistically significant.

## Results

4385 surveys representative of the Catalan population were included in the analyses. The main sociodemographic, life-style and health-related characteristics of the population are shown in Table 1. Briefly, 49% of the sample were men, mean age (SD) was 47 (19) years, 58% were never smokers, 34% non-drinkers, 51% had a high adherence to Mediterranean diet and 15% reported vigorous PA. Regarding sleep health, the population had a SATED score of 7.91 (2.17), with a 67% of subjects reporting good sleep health (SATED $\geq 8$). Finally, 81.7% of subjects reported themselves as having good self-rated health.

Table 2 shows logistic regression models examining the associations between tobacco use, alcohol consumption, diet, PA and sleep health and poor self-rated health status, adjusted for age, gender and number of comorbidities. Having poor sleep health showed the strongest independent association with a poor self-perceived health status (OR = 1.72; $p < 0.001$), followed by low adherence to Mediterranean diet (OR = 1.41; $p < 0.001$) and being a current smoker (OR = 1.38; $p = 0.01$). The predictive capacity of each of these models according to Receiver

| **Sociodemographic characteristics** | |
|---|---|
| Male gender | 49% |
| Age (years) | 47 (19) |
| Education level | |
| Primary | 24% |
| Secondary | 55% |
| University | 21% |
| **Lifestyle habits** | |
| Tobacco use | |
| Current smoker | 25% |
| Former smoker | 17% |
| Never smoker | 58% |
| Alcohol | |
| Non-drinker | 34% |
| Drinker (low risk) | 62% |
| Drinker (high risk) | 4% |
| Diet (PREDIMED) | |
| Low adherence to Mediterranean diet | 49% |
| High adherence to Mediterranean diet | 51% |
| Physical activity (IPAQ) | |
| Low | 26% |
| Moderate | 59% |
| Vigorous | 15% |
| Sleep health (SATED) | |
| Poor (SATED $<8$) | 33% |
| Good (SATED $\geq 8$) | 67% |
| **Health status** | |
| At least one chronic disease | 72% |
| Good self-rated health status | 82% |

**Table 1.** Main characteristics of the population. Proportion or mean (SD), as appropriate. PREDIMED: *PREvención con DIeta MEDiterránea* questionnaire; IPAQ: International Physical Activity Questionnaire; SATED: sleep Satisfaction Alertness Timing Efficiency and Duration scale.

operating characteristic (ROC) curves is compared in Fig. 1, and shows that PA (AUC = 0.664) and sleep health were the life-style factors that best identified individuals with poor self-rated health status (AUC = 0.626).

Table 3 shows the adjusted associations between tobacco use, alcohol consumption, diet, PA and sleep health and poor self-rated health status, in a single model that also adjusts for age, sex, education level and number of comorbidities. In this model, poor sleep health was the factor most strongly associated with poor self-perceived health status (OR = 1.70; $p < 0.001$). The associations for both smoking status and alcohol intake were not statistically significant.

Finally, a model assessing the additive effect of having multiple poor health behaviours is shown in Table 4. Having multiple poor health behaviours was associated to increased odds of poor self-rated health. This relation was dose-dependent, demonstrating an additive effect of poor health behaviours.

## Discussion

In this study, including data from a representative population sample of 4385 individuals, we assessed and compared the relative weights of diet, PA, smoking, alcohol consumption and sleep health in relation to self-perceived health status. Poor sleep health showed the strongest independent association with a poor self-perceived health status. This association held even when adjusting for the number of comorbidities and when all studied lifestyle factors were simultaneously adjusted.

It is well-known that sleep duration, either being too short or too long, is related to a poor health status at all ages[27–31]. Additionally, although less evidence is available, sleep quality has also been related to health status, showing stronger relations than sleep duration in most studies[32,33]. However, few studies up to date have tried to assess simultaneously the impact of sleep together with other key lifestyle factors in relation to health status, and only two of them included all the key modifiable risk factors identified by the WHO: smoking, alcohol intake, diet and PA[34,35]. For instance, Bayán-Bravo *et al.* prospectively assessed the impact of traditional (non-smoking, being very or moderately active and having healthy diet) and non-traditional (sleeping 7–8 h/d, being seated $<8$ h/d, and seeing friends every day) health behaviours in relation to health-related quality of life (HRQL) in a cohort of 2,388 subjects aged $\geq 60$. PA, adequate sleep duration and sitting less, were associated with better HRQL in the short-term follow-up (2.5 years), whereas in the long term (8.5 years) only PA showed a significant association with HRQL[34]. However, this study assumed that health behaviours were stable over time, and did not assess dimensions of sleep health other than duration. Both limitations are relevant to the changes in sleep patterns

| | OR (95%CI) | p-value |
|---|---|---|
| Tobacco | | |
| Non-smoker | Ref | |
| Smoker | 1.38 (1.07–1.79) | 0.01 |
| Alcohol | | |
| Low risk drinker | Ref | |
| High risk drinker | 1.25 (0.71–2.20) | 0.43 |
| Diet | | |
| High-moderate adherence to Mediterranean diet | Ref | |
| Low adherence to Mediterranean diet | 1.41 (1.12–1.77) | <0.001 |
| Physical activity | | |
| Vigorous- Moderate | Ref | |
| Low | 1.34 (1.03–1.73) | 0.003 |
| Sleep health | | |
| Good (SATED ≥ 8) | Ref | |
| Poor (SATED < 8) | 1.72 (1.39–2.13) | <0.001 |

**Table 2.** Logistic regression models examining the association between tobacco use, alcohol consumption, diet, physical activity and sleep health and poor self-rated health status. Logistic regression models adjusted for age, gender, education level and number of chronic diseases. SATED: sleep Satisfaction Alertness Timing Efficiency and Duration scale.

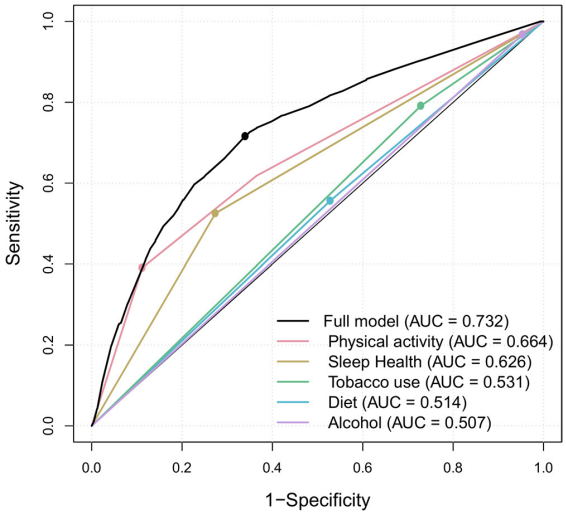


**Figure 1.** Receiver operating characteristic curves for the associations between life-style habits and self-rated health status. Logistic regression model. AUC: area under the curve.

usually seen with ageing: an increase in sleep duration combined with a decrease in sleep quality[19]. Duncan *et al.* assessed the cross-sectional associations of smoking, physical activity, diet, sitting time, sleep duration and sleep quality on self-perceived health among 10,478 individuals. Poor sleep quality, followed by low PA, had the strongest associations with self-perceived health[35]. Finally, several studies have assessed the combined effects of sleep duration and/or quality and other behavioural risk factors in relation to different health outcomes, all of them identifying significant relationships between sleep health and the studied health outcomes[36–40].

The results of this study suggest that having healthy sleep, and thus being satisfied with the way we sleep, is a key factor in the self-perception of health. Individuals describing their sleep health as poor are less likely to report good self-perceived health than individuals engaging in other unhealthy habits such as tobacco smoking or alcohol consumption. This suggests that the link between sleeping well and feeling well is, if anything, tighter than the link with other well-known unhealthy habits. However, these associations do not necessarily imply that that poor sleep habits are the strongest modifiable health risk factor. People's perceptions of sleep could lead to ratings of poor perceived health via reverse causality: "I perceive that I am not healthy because I don't feel rested when I get up in the morning" or "I am struggling to get asleep every night thus my health cannot be good". Therefore, the current results should not be interpreted as a proof of sleep health being the strongest modifiable risk factor for

| | OR (95%CI) | p-value |
|---|---|---|
| Gender: female | 0.96 (0.77–1.20) | 0.71 |
| Age | | |
| <45 years | Ref | |
| 45–64 years | 2.15 (1.63–2.83) | <0.001 |
| 65–74 years | 1.71 (1.25–2.72) | 0.02 |
| ≥75 years | 2.65 (1.35–5.19) | <0.001 |
| Number of chronic diseases | 1.47 (1.41–1.54) | <0.001 |
| Education level | | |
| Primary | Ref | |
| Secondary | 0.74 (0.57–0.95) | 0.02 |
| University | 0.57 (0.39–0.82) | <0.001 |
| Non-smoker | Ref | |
| Smoker | 1.29 (1.00–1.68) | 0.05 |
| Non-drinker/low risk drinker | Ref | |
| High risk drinker | 1.18 (0.66–2.12) | 0.57 |
| High/moderate adherence to Mediterranean diet | Ref | |
| Low adherence to Mediterranean diet | 1.37 (1.10–1.72) | <0.01 |
| Vigorous/Moderate physical activity | Ref | |
| Low physical activity | 1.31 (1.01–1.69) | 0.04 |
| Good sleep health (SATED ≥ 8) | Ref | |
| Poor sleep health (SATED < 8) | 1.70 (1.37–2.12) | <0.001 |

**Table 3.** Logistic regression model examining the mutually adjusted associations between tobacco use, alcohol consumption, diet, physical activity and sleep health and poor self-rated health status. A single logistic regression model adjusted for age, gender, education level, number of chronic diseases and all considered modifiable risk factors at the same time. SATED: sleep Satisfaction Alertness Timing Efficiency and Duration scale.

| | OR (95%CI) | p-value |
|---|---|---|
| Absence of health risk behaviours | Ref | |
| 1 Health risk behaviour | 1.27 (0.94–1.73) | 0.13 |
| 2 Health risk behaviours | 1.57 (1.13–2.18) | 0.01 |
| 3 Health risk behaviours | 2.66 (1.80–3.92) | <0.001 |
| 4 or 5 Health risk behaviours | 5.18 (2.91–9.24) | <0.001 |

**Table 4.** Adjusted logistic regression model examining the additive effect of having multiple poor health behaviours on poor self-rated health status. Model adjusted for age, gender, education level and number of chronic diseases.

overall health status, but as an indication that sleep health may have been neglected when considering modifiable risk factors related to health.

From a public health perspective, the current study increases the evidence relating sleep health with overall health status. The promotion of healthy sleep habits could, therefore, be considered as a potential strategy to promote not only the overall health status of a given population, but also the self-perception of being healthy. This study also shows that having multiple poor health behaviours is associated to increased odds of poor self-rated health. Therefore, the promotion of healthier sleep habits could have a synergistic effect with other health promotion activities[35,41].

The current study has several strengths, including: (i) a large sample size, selected to be representative of the Catalan population; (ii) comprehensive measures of behavioural risk factors; and, (iii) a detailed assessment of sleep health including multiple dimensions. On the other hand, several limitations must be acknowledged: (i) the cross-sectional design did not allow establishment of the direction of the associations and, therefore, whether poor sleep health is a cause or a consequence of a poor self-perceived health status falls beyond the scope of the current analyses; (ii) the SATED scale has yet to be formally validated, although their five dimensions have been consistently associated with health outcomes and no other validated tool is currently available to measure sleep health; (iii) all behavioural risk factors were self-reported and thus potentially subject to some degree of reporting bias and/or social desirability bias; and, (iv) although the dichotomization of the behavioural risk factors allowed for a direct comparison of the magnitude of their effects, it also implied some degree of misclassification. This could be especially relevant in the case of former smokers who quitted because of medical conditions.

In conclusion, our study suggests that sleeping habits are amongst the strongest potentially modifiable risk factors associated with the self-perception of health, independent of age, gender and the number of comorbidities. Although poor sleep health can be a cause or a consequence of a poor self-perceived health status, these findings show that sleep habits should not be neglected when defining a healthy lifestyle.

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## Author Contributions

Conceptualization: J.d.B., F.B. and M.S.d.l.T. Data Curation: I.B., O.G.-C. and A.M.-B. Formal Analysis: I.B. Resources: D.J.B., E.S. and J.E. Supervision: J.d.B. and F.B. Interpretation of data: M.D., I.B., E.S.-B., R.E.P., D.J.B., M.S.d.l.T., F.B. and J.d.B. Writing – Original Draft Preparation: M.D., I.B. and J.d.B. Writing – Review & Editing: all. M.D. and I.B. contributed equally to this work and are co-first authors.

## Additional Information

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## *5.3. Resultados del objetivo O.2.1*

**Título:** Primary versus Specialist Care for Obstructive Sleep Apnea: A Systematic Review and Individual-Participant Data-Level Meta-Analysis

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# Primary vs. Specialist Care for Obstructive Sleep Apnea: A Systematic Review and Individual Participant Data Level Meta-Analysis

**Short title:** Primary vs. specialist care for OSA: IPD meta-analysis

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**Contributors:** EV, IB, CLC, DM, and FB were responsible for the study conception and design; BK guided the cost-effectiveness analysis; EV and AS contributed to data extraction and evaluation of included studies; IB, EV and BK contributed to data analysis and interpretation; EV drafted the manuscript. All authors provided a critical review and approved the final manuscript. EV and IB contributed equally as co-first authors and are the guarantors; they had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analyses. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

**Impact statement:** Inadequate sleep disorders training and resourcing of primary care clinicians results in very high levels of underdiagnosis and inadequate management of obstructive sleep apnea (OSA), leading to unnecessary costs ranging from millions to billions, which could be reduced through improving primary care-based management. A previous systematic review comparing provider types for OSA management did not pool results, nor conduct any sub-group analyses; furthermore, two randomized controlled trials were published on the topic after the previous

review. This individual participant data level meta-analysis provides the highest level of evidence that primary care-based management of uncomplicated OSA produces very similar outcomes to specialist care at a lower cost, and indicates that sub-groups of gender, age, severity of OSA, and severity of daytime sleepiness obtain similar results in both management settings.

**Abstract**

**Rationale:** Primary care clinicians may be well placed to play a greater role in obstructive sleep apnea management.

**Objectives:** To evaluate the outcomes and cost-effectiveness of sleep apnea management in primary versus specialist care, using an individual-participant data meta-analysis to determine whether age, gender, severity of OSA and daytime sleepiness impacted outcomes.

**Methods:** Data sources were CINAHL, CENTRAL, MEDLINE Ovid SP, Scopus, ProQuest, US NIH Ongoing Trials Register, ISRCTN registry [inception until 09-25-2019]. Hand- searching was undertaken. Two authors independently assessed articles and included trials that randomized adults with a suspected diagnosis of sleep apnea to primary versus specialist management within the same study and reported daytime sleepiness using the Epworth Sleepiness Scale (range 0-24; >10 indicates pathological sleepiness; minimum clinically important difference two units) at baseline and follow-up.

**Results:** The primary analysis combined data from 970 (100%) participants **(**four trials). Risk of bias was assessed (Cochrane Tool). One-stage intention-to-treat analysis showed a slightly smaller decrease in daytime sleepiness (0.8; 0.2 to 1.4), but greater reduction in diastolic blood pressure in primary care (-1.9; -3.2 to -0.6 mmHg), with similar findings

in the per protocol analysis. Primary care-based within-trial healthcare system costs per participant were lower (-$448.51 USD), and quality-adjusted life years and daytime sleepiness improvements were less expensive. Similar primary outcome results were obtained for sub- groups in both management settings.

**Conclusions:** Similar outcomes in primary care at a lower cost provide strong support for implementation of primary care-based management of sleep apnea.

**Registration:** PROSPERO (CRD42020154688).

**Key words:** Sleep Apnea, Obstructive, Primary Health Care, Systematic Review, Meta- Analysis

## Introduction

Obstructive sleep apnea (OSA) is a common chronic disorder characterized by repeated episodes of upper airway collapse during sleep, which results in nocturnal hypoxemia and sleep fragmentation. OSA is strongly associated with increased risk for cardiovascular disease (1), traffic accidents (2), poor hypertensive control (3), cognitive impairment (4) and reduced quality of life (5). Almost one billion adults worldwide are affected by OSA, and under-diagnosis and under-treatment is widespread (6, 7).

A lack of sleep-specific training for primary care physicians contributes to widespread under recognition of sleep disorders, and an over-reliance on specialist care when problems are detected, and this, in combination with a large and increasing number of presentations to primary care, has led to long waiting times for access to specialist care ranging from several months to years in the United States (US) and elsewhere (8-11). In the US, it is estimated that just 20% of those with clinically significant OSA are currently receiving treatment (6, 12) with a similar figure estimated in the United Kingdom (UK) (13). In 2015, the net estimated economic benefit of identifying and treating those with undiagnosed OSA in the US was

$100 billion (14).

A 2018 systematic review compared sleep specialists with non-sleep specialists in OSA identification and treatment (15), and found similar outcomes with both provider types, but did not pool and meta-analyze the data. Furthermore, at least two randomized controlled trials (RCTs) with the largest series of participants were published after the review (16, 17). To address this shortfall in knowledge, we undertook an individual-participant data (IPD)-level meta-analysis. This type of meta-analysis

provides greater precision and power to assess the overall efficacy of primary care vs specialist care for uncomplicated OSA compared with traditional meta-analytical methods (18), and the performance of primary care-based management in clinically important subgroups based on age, gender, severity of the condition and severity of daytime sleepiness.

## Methods

This IPD systematic review was prospectively registered (CRD42020154688) and was conducted in accordance with the PRISMA-IPD Checklist (19).

*Data sources and searches*

To be eligible for inclusion, trials were required to be closed to participant accrual (i.e. no longer recruiting) and to have:

a. reported the primary outcome of daytime sleepiness at both baseline and follow-up;
b. adequate random sequence generation and allocation concealment methods;
c. randomized adults (18+ years) with a suspected diagnosis of OSA;
d. randomized participants to management of OSA in primary care vs in a specialist sleep unit within the same study.

Trials were excluded if the primary care management arm treated participants with OSA who had previously been treated within a specialist sleep unit (e.g. annual review in primary care rather than initial treatment).

*Study selection*

Our search strategy utilized the following databases and trial registries from inception to 25th September 2019:

1. The Cumulative Index to Nursing and Allied Health Literature (CINAHL) database;
2. Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library, via the Cochrane Register of Studies;
3. MEDLINE Ovid SP;
4. Scopus;
5. ProQuest;
6. US National Institutes of Health Ongoing Trials Register (www.ClinicalTrials.gov);
7. ISRCTN registry (https://www.isrctn.com/).

The search strategy was developed by EV, in conjunction with a librarian specializing in systematic review searches (SB). We identified relevant search terms by manually reviewing the MeSH terms and keywords in a small sample of relevant studies in MEDLINE and assessing other likely search terms. We adapted the MEDLINE search strategy for use in the other databases (full strategy provided in Table E1). No date or language restrictions were utilized.

*Specification of outcomes and effect measures*

The primary outcome was prespecified as change in daytime sleepiness, from baseline to latest follow-up, measured using the Epworth Sleepiness Scale score [ESS] (20), which is a widely used questionnaire in which respondents are asked to rate (between 0 and 3) their chances of falling asleep while engaged in 8 different daily activities (range 0 to 24, with higher scores indicating greater daytime sleepiness and a minimum clinically important difference of 2-points (21)). The ESS has been shown to have good test-retest reliability, adequate internal consistency,

concurrent validity with objective tests of sleepiness, and discriminate validity compared to other symptom dimensions (22, 23).

*Secondary outcomes:*

1. Treatment adherence (Continuous Positive Airways Pressure [CPAP] use in hours/night)
2. Quality of life
3. Patient satisfaction
4. Cost-effectiveness
5. Change in blood pressure (systolic and diastolic)
6. Change in body mass index (BMI).

*Study selection processes*

Two authors (EVR, AS) independently assessed abstracts, then reviewed relevant full texts for inclusion. Hand-searching of reference lists of included studies and relevant review articles was undertaken.

*Data extraction and quality assessment*

IPD from each included study was available within the authorship group. Data items were selected based on review of included studies, and clinical experience. Data from each included study was shared with the co-first author/statistician (IB) to allow meta-analysis.

Two reviewers (EV and AS) independently assessed the risk of bias for the included studies using the Cochrane Risk of Bias tool (24). The cumulative body of trials was also assessed for overall risk of bias pertaining to completeness of available data in all pre-specified outcomes.

*Statistical analysis*

Intention-to-treat and per protocol analyses were undertaken for primary,

secondary and cost- effectiveness outcomes. The intention-to-treat sample included all randomized participants.

The per protocol sample included participants who completed follow-up. Details of methods for accounting for missing data are provided in the Online Data Supplement Methods E1. Analysis was undertaken using R-Project Software (version 3.6) (25). To ensure data integrity, a data-checking report was generated for each trial to check: (a) whether all values were within expected ranges; (b) the missing data profile; and (c) for outliers. Data were meta-analyzed using both a "one-stage" approach as the primary analysis, and a "two-stage" approach as a sensitivity analysis (26).

We chose a one-stage model as the primary meta-analytical method due to: (a) increased power to detect treatment-covariate interactions; (b) ability to control for aggregation bias; and (c) use of a more exact likelihood specification that avoids assumptions of within-study normality and known within-study variances (18, 26). The one-stage method combined all IPD in a single meta-analysis based on a linear mixed-effects model that included baseline measurement and allocated group (i.e. primary care or specialist care) as fixed effects, and trial as random effect for the intercept, using the R-Project statistical package titled Linear and Nonlinear Mixed Effects Models (i.e. ‘nlme’) (27). Additionally, as was done in each of the trials, a non-inferiority test of primary care vs specialist sleep unit care was performed for the primary outcome (ESS) with a pre-established limit of 2-points (21). Details of subgroup and interaction rationale and analyses are provided in Methods E1. In the two-stage analysis, the IPD from each study were analyzed separately using a linear model that was fitted separately for each study (with baseline measurement and allocated group) and then aggregate, or summary data calculated and

combined in a random effects meta-analysis model (26, 28). Heterogeneity was assessed using $I^2$ (29) and $\tau^2$ (30). The R- Project statistical package titled 'meta' (31) was used for the for the two-stage meta-analyses.

The cost-effectiveness analysis was performed by combining costs for each trial arm with measures of effectiveness (ESS score and QALYs). To depict the uncertainty in the cost- effectiveness results, cost and effectiveness replicate pairs were simulated using the bootstrap method and presented in a cost-effectiveness plane. Within-trial costs from a healthcare system perspective were sought, and included: nurse consultations, primary care physician consultations, sleep physician consultations, and diagnostic and CPAP titration studies. The costs of delivery of the education programs in primary care were also included. The cost of CPAP machines and consumables were excluded due to inconsistent reporting and differences in cost coverage between the healthcare systems. Participant travel costs were also excluded due to our focus on healthcare system costs, inconsistent reporting and because they represented only one component of participant costs. Within-trial costs were updated to reflect the specific inflation rate for each country as of January 2020. Within-trial costs are reported in both US dollars and Euros. QALYs were calculated based on EQ-5D-5L scores. As one of the studies reported only short-form 36 dimensions (SF-36) scores, these scores were mapped onto the EQ-5D-5L using model 3 by Rowen et al (32), which has the lowest predictive error.

**Results**

A total of 885 records were identified through database searching (Figure E1), and a further 162 studies were identified through hand searching the reference lists of related studies. 706 studies remained after duplicates

were excluded and 673 studies were excluded based on title and abstract screening. Full-text retrieval was attempted in 33 studies. Following full-text exclusion (Table E2), and further duplicate removal, four studies were assessed as eligible for inclusion. IPD was sought and obtained for all included studies.

*Study characteristics*

The characteristics of included studies are presented in Table 1. Each of the included studies were parallel-group, non-inferiority RCTs, conducted in both metropolitan and rural centers. Data from a total of 970 (range 155 to 303) participants (75% male) were available, and in each study, most included participants had moderate-to-severe OSA. All studies included a six-month follow-up and reported average CPAP adherence, and change in daytime sleepiness using the ESS, as well as blood pressure, and either BMI or weight.

Whilst there was some variation in diagnostic methods across the included trials, each study used a type III or IV portable monitoring device for at least a subset of the participants. Chai- Coetzer 2013 (33) used a validated two-step screening process for both primary care and specialist care arms, consisting of a positive result on the OSA50 questionnaire (34) and type IV portable monitoring device (ApneaLink, ResMed). Sánchez-de-la-Torre 2015 (35) included participants diagnosed within a specialist sleep unit according to either a conventional polysomnography (PSG) or respiratory polygraphy. Sánchez-Quiroga 2018 (36) used a type IV portable monitoring device (ApneaLink Air, ResMed) in their primary care- arm, and used full PSG in their specialist care-arm. In Tarraubella 2018 (37), the majority of participants in both management settings were diagnosed with OSA using respiratory polygraphy (96% in primary care and 73% in specialist care) with the remainder diagnosed using

polysomnography.

Educational and management approaches were similar. Each study provided a minimum of six-hours of education to primary care-based clinicians. In the Australian study, community- based nurses received five days of in-service training by specialist nurses at the tertiary sleep center (33). One study (Sanchez Quiroga 2018) took an alternative approach of providing a semi-automatic management protocol to clinicians. Both doctors and nurses managed participants in the primary care setting in each included study.

The specialist arm varied between studies; in two studies, specialist care was delivered by either a specialist sleep physician or sleep nurse (Sánchez-de-la-Torre 2015, Tarraubella 2018). In another study, whilst specialist sleep physicians were the principal decision-makers, both specialist sleep nurses and sleep physicians delivered care (Chai-Coetzer 2013), whereas in Sanchez Quiroga 2018, specialist sleep physicians made protocol-based treatment decisions.

*Participant characteristics*

Table E3 summarizes the characteristics of the participants within the IPD meta-analysis. Mean age was 54 years (74% male). Most participants were classified as either overweight or obese. 73% of participants were hypertensive according to American Heart Association criteria (39). The proportion of participants with various levels of daytime sleepiness differed more between studies than other characteristics. Most participants had either severe (50%) or moderate (28%) OSA; 15% had mild OSA and a small number of participants had none i.e. AHI < 5 (7%). Most participants prescribed CPAP therapy were adherent to the treatment at 6 months (67% using CPAP for ≥ 4 hours/night).

*IPD integrity*

There were no important issues identified in the data checking process. All observations for primary and secondary outcomes were within the expected clinical range. There were 19 (2%) participants without a primary outcome record (ESS) at the initial visit since they did not complete the visit, and <3% missing data across each of the secondary outcomes and sub- group categories.

*Risk of bias within studies*

All included studies had low risk of bias with regards to sequence generation methods, outcome data reporting, allocation concealment and selective reporting (Figure E2). Due to the nature of the intervention, it was not feasible to blind participants and personnel to treatment allocation, so it was not possible to exclude some risk of bias due to non-blinding; therefore, this criterion was assessed as "unclear." Outcome assessment was also undertaken non-blinded; many of the key study outcomes were self-reported, and therefore subject to potential bias due to participant knowledge of their treatment group allocation (40). No other forms of potential bias were identified.

*Risk of bias across studies*

Our search of clinical trial registries revealed no registered unpublished studies and therefore no evidence of publication bias. Each of the included studies reported all relevant outcomes.

*Primary synthesis results*

Table 2 describes the difference in mean change (comparing values at six-month follow-up with baseline) computed as the difference of primary care with respect to specialist care values for each of the primary and secondary outcomes using the one-stage IPD meta- analysis method. For the one-

stage primary outcome intention-to-treat analysis, data was available from 970 participants (100%) across each of the four included studies. This analysis showed a smaller decrease in daytime sleepiness in the primary care-setting (mean change difference of ESS was 0.8, 0.2 to 1.4, $P = 0.006$), which was significantly non-inferior to the two points of pre-established clinical relevance ($P < 0.001$) (21). A greater reduction in diastolic BP (-1.9; -3.2 to -0.6 mmHg, $P = 0.005$) was also found in the primary care arm. No other significant differences were detected; in particular, adherence to CPAP, the main therapy for OSA, did not differ between settings. Very similar findings were revealed by the per protocol analysis of the same outcomes. The lower powered two-stage analysis had

similar results but revealed no significant differences between the models of care (Table E4); a moderate, but non-concerning level of statistical heterogeneity was detected for the primary outcome ($I^2 = 34\%$) (Figure E3**)**. Patient satisfaction results were not reported due to non- comparability of assessment methods and lack of assessment in one trial.

*Additional analyses*

There were no significant differences between efficacy of models of care for any of the subgroup analyses. There was no significant interaction between OSA severity and care setting for the primary outcome of change in daytime sleepiness (Figure 1), nor for any of the secondary outcomes (Table E5). A non-clinically significant interaction favoring primary care-based management in older adults (≥ 65 years) was found in the per protocol analyses for the primary outcome (Table E6), but none were detected in the intention-to-treat analysis nor for any of the secondary outcomes. No significant interactions with model of care were detected for either the primary or secondary outcomes with regards to gender (Table E7), or severity of daytime sleepiness (Table E8a and E8b).

*Cost-effectiveness analysis results*

Average within-trial healthcare system costs per participant were lower for primary care- based management compared to specialist care-based OSA management by $448.51 USD (€399.49), 95% CI: -$492.78 to -$404.24 USD (Table E9). Although, there was an additional cost of provision of training to primary care-based clinicians, which was $41.5 USD (€37.09) per participant, this training cost was outweighed by cost savings resulting from much lower diagnostic testing costs (-$417.28 (€-371.68) and moderately lower clinician consultation costs -$72.77 USD (€64.81).

Figure 2 shows the cost-effectiveness analysis planes for outcomes based on both QALYs (a) and the ESS (b). Figure 2(a) indicates that 92% of the cost-QALY pairs in the Australian study (Chai-Coetzer 2013; Table E11) were in the south-east quadrant suggesting a very high probability (of at least 92%) that primary care-based OSA management was cost-saving and more effective as it dominated the specialist sleep unit-based OSA management model.

Similarly, for the Tarraubella 2018 study, 81% of the cost-QALY pairs were in the south-east quadrant suggesting that primary care-based OSA management had an 81% likelihood of being cost-saving and more effective compared to specialist care. Results for both the Sanchez-de-la-Torre 2015 and Sanchez-Quiroga 2018 studies indicated that primary care-based OSA management was cheaper, but less effective, to a non-clinically significant degree of <0.1 QALY (41). With regards to incremental daytime sleepiness (ESS) improvements (Figure 2b), the primary care model had a 67% probability of being cost-saving and more effective in Chai-Coetzer 2013 compared to specialist care. Results for the other three studies indicated that primary care-based OSA management was less expensive but also less efficacious, to a non-clinically relevant degree (i.e.

< 2 ESS points).

**Discussion**

*Summary of evidence*

Our IPD meta-analysis provides the highest level of evidence that primary care-based management of uncomplicated OSA is not only closely comparable to specialist-based care, but also deliverable at a lower cost. Importantly, we did not observe any clinically significant differences between the outcomes of the different settings. We observed a slightly smaller decrease in daytime sleepiness in the primary care-setting, which is less than the minimal clinically important difference (MCID) of two points (21). Notably, primary care-settings resulted in modest but greater reductions in diastolic blood pressure and a lower cost of care.

The greater reduction in diastolic blood pressure in the primary care setting may have reflected a greater tendency for primary care doctors to adjust hypertension medications, as part of their usual care responsibilities, and may also have reflected differences in methods of blood pressure determination (i.e. primary care physicians may have been more likely to take and average serial measures of blood pressure rather than recording the initial blood pressure, which is usually higher) (42). However, whilst limited data is available regarding the MCID for diastolic blood pressure, current evidence suggests a MCID of ≥ 2 mmHg DBP is required for significant reductions in cardiovascular events (43). Therefore, the larger reduction in diastolic BP in the primary care versus specialist arm (-1.9; -3.2 to -0.6 mmHg) is just under that required for clinical significance.

*Strengths and limitations*

This is the largest dataset assembled comparing primary with specialist

sleep unit care for management of OSA, and the first ever IPD on this topic. All data underwent additional checking by our statistician/co-first-author (IB). Our review was conducted in accordance with the PRISMA-IPD Checklist (19), and was prospectively registered (CRD42020154688).

For reasons outlined in the methods section, our cost-effectiveness analysis was limited to the healthcare system/provider perspective. Generalizability was limited by exclusion of participants with significant comorbidities. Whilst all studies were conducted in either Spain or Australia, the high number of participants (970) in conjunction with consistent findings indicate likely translatability of the findings into other healthcare systems, particularly in those countries that have similarities in their system, such as universal coverage/access (44). Additionally, generalizability was limited by inclusion of clinicians with and without prior sleep-disorder management experience in the primary care-arm of two trials (17, 33). Finally, due to the nature of the intervention, none of the participants nor clinicians were blinded. Outcome assessment was also undertaken non-blinded.

*Implications*

This IPD meta-analysis comprises the best available data for making policy decisions relating to uncomplicated OSA management in a primary care-setting. The results were consistently favorable for primary care-based management despite there being differences in the methods of up-skilling of clinicians across studies. Additionally, whilst there was some variation in diagnostic methods used, each study used a type III or IV portable monitoring device for at least a subset of the participants, providing further evidence of their utility in a primary care- setting. Each of the four trials excluded potential participants severe co-morbid disease (including advanced heart failure, any active neoplasm or tumour, active

psychiatric disorders and severe lung disease), other sleep disorders and/or previous CPAP treatment. Therefore, it is still recommended that patients with severe comorbidities be referred for specialist treatment.

A paradigm shift in how OSA is diagnosed and managed is occurring in Australia, and our findings provide strong support in favor of a further move towards primary care-based OSA management. In 2008, home-based sleep testing was approved in Australia (45); since then, a rapid rise in home-based sleep testing has occurred (45, 46). Since 2018, Australia's primary care doctors have been able to order a diagnostic sleep test for those who meet questionnaire- based criteria for a high probability of OSA without needing prior specialist review (9, 47). In 2019, Australia had a groundbreaking Parliamentary Inquiry into Sleep Health Awareness, which emphasized that improved education and upskilling of primary care clinicians is essential to enhance access to evidence-based sleep health services in the Australian community (48). In the same year, an Australian National Centre for Sleep Health Services Research was established, which is systematically working towards implementation of primary care-based management of sleep disorders.

Similarly, a transformation is occurring in how OSA is managed in the UK and Europe, where wait times to access specialist care are long due to a large number of patients requiring assessment and follow-up of OSA (49, 50). Therefore, primary care practices are already taking on a greater role in OSA management, including administering home sleep studies (which they fund through redirecting the practice income that would have gone to secondary care). More training in interpreting home sleep studies has been recommended in the UK (49, 50), and our systematic review indicates that just six-hours of education provided to primary care-based doctors/nurses is sufficient to produce effective care.

There is a clear need to address the large mismatch between sleep services and the number of patients with undiagnosed OSA requiring diagnosis and management in the United States, which experts believe will rapidly worsen for a number of reasons (12). Primary-care based management is a key possible solution that requires further investigation, and it's important to assess and address the interest and needs of primary care clinicians within the United States on this topic. Different levels of primary-care based involvement depending on locations and circumstances is likely to be necessary. In response to similar disease overburden issues, other medical specialties have established clinical pathways that have facilitated successful management of patients with chronic diseases such as asthma, chronic obstructive pulmonary disease and diabetes by primary care practitioners (51). Primary care- based management of these disorders has not uniformly been taken up given the high burden of disease management in this setting; often practitioners with special interests have taken on the role (52). It's likely that this kind of model would allow for adjustment to the diagnostic complexities and swift developments in the rapidly maturing sleep medicine field (51). For example, in the United Kingdom, some general practitioners have taken a special interest in sleep and have been providing diagnostic sleep services for many years (53). In Alberta, Canada, ongoing management of OSA is commonly undertaken in primary care (after diagnostic testing and CPAP set up is conducted by "respiratory homecare companies") (54).

Results from qualitative research in Australia and Canada indicates that a major motivating factor to increased participation in OSA management is primary care doctors' concerns about lack of access to diagnostic and management services for patients (54, 55). In qualitative/survey studies from various countries, including the United States, the main barriers to

providing primary-care based OSA management, from the perspective of primary care providers, were: poor self-rated knowledge of sleep disorders, a lack of confidence in management of OSA, a lack of clarity about different provider roles and the ease of referral to commercial providers (in some locations) (54-60). Additionally, the heterogeneity of types of clinicians providing primary care may pose an added barrier to implementation in the US. Addressing the knowledge and confidence gaps with better education and resources to support primary-care based management, and development and testing of innovative models of primary-care based management with input from primary care clinicians is essential.

The included studies provided a minimum of six hours of face-to-face education, including lectures and practical instruction. Whilst this resulted in comparable care outcomes, multiple hours of face-to-face training may not be feasible for many busy primary care practitioners. A survey of primary care physicians in Ohio indicated that the factors which most influenced current sleep-related practices were articles in journals, continuing medical education courses and discussions with specialists (56). In Australia, our National Centre for Sleep Health Services Research has assessed primary care clinician views, and has been developing a primary care practice change support suite to address barriers, including online guidelines, education modules with associated continuing medical education credit, education videos and resources (including funding and equipment) to work towards implementation of primary- care based management of OSA within Australian general practice. Similar work in other countries is needed.

In conclusion, this IPD-meta-analysis provides the highest level of evidence that comparable outcomes for OSA diagnosis and management

are achievable in primary care. Health services research into optimal methods of implementation of these findings is necessary.

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***Figure 1.*** Interaction between model of care and OSA severity for the primary outcome (change in daytime sleepiness)

ESS = Epworth Sleepiness Scale; OSA = obstructive sleep apnea; AHI = apnea-hypopnea index; h = hour.

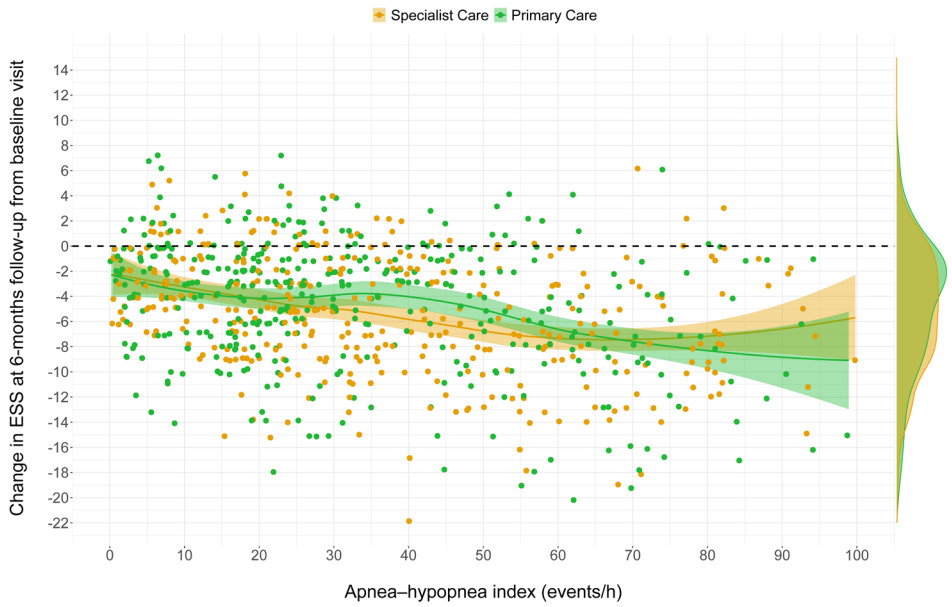
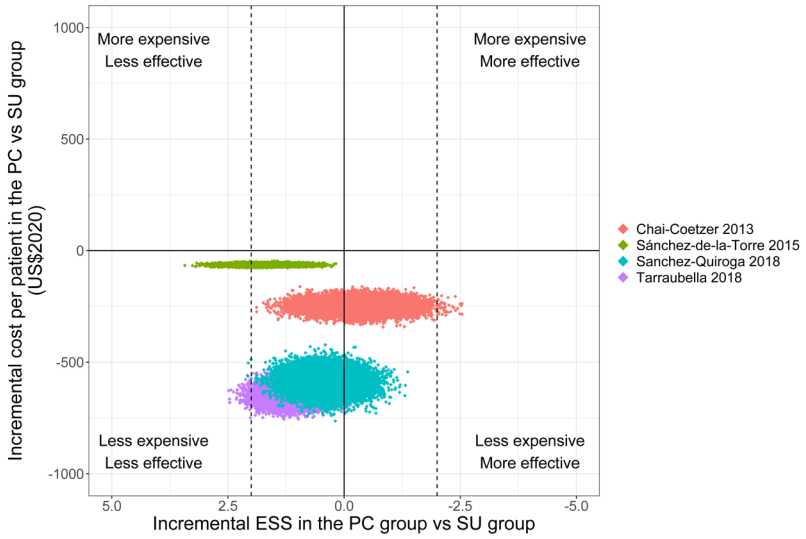



***Figure 2.*** Incremental cost per patient in primary care vs specialist sleep unit settings (in 2020 USD) vs (a) incremental ESS and (b) incremental QALY. The vertical dashed lines indicate the minimum clinically important differences in ESS and QALY respectively. The figure compares PC-based with SSU-based OSA management i.e. the descriptions such as "Less expensive" refer to PC. ESS = Epworth Sleepiness Scale; PC = Primary Care; QALY = Quality-Adjusted Life Years; SU = Specialist Sleep Unit; US$2020 = In 2020 equivalent United States Dollars.

A)


More expensive
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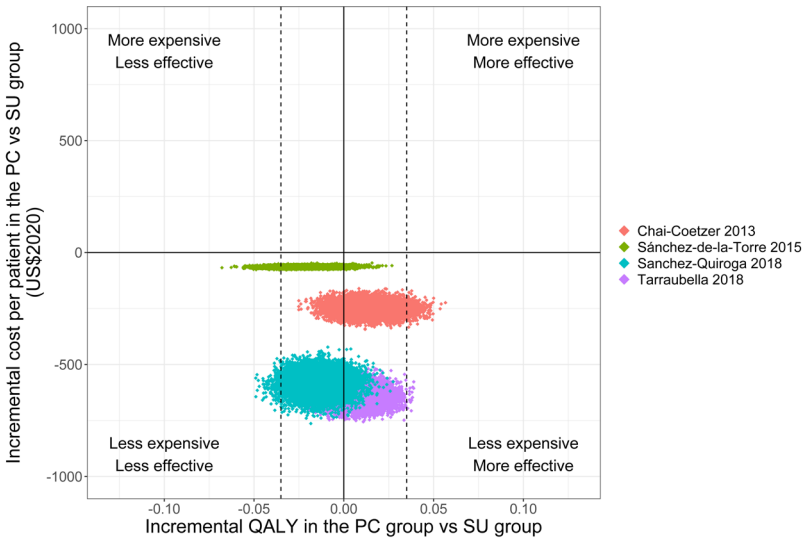
-5.0
Incremental cost per patient in the PC vs SU group
(US$2020)
Incremental ESS in the PC group vs SU group
Chai-Coetzer 2013
Sánchez-de-la-Torre 2015
Sanchez-Quiroga 2018
Tarraubella 2018

B)


More expensive
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0.05
0.10
Incremental cost per patient in the PC vs SU group
(US$2020)
Incremental QALY in the PC group vs SU group
Chai-Coetzer 2013
Sánchez-de-la-Torre 2015
Sanchez-Quiroga 2018
Tarraubella 2018

***Table 1.*** Characteristics of included studies

| Study, year | Design | Setting | Total n, (%male) | Diagnostic method | PC Education | PC Arm Management | Specialist Care Arm Management | Outcomes |
|---|---|---|---|---|---|---|---|---|
| Chai-Coetzer 2013 | 6-month non-inferiority, parallel group RCT | Metropolitan Adelaide & 3 rural regions of South Australia | 155 (81%) | Validated 2-step method (OSA50 and ApneaLink) for both PC and SSU arms (PSG also in SSU) | 6-hour education program and 1 week of in-service CPAP training (nurses only) | Delivered by PCPs and nurses | Delivered by 1 of 9 SSPs for ongoing management | ○ Δ ESS<br>○ Adherence<br>○ Δ FOSQ<br>○ VSQ-9<br>○ Δ BP<br>○ Δ weight<br>○ Δ SASQ<br>○ Δ SF-36<br>○ Within-trial costs |
| Sánchez-de-la-Torre 2015 | 6-month non-inferiority, parallel group RCT | SU of 1 teaching hospital and 8 PC units in Lleida, Spain | 210 (75%) | All participants were diagnosed in SSU using either PSG or RP | 6-hour education program | Delivered by PCPs and nurses | Delivered by SU specialist nurse (or SSP, if necessary) | ○ Δ ESS<br>○ Adherence<br>○ Δ BP<br>○ Δ BMI<br>○ EQ-5D<br>○ Visual analogue-scale<br>○ Cost-effectiveness |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Sanchez-Quiroga 2018 | 6-month non-inferiority, parallel group RCT | 20 PC units & 6 tertiary hospitals in Spain | 303 (72%) | PC: ApneaLink<br>SSU: PSG | A protocol for management decisions was provided to PCPs and a 6-hour education program for nurses | Delivered by PCPs and nurses according to a protocol | Delivered by SSP, with therapeutic decision based on standardised set of variables | ○ Δ ESS<br>○ Adherence<br>○ EQ-5D<br>○ Δ BP<br>○ Δ BMI<br>○ Cost-effectiveness<br>○ Hospital admissions<br>○ Traffic accidents<br>○ CV events |
| Tarraubella 2018 | 6-month non-inferiority, parallel group RCT | SU of 1 teaching hospital and 11 PC units in Lleida, Spain | 302 (71%) | Either PSG or RP in PC arm, and according to SU protocol in SU. | 6-hour education program | Delivered by PCPs and nurses | Delivered by SSP or a specialist sleep nurse | ○ Δ ESS<br>○ Adherence<br>○ Δ EQ-5D<br>○ Δ BP<br>○ Δ BMI<br>○ Visual analogue-scale<br>○ Cost-effectiveness |

AHI = apnea-hypopnea index; ApneaLink = ResMed Portable Diagnostic Device; BMI = body mass index; BP = blood pressure; CV = cardiovascular; Δ = Change; ESS = Epworth Sleepiness Scale; EQ-5D = The EuroQoL five-dimensions questionnaire; FOSQ = Functional Outcomes of Sleep Questionnaire; OSA50 = 4 item screening questionnaire for obstructive sleep apnea; PC = Primary Care; PCPs = primary care physicians; PSG = polysomnogram; RCT = randomized controlled trial; RP = respiratory polygraphy; SA = South Australia; SASQ = Sleep Apnea Symptoms Questionnaire; SF-36 = 36-item short form survey quality of life measure; SSP = Specialist Sleep Physician; SU = Sleep Unit; VSQ-9 = Visit Specific Questionnaire (for participant satisfaction).

***Table 2.*** Difference in mean change in primary and secondary outcomes (comparing values at 6-month follow-up with baseline) in Primary Care (PC) compared with Specialist Sleep Units (SSU) (one stage estimation)

| | **SSU vs PC ITT** | | **SSU vs PC PP** | |
|---|---|---|---|---|
| | *Mean (95% CI)* | *P-value* | *Mean (95% CI)* | *P-value* |
| *Primary outcome* | | | | |
| Epworth Sleep Scale Score | ***n = 970*** | | ***n = 779*** | |
| Change | 0.82 (0.24 to 1.40) | **0.006** | 0.96 (0.42 to 1.50) | **0.001** |
| *Secondary outcomes* | | | | |
| EQ-5D (Health Utility Index) | ***n = 970*** | | ***n = 765*** | |
| Change | -0.02 (-0.04 to 0.01) | 0.136 | -0.02 (-0.04 to 0.00) | 0.095 |
| BMI (kg/m$^2$) | ***n = 970*** | | ***n = 760*** | |
| Change | -0.44 (-1.03 to 0.14) | 0.139 | -0.35 (-0.98 to 0.28) | 0.280 |
| SBP (mm Hg) | ***n = 970*** | | ***n = 746*** | |
| Change | -0.66 (-2.66 to 1.34) | 0.518 | -0.75 (-2.77 to 1.27) | 0.467 |
| DBP (mm Hg) | ***n = 970*** | | ***n = 746*** | |
| Change | -1.90 (-3.20 to -0.57) | **0.005** | -1.79 (-3.18 to -0.39) | **0.012** |
| CPAP Adherence (hours/night)* | ***n = 676*** | | ***n = 601*** | |
| 6-months | 0.04 (-0.32 to 0.40) | 0.832 | 0.04 (-0.30 to 0.39) | 0.811 |

BMI = body mass index; DBP = diastolic blood pressure; ITT = Intention-to-treat analysis; PC = Primary Care; PP = Per Protocol analysis; SBP = systolic blood pressure; SSU = Specialist Sleep Unit.

Difference in mean change represents the change in values in PC in comparison with the change in values in SSU-based care (where change was computed as the difference between 6-month values and baseline).

In the ITT analysis, multiple imputation was used.

*Non-Adjusted for baseline

The statistically significant *P*-values (< 0.05) are bolded.

# Primary vs. Specialist Care for Obstructive Sleep Apnea: A Systematic Review and Individual Participant Data Level Meta-Analysis

Emer M Van Ryswyk (Co-First Author), Iván D Benitez (Co-First Author), Alexander M Sweetman, Nuria Nadal, Ching Li Chai-Coetzer, Juan Fernando Masa, Francisco Javier Gómez de Terreros, Robert J Adams, Manuel Sánchez-de-la-Torre, Nigel Stocks, Billingsley Kaambwa, R. Doug McEvoy (Co-Senior Author), Ferran Barbé (Co-Senior Author)

ONLINE DATA SUPPLEMENT

**ONLINE DATA SUPPLEMENT CONTENTS**

**Table E11.** Probabilities (%) of cost-pairs appearing in each cost-effectiveness plane quadrant

**Methods E1. Additional statistical analysis description**

**MULTIPLE IMPUTATION**

To avoid biased estimates resulting from ignoring missing data (E1), we used multilevel multiple imputation (MI) by chained equations of missing data (E2, E3). The MI procedure constructed 20 complete data sets and study was included as cluster variable. The methodology proposed by Groothuis-Oudshoorn and Buuruen (E4) was used to carry out the multilevel MI using the 'micemd' package (E5). Results across the multiply imputed data sets were combined by using the Rubin rule (E6).

**SUBGROUP AND INTERACTION ANALYSES**

Older adults with OSA exhibit more severe and deeper nocturnal intermittent hypoxia than younger adults, independent of severity of OSA (E7, E8), and this may impact the results of management in PC, so a subgroup analysis with age < 65 and ≥ 65 years was carried out. Some studies indicate that compared to men with OSA, women with OSA may have differing polysomnographic features, under-representation in clinical samples compared with community samples, and differing symptomatic presentations (E9). Therefore, we also conducted a subgroup analysis by gender. The impact of OSA severity on management outcomes in PC has not previously been investigated, so we undertook a subgroup analysis by OSA severity. OSA severity was classified using AHI in each of the Spanish trials (i.e. None = AHI < 5; Mild AHI 5 to < 15; Moderate AHI 15 to < 30; Severe AHI ≥ 30 (E10)) and using the oxygen desaturation index (ODI), with Severe OSA classified as ODI ≥ 30) for the Australian trial (E11). These subgroup analyses were performed using a two-stage approach (E12), in which the linear models also included the subgroup variable and its interaction with group. Interactions between outcomes of the differing models of care and gender, sleepiness, OSA severity and age were also assessed using the results of the two-stage methodology as per Riley et al 2020 (E12).

**Table E1. Full electronic search strategy for MEDLINE**

| # | Searches | Results |
|---|---|---|
| 1 | apnea/ or sleep apnea syndromes/ or sleep apnea, obstructive/ or obesity hypoventilation syndrome/ | 39472 |
| 2 | (apnea or apnoea or OSA or OSAS or hypopnoea or hypopnea or snore or snoring or obesity hypoventilation).tw,kf. | 50967 |
| 3 | or/1-2 | 59321 |
| 4 | Primary Health Care/ | 73339 |
| 5 | general practice/ or family practice/ | 73657 |
| 6 | general practitioners/ or physicians, family/ or physicians, primary care/ | 26189 |
| 7 | Primary Care Nursing/ | 443 |
| 8 | ((primary or general or family) adj2 (doctor* or physician* or practitioner* or nurs* or care)).tw,kf. | 209908 |
| 9 | or/4-8 | 277654 |
| 10 | ((respiratory or sleep or apnea) adj2 (unit or doctor or specialist or physician or center or centre)).tw,kf. | 3800 |
| 11 | (in patient or in-patient or laboratory or hospitali?ation or hospital).tw,kw. | 1495195 |
| 12 | academic medical centers/ or ambulatory care facilities/ or exp hospital units/ or exp hospitals/ or Universities/ | 427357 |
| 13 | or/10-12 | 1756747 |
| 14 | (RCT or random* or assign or placebo or trial or group).tw,kw. | 3407829 |
| 15 | randomized controlled trial.pt. | 489506 |
| 16 | controlled clinical trial.pt. | 93258 |

| | |
|---|---|
| 17 clinical study/ or exp clinical trial/ or randomized controlled trial/ | 839596 |
| 18 or/14-17 | 3689042 |
| 19 3 and 9 and 13 and 18 | 52 |

| Database | Number of Results | Date of Search |
|---|---|---|
| CINAHL | 70 | 25/09/2019 |
| Medline | 52 | 25/09/2019 |
| Cochrane Central | 68 | 25/09/2019 |
| Scopus | 184 | 25/09/2019 |
| ProQuest | 113 | 25/09/2019 |
| Clinicaltrials.gov | 245 | 25/09/2019 |
| https://www.isrctn.com/ | 153 | 25/09/2019 |
| Total records identified through database searching | 885 | |

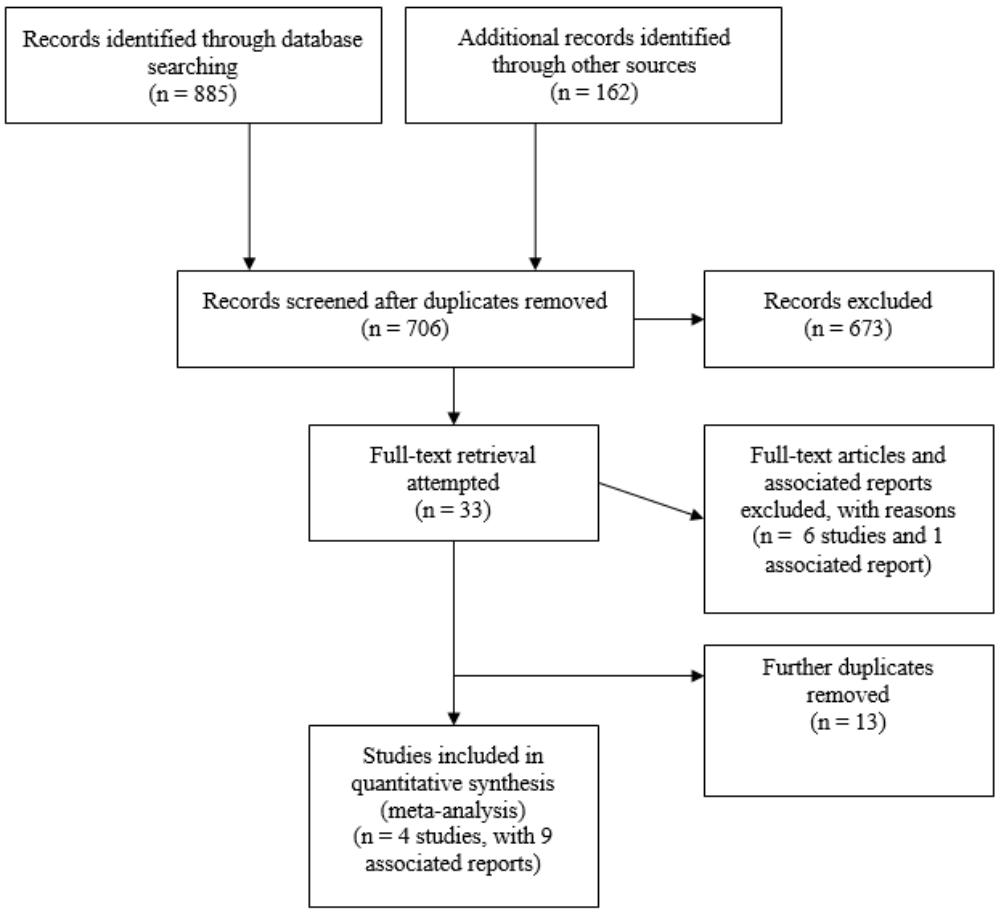


**Figure E1. Flow diagram of study selection**

**Table E2. List of non-included studies**

| First Author | Year | Journal | Article title | Reason for Noninclusion |
|---|---|---|---|---|
| Andreu | 2012 | *Eur Respir J* | Effect of an ambulatory diagnostic and treatment programme in patients with sleep apnoea. | The study was not undertaken in a primary care setting. Participants were allocated to follow-up with either a sleep unit nurse or a sleep unit pulmonologist. |
| Antic | 2009 | *Am J Respir Crit Care Med* | A Randomized Controlled Trial of Nurse-led Care for Symptomatic Moderate-Severe Obstructive Sleep Apnea. | Although the study compared nurse-led care with physician-led care, there was no specific primary care arm; instead, the study was conducted at three separate academic sleep medicine Services. |
| Bertisch | 2018 | *Sleep* | Impact of a Novel Sleep Medicine Neighborhood Model for Obstructive Sleep Apnea Care. | Non-randomized (quasi-experimental due to pragmatic issues). |
| Chamorro | 2013 | *Eur Respir J* | An integrated model involving sleep units and primary care for | Not a randomized controlled trial. |

| | | | | |
|---|---|---|---|---|
| | | | the diagnosis of sleep apnoea. | |
| Palmer | 2012 | *Sleep Med* | Annual review of patients with sleep apnea/hypopnea syndrome--a pragmatic randomized trial of nurse home visit versus consultant clinic review. | Participants had already received specialist treatment of their obstructive sleep apnea prior to randomization to have their annual review undertaken by either a hospital-based consultant or by a specialist nurse (in a home visit). Therefore, there was no specific primary care management arm either. |
| Pelletier-Fleury | 2012 | *https://clinicaltrials.gov/ct2/show/NCT01552083* | A Community Pharmacist-led Intervention to Improve Screening of Sleep Apnea in Primary Care. | Not a randomized controlled trial. |

**Table E3. Characteristics of included participants**

| Characteristic | Overall (n = 970) | N | Chai-Coetzer 2013 (n = 155) | Sánchez-de-la-Torre 2015 (n = 210) | Sanchez-Quiroga 2018 (n = 303) | Tarraubella 2018 (n = 302) |
|---|---|---|---|---|---|---|
| ***Baseline values*** | | | | | | |
| Mean age (SD), *y* | 54.0 (11.5) | 970 | 55.9 (11.3) | 56.0 (11.1) | 51.2 (10.6) | 54.3 (12.2) |
| Age categories, *n (%)* | | 970 | | | | |
| < 65 | 791 (81.5) | | 122 (78.7) | 164 (78.1) | 269 (88.8) | 236 (78.1) |
| ≥65 | 179 (18.5) | | 33 (21.3) | 46 (21.9) | 34 (11.2) | 66 (21.9) |
| Gender *n (%)* | | 970 | | | | |
| Female | 253 (26.1) | | 29 (18.7) | 51 (24.3) | 86 (28.4) | 87 (28.8) |
| Male | 717 (73.9) | | 126 (81.3) | 159 (75.7) | 217 (71.6) | 215 (71.2) |
| BMI categories, *n (%)* | | 955 | | | | |
| < 18.5 Underweight | 1 (0.1) | | 0 (0.0) | 0 (0.0) | 1 (0.3) | 0 (0.00) |
| 18.5 to 24.9 Normal weight | 72 (7.5) | | 5 (3.2) | 7 (3.33) | 28 (9.2) | 32 (11.1) |
| 25.0 to 29.0 Overweight | 301 (31.5) | | 42 (27.1) | 64 (30.5) | 100 (33.0) | 95 (33.1) |
| 30 to 34.9 Obesity Class I | 308 (32.3) | | 49 (31.6) | 67 (31.9) | 97 (32.0) | 95 (33.1) |
| 35.0 to 30.9 Obesity Class II | 171 (17.9) | | 40 (25.8) | 41 (19.5) | 47 (15.5) | 43 (15.0) |
| Above 40 Obesity Class III | 102 (10.7) | | 19 (12.3) | 31 (14.8) | 30 (9.9) | 22 (7.7) |
| Blood pressure category* *n (%)* | | 946 | | | | |
| Normal | 158 (16.7) | | 18 (11.6) | 18 (8.6) | 76 (25.5) | 46 (16.2) |
| Elevated | 95 (10.0) | | 14 (9.0) | 14 (6.7) | 40 (13.4) | 27 (9.5) |

| | | | | | | |
|---|---|---|---|---|---|---|
| Hypertension stage 1 | 285 (30.1) | | 52 (33.5) | 53 (25.4) | 97 (32.6) | 83 (29.2) |
| Hypertension stage 2 or above | 408 (43.1) | | 71 (45.8) | 124 (59.3) | 85 (28.5) | 128 (45.1) |
| Daytime Sleepiness (ESS), *n (%)* | | 951 | | | | |
| 0 to 5 Lower normal | 116 (12.2) | | 2 (1.3) | 46 (22.3) | 4 (1.3) | 64 (22.3) |
| 6 to 10 Higher Normal | 214 (22.5) | | 49 (31.6) | 61 (29.6) | 7 (2.3) | 97 (33.8) |
| 11 to 12 Mild Excessive | 175 (18.4) | | 34 (21.9) | 22 (10.7) | 79 (26.1) | 40 (13.9) |
| 13 to 15 Moderate Excessive | 227 (23.9) | | 31 (20.0) | 33 (16.0) | 108 (35.6) | 55 (19.2) |
| 16+ Severe Excessive | 219 (23.0) | | 39 (25.2) | 44 (21.4) | 105 (34.7) | 31 (10.8) |
| OSA Severity Class† (10), n (%) | | 951 | | | | |
| None | 68 (7.2) | | 0 (0.0) | 0 (0.0) | 33 (10.9) | 35 (12.4) |
| Mild | 138 (14.5) | | 0 (0.0) | 3 (1.4) | 64 (21.1) | 71 (25.1) |
| Moderate | 268 (28.2) | | 82 (52.9) | 39 (18.6) | 71 (23.4) | 76 (26.9) |
| Severe | 477 (50.2) | | 73 (47.1) | 168 (80.0) | 135 (44.6) | 101 (35.7) |
| ***Non-baseline values*** | | | | | | |
| CPAP adherence at 6 months | | 604 | | | | |
| < 4 hours/night | 201 (33.3) | | 25 (26.0) | 49 (25.7) | 86 (44.6) | 41 (33.1) |
| ≥ 4 hours/night | 403 (66.7) | | 71 (74.0) | 142 (74.3) | 107 (55.4) | 83 (66.9) |

AHI = apnea-hypopnea index in events/hour; BMI = body mass index; CPAP = continuous positive airways pressure.

* Blood pressure categories are: Normal = systolic <120 & diastolic <80; Elevated = if (systolic ≥ 120 & systolic <130) & diastolic < 80 "Elevated"; Hypertension stage 1 = if (systolic ≥ 130 & systolic <140) or (diastolic ≥80 & diastolic <90); Hypertension stage 2 or above = if (systolic ≥140 or diastolic ≥ 90.

† None = AHI < 5; Mild AHI 5 to < 15; Moderate AHI 15 to < 30; Severe AHI ≥ 30 (or oxygen desaturation index ≥ 30).

**Table E4. Difference in mean change in primary and secondary outcomes (comparing values at 6-month follow-up with baseline) in PC compared with SSU (two stage estimation)**

| | **Sleep unit vs Primary care ITT** | | **Sleep unit vs Primary care PP** | |
|---|---|---|---|---|
| | *Mean (95% CI)* | *P-value* | *Mean (95% CI)* | *P-value* |
| *Primary outcome* | | | | |
| Epworth Sleep Scale Score | ***n = 970*** | | ***n = 779*** | |
| Change | 0.78 (-0.39 to 1.96) | 0.124 | 0.94 (0.66 to 2.54) | 0.158 |
| *Secondary outcomes* | | | | |
| EQ-5D (Health Utility Index) | ***n = 970*** | | ***n = 765*** | |
| Change | -0.02 (-0.05 to 0.02) | 0.265 | -0.02 (-0.06 to 0.02) | 0.195 |
| BMI (kg/m$^2$) | ***n = 970*** | | ***n = 760*** | |
| Change | 0.02 (-0.8 to 0.85) | 0.940 | -0.03 (-0.81 to 0.75) | 0.903 |
| SBP (mm Hg) | ***n = 970*** | | ***n = 746*** | |
| Change | -0.70 (-6.4 to 5.00) | 0.722 | -0.99 (-7.25 to 5.27) | 0.649 |
| DBP (mm Hg) | ***n = 970*** | | ***n = 746*** | |
| Change | -2.07 (-7.12 to 2.98) | 0.283 | -2.20 (-7.59 to 3.20) | 0.286 |
| CPAP Adherence (hours/night)* | ***n = 676*** | | ***n = 601*** | |
| 6-months | 0.02 (-0.73 to 0.78) | 0.923 | 0.01 (-0.03 to 0.01) | 0.195 |

BMI = body mass index; DBP = diastolic blood pressure; EQ-5D = EuroQol-5D; ITT = Intention-to-treat analysis; PP = Per Protocol analysis; SBP = systolic blood pressure.

Change = 6-month values compared with baseline values.

Difference in mean change computed as the change in primary care values compared with change in sleep unit values.

In the ITT analysis, multiple imputation was used.

*Non-Adjusted for baseline

The statistically significant *P*-values (< 0.05) are bolded.

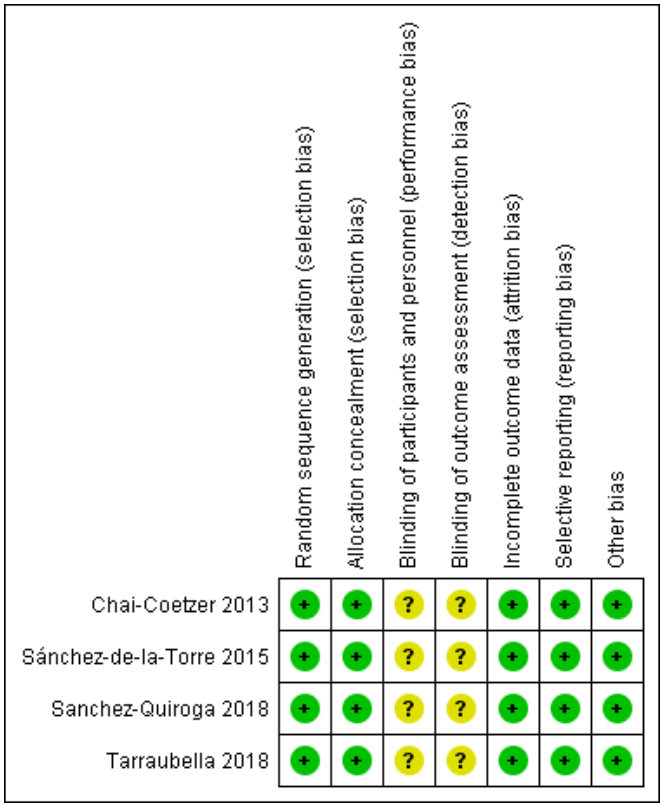


**Figure E2. Summary of risk of bias findings**

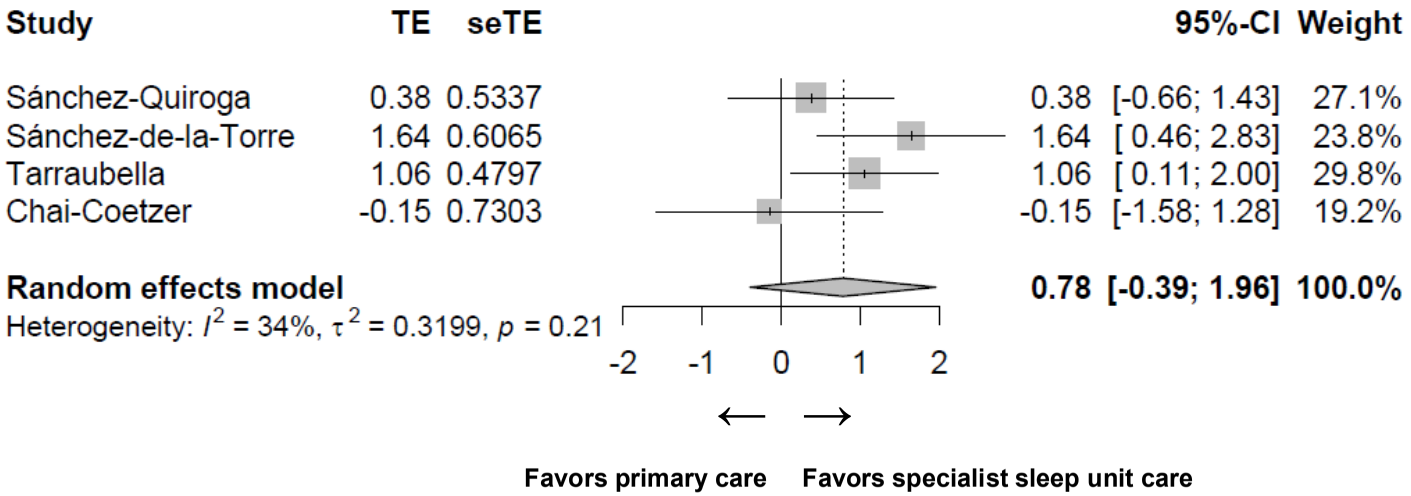


**Figure E3. Forest plot of treatment effects for the primary outcome of change in daytime sleepiness according to the Epworth Sleepiness Scale (two-stage analysis)**

TE = Treatment effect; seTE = standard error of the treatment effect.

**Table E5. Interaction analysis assessing primary care effect in non-severe versus severe OSA**

| | Non-Severe OSA | | Severe OSA | | Differential effect of primary care between severity groups | | | |
|---|---|---|---|---|---|---|---|---|
| | Sleep Unit | Primary Care | Sleep Unit | Primary Care | ITT | | PP | |
| | *Mean (95% CI)* | *Mean (95% CI)* | *Mean (95% CI)* | *Mean (95% CI)* | *Mean (95% CI)* | *P-value* | *Mean (95% CI)* | *P-value* |
| *Primary outcome* | | | | | | | | |
| Epworth Sleep Scale Score | | | | | | | | |
| Baseline | 11.4 (10.7 to 12.1) | 12.2 (11.6 to 12.8) | 11.8 (11.1 to 12.5) | 12.1 (11.4 to 12.8) | | | | |
| 6 months | 7.6 (7.0 to 8.3) | 8.5 (7.9 to 9.1) | 5.2 (4.7 to 5.6) | 6.3 (5.7 to 7.0) | | | | |
| Change | -3.7 (-4.3 to -3.1) | -3.7 (-4.3 to -3.1) | -6.6 (-7.3 to -5.9) | -5.8 (-6.6 to -4.9) | -0.21 (-1.02 to 0.61) | 0.473 | 0.06 (-1.69 to 0.11) | 0.922 |
| *Secondary outcomes* | | | | | | | | |
| EQ-5D (HUI) | | | | | | | | |
| Baseline | 0.77 (0.73 to 0.80) | 0.76 (0.73 to 0.78) | 0.77 (0.74 to 0.79) | 0.76 (0.73 to 0.79) | | | | |
| 6 months | 0.79 (0.76 to 0.82) | 0.77 (0.75 to 0.80) | 0.82 (0.80 to 0.85) | 0.80 (0.77 to 0.82) | | | | |
| Change | 0.03 (0.00 to 0.05) | 0.02 (-0.01 to 0.04) | 0.06 (0.03 to 0.08) | 0.04 (0.02 to 0.06) | 0.01 (-0.03 to 0.04) | 0.601 | -0.01 (-0.06 to 0.04) | 0.48 |
| BMI (kg/m$^2$) | | | | | | | | |
| Baseline | 30.5 (29.8 to 31.3) | 30.6 (29.9 to 31.3) | 34.0 (33.1 to 34.9) | 33.7 (32.8 to 34.5) | | | | |
| 6 months | 31.2 (30.4 to 31.9) | 30.9 (30.2 to 31.6) | 33.7 (32.8 to 34.6) | 33.1 (32.3 to 33.9) | | | | |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Change | 0.64 (-0.18 to 1.46) | 0.33 (-0.30 to 0.96) | -0.27 (-0.96 to 0.42) | -0.52 (-1.25 to 0.21) | 0.21 (-1.27 to 1.69) | 0.678 | 0.09 (-2.24 to 2.41) | 0.913 |
| SBP (mm Hg) | | | | | | | | |
| Baseline | 130 (127 to 133) | 130 (128 to 132) | 135 (132 to 137) | 138 (135 to 140) | | | | |
| 6 months | 127 (125 to 130) | 130 (128 to 132) | 134 (131 to 137) | 132 (129 to 134) | | | | |
| Change | -2.56 (-4.90 to -0.22) | -0.06 (-2.11 to 1.99) | -0.90 (-3.29 to 1.49) | -5.78 (-8.41 to -3.15) | 4.01 (-0.96 to 8.98) | 0.083 | 4.6 (-2.55 to 11.75) | 0.133 |
| DBP (mm Hg) | | | | | | | | |
| Baseline | 81.3 (79.4 to 83.2) | 79.8 (78.3 to 81.3) | 85.1 (83.5 to 86.8) | 85.9 (84.0 to 87.8) | | | | |
| 6 months | 80.0 (78.3 to 81.6) | 79.4 (77.8 to 81.0) | 83.5 (81.8 to 85.1) | 80.3 (78.6 to 82.0) | | | | |
| Change | -1.36 (-3.06 to 0.33) | -0.43 (-1.91 to 1.06) | -1.66 (-3.34 to 0.02) | -5.59 (-7.50 to -3.67) | 1.67 (-2.22 to 5.57) | 0.265 | 0.94 (-5.49 to 7.37) | 0.673 |
| CPAP Adherence (hours/night) | | | | | | | | |
| 6 months | 1.57 (1.23 to 1.92) | 1.90 (1.56 to 2.23) | 4.76 (4.46 to 5.07) | 4.71 (4.38 to 5.05) | 0.42 (-1.34 to 2.18) | 0.505 | 0.06 (-1.11 to 1.24) | 0.872 |

BMI = body mass index; DBP = diastolic blood pressure; HUI = Health Utility Index; ITT = Intention-to-treat analysis; PP = Per Protocol analysis; SBP = systolic blood pressure.

Change = 6-month values compared with baseline values.

Difference in mean change computed as the change in primary care values compared with change in sleep unit values.

In the ITT analysis, multiple imputation was used.

[¥]Non-Adjusted for baseline.

The statistically significant p-values (< 0.05) are bolded.

**Table E6. Interaction analysis assessing primary care effect in older adults (≥65 years) versus younger adults (<65 years)**

| | Age < 65 years | | Age ≥ 65 years | | Differential effect of primary care between age groups | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Sleep Unit | Primary Care | Sleep Unit | Primary Care | ITT | | PP | | |
| | *Mean (95% CI)* | *Mean (95% CI)* | *Mean (95% CI)* | *Mean (95% CI)* | *Mean (95% CI)* | *P-value* | *Mean (95% CI)* | *P-value* | |
| *Primary outcome* | | | | | | | | | |
| Epworth Sleep Scale Score (ITT) | | | | | | | | | |
| Baseline | 12.0 (11.5 to 12.5) | 12.3 (11.8 to 12.8) | 10.0 (8.7 to 11.3) | 11.2 (10.0 to 12.5) | | | | | |
| 6 months | 6.5 (6.0 to 6.9) | 7.8 (7.3 to 8.3) | 5.5(4.7 to 6.3) | 6.1 (5.2 to 7.1) | | | | | |
| Change | -5.5 (-6.0 to -4.9) | -4.5 (-5.1 to -4.0) | -4.5 (-5.6 to -3.4) | -5.1 (-6.3 to -4.0) | -0.85 (-1.89 to 0.19) | 0.080 | -1.2 (-2.0 to -4.7) | **0.019** | |
| *Secondary outcomes* | | | | | | | | | |
| EQ-5D (HUI) | | | | | | | | | |
| Baseline | 0.77 (0.75 to 0.79) | 0.76 (0.74 to 0.78) | 0.76 (0.71 to 0.81) | 0.75 (0.70 to 0.79) | | | | | |
| 6 months | 0.81 (0.79 to 0.83) | 0.79 (0.77 to 0.81) | 0.81 (0.77 to 0.85) | 0.78 (0.73 to 0.82) | | | | | |
| Change | 0.04 (0.02 to 0.06) | 0.03 (0.01 to 0.04) | 0.05 (0.01 to 0.09) | 0.03 (-0.01 to 0.07) | -0.01 (-0.13 to 0.1) | 0.726 | 0 (-0.12 to 0.13) | 0.949 | |
| BMI ($kg/m^2$) | | | | | | | | | |
| Baseline | 32.5 (31.7 to 33.2) | 32.0 (31.4 to 32.6) | 32.1 (31.0 to 33.2) | 31.9 (30.8 to 32.9) | | | | | |
| 6 months | 32.6 (31.9 to 33.3) | 31.9 (31.3 to 32.5) | 32.3 (31.1 to 33.6) | 32.1 (31.0 to 33.1) | | | | | |
| Change | 0.13 (-0.50 to 0.76) | -0.11 (-0.66 to 0.45) | 0.29 (-0.53 to 1.10) | 0.20 (-0.53 to 0.93) | -0.03 (-0.89 to 0.82) | 0.914 | 0.35 (-1.03 to 1.73) | 0.475 | |
| SBP (mm Hg) | | | | | | | | | |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Baseline | 130 (128 to 132) | 132 (130 to 134) | 142 (138 to 147) | 138 (134 to 143) | | | | |
| 6 months | 128 (126 to 130) | 130 (128 to 131) | 142 (138 to 147) | 136 (131 to 140) | | | | |
| Change | -2.05 (-3.85 to -0.25) | -2.61 (-4.44 to -0.78) | 0.01 (-4.38 to 4.40) | -2.91 (-6.88 to 1.06) | -2.53 (-6.91 to 1.85) | 0.163 | -4.53 (-11.16 to 2.09) | 0.118 |
| DBP (mm Hg) | | | | | | | | |
| Baseline | 83.4 (82.0 to 84.9) | 83.0 (81.7 to 84.4) | 83.3 (80.9 to 85.8) | 80.8 (77.8 to 83.9) | | | | |
| 6 months | 81.4 (80.2 to 82.7) | 80.4 (79.1 to 81.6) | 83.7 (81.0 to 86.3) | 77.5 (74.8 to 80.3) | | | | |
| Change | -1.97 (-3.29 to -0.65) | -2.66 (-4.02 to -1.31) | 0.34 (-2.44 to 3.12) | -3.27 (-6.07 to -0.47) | -2.02 (-6.71 to 2.67) | 0.264 | -3.38 (-10.12 to 3.37) | 0.209 |
| CPAP Adherence (hours/night) | | | | | | | | |
| 6-months | 3.08 (2.79 to 3.38) | 3.01 (2.71 to 3.31) | 3.42 (2.76 to 4.08) | 3.84 (3.20 to 4.47) | -0.02 (-0.42 to 0.39) | 0.900 | -0.4 (-1.27 to 0.48) | 0.245 |

BMI = body mass index; DBP = diastolic blood pressure; HUI = Health Utility Index; ITT = Intention-to-treat analysis; PP = Per Protocol analysis; SBP = systolic blood pressure.

Change = 6-month values compared with baseline values.

Difference in mean change computed as the change in primary care values compared with change in sleep unit values.

In the ITT analysis, multiple imputation was used.

¥Non-Adjusted for baseline.

The statistically significant p-values (< 0.05) are bolded.

**Table E7. Interaction analysis assessing primary care effect in females versus males**

| | Female | | Male | | Differential effect of primary care between genders | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | ITT | | PP | |
| | **Sleep Unit** | **Primary Care** | **Sleep Unit** | **Primary Care** | | | | |
| | ***Mean (95% CI)*** | ***Mean (95% CI)*** | ***Mean (95% CI)*** | ***Mean (95% CI)*** | ***Mean (95% CI)*** | ***P-value*** | ***Mean (95% CI)*** | ***P-value*** |
| *Primary outcome* | | | | | | | | |
| Epworth Sleep Scale Score (ITT) | | | | | | | | |
| Baseline | 11.9 (10.9 to 12.9) | 12.1 (11.2 to 12.9) | 11.5 (10.9 to 12.1) | 12.2 (11.6 to 12.7) | | | | |
| 6 months | 6.5 (5.8 to 7.2) | 8.1 (7.2 to 9.0) | 6.3 (5.78 to 6.72) | 7.28 (6.77 to 7.79) | | | | |
| Change | -5.4 (-6.4 to -4.5) | -4.0 (-4.8 to -3.2) | -5.3 (-5.8 to -4.7) | -4.9 (-5.5 to -4.3) | -0.46 (-2.29 to 1.36) | 0.478 | -0.4 (-2.2 to -0.72) | 0.524 |
| *Secondary outcomes* | | | | | | | | |
| Eq-5D (HUI) | | | | | | | | |
| Baseline | 0.66 (0.62 to 0.71) | 0.68 (0.64 to 0.72) | 0.80 (0.78 to 0.82) | 0.79 (0.76 to 0.81) | | | | |
| 6 months | 0.72 (0.67 to 0.76) | 0.70 (0.66 to 0.75) | 0.84 (0.82 to 0.86) | 0.81 (0.79 to 0.83) | | | | |
| Change | 0.05 (0.01 to 0.09) | 0.02 (-0.02 to 0.06) | 0.04 (0.02 to 0.06) | 0.03 (0.01 to 0.05) | 0.02 (-0.03 to 0.06) | 0.366 | 0 (-0.12 to 0.12) | 0.962 |
| BMI ($kg/m^2$) | | | | | | | | |
| Baseline | 32.8 (31.2 to 34.5) | 32.5 (31.1 to 33.8) | 32.2 (31.6 to 32.9) | 31.8 (31.2 to 32.4) | | | | |
| 6 months | 32.9 (31.3 to 34.5) | 32.4 (31.1 to 33.7) | 32.4 (31.8 to 33.0) | 31.8 (31.2 to 32.3) | | | | |
| Change | 0.08 (-1.24 to 1.40) | -0.08 (-0.90 to 0.75) | 0.18 (-0.38 to 0.74) | -0.04 (-0.62 to 0.53) | -0.17 (-0.86 to 0.51) | 0.481 | -0.32 (-1.59 to 0.94) | 0.474 |
| SBP (mm Hg) | | | | | | | | |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Baseline | 129 (125 to 134) | 128 (125 to 132) | 134 (132 to 136) | 135 (133 to 137) | | | | |
| 6 months | 126 (122 to 131) | 126 (123 to 129) | 132 (130 to 135) | 132 (131 to 134) | | | | |
| Change | -2.83 (-6.02 to 0.37) | -2.23 (-5.73 to 1.28) | -1.28 (-3.25 to 0.69) | -2.83 (-4.70 to -0.95) | -1.12 (-3.88 to 1.65) | 0.288 | -0.46 (-3.75 to 2.82) | 0.684 |
| DBP (mm Hg) | | | | | | | | |
| Baseline | 82.0 (79.3 to 84.7) | 80.8 (78.3 to 83.4) | 83.8 (82.4 to 85.2) | 83.2 (81.9 to 84.6) | | | | |
| 6 months | 80.3 (77.7 to 82.8) | 78.5 (75.8 to 81.2) | 82.4 (81.1 to 83.7) | 80.3 (79.1 to 81.5) | | | | |
| Change | -1.77 (-4.08 to 0.54) | -2.30 (-5.13 to 0.53) | -1.45 (-2.85 to -0.05) | -2.95 (-4.26 to -1.64) | -0.63 (-4.8 to 3.53) | 0.661 | -0.53 (-7.43 to 6.37) | 0.824 |
| CPAP Adherence (hours/night) | | | | | | | | |
| 6-months | 2.25 (1.75 to 2.75) | 2.79 (2.25 to 3.34) | 3.47 (3.15 to 3.78) | 3.28 (2.97 to 3.59) | -0.8 (-2.61 to 1.02) | 0.256 | -0.89 (-3 to 1.23) | 0.275 |

BMI = body mass index; DBP = diastolic blood pressure; HUI = Health Utility Index; ITT = Intention-to-treat analysis; PP = Per Protocol analysis; SBP = systolic blood pressure.

Change = 6-month values compared with baseline values.

Difference in mean change computed as the change in primary care values compared with change in sleep unit values.

In the ITT analysis, multiple imputation was used.

[¥]Non-Adjusted for baseline.

The statistically significant p-values (< 0.05) are bolded.

**Table E8a. Interaction analysis assessing primary care effect according to baseline daytime sleepiness level (continued below)**

| | Normal daytime sleepiness | | Mild/moderate daytime sleepiness | | Severe daytime sleepiness | |
|---|---|---|---|---|---|---|
| | **Sleep Unit** | **Primary Care** | **Sleep Unit** | **Primary Care** | **Sleep Unit** | **Primary Care** |
| | ***Mean (95% CI)*** | ***Mean (95% CI)*** | ***Mean (95% CI)*** | ***Mean (95% CI)*** | ***Mean (95% CI)*** | ***Mean (95% CI)*** |
| *Primary outcome* | | | | | | |
| Epworth Sleep Scale Score (ITT) | | | | | | |
| Baseline | 6.52 (6.06 to 6.97) | 6.33 (5.86 to 6.81) | 13.1 (12.9 to 13.3) | 12.9 (12.7 to 13.1) | 17.8 (17.4 to 18.2) | 17.9 (17.5 to 18.2) |
| 6 months | 4.64 (4.21 to 5.06) | 5.28 (4.68 to 5.88) | 6.66 (6.06 to 7.26) | 7.94 (7.34 to 8.55) | 8.56 (7.52 to 9.61) | 9.40 (8.34 to 10.5) |
| Change | -1.88 (-2.36 to -1.40) | -1.05 (-1.63 to -0.47) | -6.40 (-7.02 to -5.78) | -4.94 (-5.56 to -4.32) | -9.23 (-10.29 to -8.17) | -8.49 (-9.65 to -7.33) |
| *Secondary outcomes* | | | | | | |
| Eq-5D (HUI) | | | | | | |
| Baseline | 0.80 (0.77 to 0.83) | 0.82 (0.79 to 0.85) | 0.76 (0.72 to 0.79) | 0.76 (0.73 to 0.79) | 0.73 (0.68 to 0.78) | 0.69 (0.65 to 0.73) |
| 6 months | 0.84 (0.81 to 0.87) | 0.82 (0.79 to 0.86) | 0.81 (0.78 to 0.84) | 0.78 (0.75 to 0.81) | 0.76 (0.71 to 0.80) | 0.74 (0.71 to 0.78) |
| Change | 0.04 (0.02 to 0.06) | 0.01 (-0.03 to 0.04) | 0.05 (0.02 to 0.08) | 0.03 (0.00 to 0.05) | 0.02 (-0.03 to 0.07) | 0.05 (0.02 to 0.09) |
| BMI ($kg/m^2$) | | | | | | |
| Baseline | 32.5 (31.5 to 33.6) | 32.0 (31.0 to 32.9) | 31.9 (30.9 to 32.8) | 31.3 (30.4 to 32.1) | 32.8 (31.2 to 34.5) | 33.3 (32.2 to 34.4) |
| 6 months | 32.7 (31.7 to 33.8) | 32.1 (31.1 to 33.1) | 31.9 (31.0 to 32.8) | 31.8 (31.0 to 32.6) | 33.9 (32.5 to 35.4) | 32.0 (30.9 to 33.1) |
| Change | 0.19 (-0.16 to 0.54) | 0.13 (-0.26 to 0.52) | 0.04 (-0.92 to 1.00) | 0.54 (-0.20 to 1.27) | 1.08 (-0.25 to 2.41) | -1.29 (-2.56 to -0.02) |
| SBP (mm Hg) | | | | | | |
| Baseline | 138 (135 to 141) | 135 (132 to 138) | 130 (127 to 133) | 134 (131 to 136) | 128 (124 to 132) | 132 (128 to 136) |

| | | | | | | |
|---|---|---|---|---|---|---|
| 6 months | 136 (133 to 139) | 133 (130 to 136) | 128 (125 to 131) | 130 (128 to 133) | 128 (124 to 132) | 129 (126 to 133) |
| Change | -1.88 (-4.50 to 0.73) | -1.47 (-4.34 to 1.40) | -2.30 (-5.06 to 0.47) | -3.25 (-5.93 to -0.57) | -0.04 (-3.97 to 3.89) | -2.65 (-5.91 to 0.61) |
| DBP (mm Hg) | | | | | | |
| Baseline | 87.0 (85.0 to 89.0) | 82.9 (81.0 to 84.9) | 81.0 (78.9 to 83.1) | 82.5 (80.6 to 84.3) | 82.0 (79.5 to 84.6) | 82.8 (80.0 to 85.7) |
| 6 months | 84.6 (82.9 to 86.4) | 79.8 (77.8 to 81.7) | 80.1 (78.1 to 82.1) | 79.8 (78.0 to 81.6) | 80.9 (78.4 to 83.3) | 80.1 (77.6 to 82.7) |
| Change | -2.39 (-4.24 to -0.53) | -3.19 (-5.35 to -1.04) | -0.90 (-2.86 to 1.06) | -2.69 (-4.57 to -0.81) | -1.13 (-3.88 to 1.63) | -2.75 (-5.24 to -0.25) |
| CPAP Adherence (hours/night) | | | | | | |
| 6-months | 2.92 (2.43 to 3.41) | 3.46 (2.93 to 3.98) | 3.80 (3.35 to 4.25) | 3.02 (2.59 to 3.45) | 3.74 (3.12 to 4.37) | 3.82 (3.23 to 4.41) |

**Table E8b. Interaction analysis assessing primary care effect according to baseline daytime sleepiness level**

| | ITT | | | | PP | | | |
|---|---|---|---|---|---|---|---|---|
| | **Mild/Moderate ESS Vs Normal ESS** | | **Severe ESS VS Normal ESS** | | **Mild/Moderate ESS Vs Normal ESS** | | **Severe ESS VS Normal ESS** | |
| | ***Mean (95% CI)*** | ***P-value**** | ***Mean (95% CI)*** | ***P-value**** | ***Mean (95% CI)*** | ***P-value**** | ***Mean (95% CI)*** | ***P-value**** |
| *Primary outcome* | | | | | | | | |
| Epworth Sleep Scale Score (ITT) | | | | | | | | |
| Change | 0.83 (-0.66 to 2.31) | 0.175 | 1 (-0.69 to 2.68) | 0.157 | 1.58 (-0.53 to 2.38) | 0.098 | 1.2 (-0.46 to 2.85) | 0.105 |
| *Secondary outcomes* | | | | | | | | |
| Eq-5D (HUI) | | | | | | | | |
| Change | 0.02 (-0.1 to 0.13) | 0.663 | 0.02 (-0.11 to 0.15) | 0.655 | 0.02 (-0.12 to 0.16) | 0.662 | 0.03 (-0.15 to 0.21) | 0.612 |
| BMI ($kg/m^2$) | | | | | | | | |
| Change | -0.05 (-1.41 to 1.32) | 0.922 | -0.4 (-2.17 to 1.38) | 0.527 | 0.4 (-2.29 to 3.08) | 0.671 | -0.06 (-2.85 to 2.74) | 0.954 |
| SBP (mm Hg) | | | | | | | | |
| Change | -1.99 (-5.47 to 1.48) | 0.166 | -1.2 (-6.84 to 4.44) | 0.548 | -2.55 (-8.47 to 3.36) | 0.263 | -1.87 (-10.25 to 6.51) | 0.528 |
| DBP (mm Hg) | | | | | | | | |
| Change | -0.23 (-3.61 to 3.15) | 0.843 | -0.14 (-3.81 to 3.54) | 0.914 | -0.43 (-3.47 to 2.61) | 0.681 | 0.14 (-4.73 to 5.01) | 0.931 |
| CPAP Adherence (hours/night) | | | | | | | | |
| 6-months | -0.58 (-1.81 to 0.65) | 0.229 | -0.2 (-1.77 to 1.37) | 0.712 | -0.87 (-2.03 to 0.29) | 0.097 | -0.61 (-2.04 to 0.81) | 0.263 |

BMI = body mass index; DBP = diastolic blood pressure; HUI = Health Utility Index; ITT = Intention-to-treat analysis; PP = Per Protocol analysis; SBP = systolic blood pressure.

Change = 6-month values compared with baseline values.

Difference in mean change computed as the change in primary care values compared with change in sleep unit values.

In the ITT analysis, multiple imputation was used.

[¥]Non-Adjusted for baseline.

P-value* = P-for-interaction; the statistically significant p-values (< 0.05) are bolded.

**Table E9. Within-trial sleep diagnostic and treatment costs in US dollars (average cost per randomized participant) and cost of training delivery**

| Study | Primary Care mean (95% CI) | Specialist Care mean (95% CI) | Difference mean (95% CI) |
|---|---|---|---|
| All studies (overall) | *n = 489* | *n = 481* | |
| Training cost | 41.54 (35.34 to 47.74) | 0.00 (-) | 41.54 (35.34 to 47.74) |
| Diagnostic | 297.94 (266.01 to 329.87) | 715.22 (686.96 to 743.48) | -417.28 (-459.87 to -374.69) |
| Physician/nurse visits | 133.96 (126.22 to 141.71) | 206.73 (195.29 to 218.18) | -72.77 (-86.57 to -58.97) |
| Total | 473.44 (441.83 to 505.05) | 921.95 (890.88 to 953.02) | -448.51 (-492.78 to -404.24) |
| | | | |
| Chai-Coetzer 2013 | *n = 81* | *n = 74* | |
| Training cost* | 199.00 (-) | 0.00 (-) | 199.00 (-) |
| Diagnostic | 143.89 (128.48 to 159.3) | 491.54 (450.78 to 532.31) | -347.66 (-391.09 to -304.23) |
| Physician/nurse visits | 167.65 (156.64 to 178.66) | 266.94 (253.43 to 280.44) | -99.29 (-116.58 to -82.01) |
| Total | 510.27 (491.26 to 529.29) | 758.48 (713.65 to 803.32) | -248.21 (-296.7 to -199.71) |
| | | | |
| Sánchez-de-la-Torre 2015 | *n = 101* | *n = 109* | |
| Training cost* | 15.00 (-) | 0.00 (-) | 15.00 (-) |
| Diagnostic* | 917.19 (-) | 917.19 (-) | 0.00 (-) |
| Physician/nurse visits | 106.42 (100.94 to 111.91) | 185.4 (179.83 to 190.98) | -78.98 (-86.76 to -71.21) |
| Total | 1038.57 (1033.08 to 1044.05) | 1102.6 (1097.02 to 1108.17) | -64.03 (-71.81 to -56.26) |
| | | | |
| Sanchez-Quiroga 2018 | *n = 158* | *n = 145* | |
| Training cost* | 3.21 (-) | 0.00 (-) | 3.21 (-) |
| Diagnostic | 175.72 (131.27 to 220.18) | 743.04 (676.62 to 809.45) | -567.31 (-646.95 to -487.67) |
| Physician/nurse visits | 46.61 (41.96 to 51.26) | 68.76 (64.05 to 73.48) | -22.15 (-28.75 to -15.56) |
| Total | 225.54 (178.21 to 272.88) | 811.8 (744.25 to 879.35) | -586.26 (-668.45 to -504.07) |
| | | | |
| Tarraubella 2018 | *n = 149* | *n = 153* | |
| Training cost* | 15.00 (-) | 0.00 (-) | 15.00 (-) |
| Diagnostic | 91.52 (80.26 to 102.78) | 653.15 (606.32 to 699.99) | -561.63 (-609.76 to -513.05) |

| | | | |
|---|---|---|---|
| Physician/nurse visits | 226.96 (216.38 to 237.53) | 323.56 (304.33 to 342.8) | -96.61 (-118.49 to -74.72) |
| Total | 333.23 (315.18 to 351.27) | 976.72 (914.91 to 1038.53) | -643.49 (-707.81 to -579.18) |

CI = Confidence Interval; ESS = Epworth Sleepiness Scale Score; QALY = Quality-Adjusted Life Year.

Training cost = Average cost per randomized participant of delivering training in terms of salaried time of those delivering the training.

Diagnostic costs = Average cost to the healthcare system per randomized participant of diagnostic testing, utilizing costs reported by trial authors.

Physician/nurse visits = Average cost to the healthcare system per randomized participant of physician or nurse consultations, utilizing costs reported by trial authors.

*Confidence intervals not performed due to constant cost per participant.

**Table E10. Within-trial sleep diagnostic and treatment costs in Euros (€) (average cost per randomized participant) and cost of training delivery**

| Study | Primary Care mean (95% CI) | Specialist Care mean (95% CI) | Difference mean (95% CI) |
|---|---|---|---|
| All studies (overall) | *n = 489* | *n = 481* | |
| Training cost | 37.01 (31.05 to 42.97) | 0.00 (-) | 37.01 (31.05 to 42.97) |
| Diagnostic | 265.38 (236.93 to 293.82) | 637.05 (611.88 to 662.22) | -371.68 (-409.61 to -333.74) |
| Physician/nurse visits | 119.32 (112.43 to 126.22) | 184.14 (173.95 to 194.33) | -64.81 (-77.11 to -52.52) |
| Total | 421.70 (393.55 to 449.86) | 821.19 (793.52 to 848.87) | -399.49 (-438.92 to -360.06) |
| | | | |
| Chai-Coetzer 2013 | *n = 81* | *n = 74* | |
| Training cost* | 177.00 (0.00) | 0.00 (-) | 177.00 (-) |
| Diagnostic | 128.16 (114.44 to 141.89) | 437.82 (401.51 to 474.14) | -309.66 (-348.34 to -270.98) |
| Physician/nurse visits | 149.33 (139.52 to 159.13) | 237.76 (225.73 to 249.79) | -88.44 (-103.84 to -73.03) |
| Total | 454.51 (437.57 to 471.45) | 675.59 (635.65 to 715.52) | -221.08 (-264.28 to -177.88) |
| | | | |
| Sánchez-de-la-Torre 2015 | *n = 101* | *n = 109* | |
| Training cost* | 13.30 (-) | 0.00 (-) | 13.30 (-) |
| Diagnostic* | 816.95 (-) | 816.95 (-) | 0.00 (-) |
| Physician/nurse visits | 94.79 (89.91 to 99.68) | 165.14 (160.17 to 170.11) | -70.35 (-77.28 to -63.42) |
| Total | 925.06 (920.17 to 929.95) | 982.09 (977.13 to 987.06) | -57.03 (-63.96 to -50.11) |
| | | | |
| Sanchez-Quiroga 2018 | *n = 158* | *n = 145* | |
| Training cost* | 2.86 (0.00) | 0.00 (-) | 2.86 (-) |
| Diagnostic | 156.52 (116.92 to 196.12) | 661.83 (602.68 to 720.98) | -505.31 (-576.25 to -424.37) |
| Physician/nurse visits | 41.51 (37.37 to 45.66) | 61.25 (57.05 to 65.45) | -19.73 (-25.61 to -14.86) |
| Total | 200.89 (158.73 to 243.05) | 723.08 (662.91 to 783.24) | -522.18 (-595.39 to -448.98) |
| | | | |
| Tarraubella 2018 | *n = 149* | *n = 153* | |
| Training cost* | 13.30 (-) | 0.00 (-) | 13.30 (-) |
| Diagnostic | 81.52 (71.49 to 91.55) | 581.77 (540.05 to 623.49) | -500.25 (-543.12 to -457.38) |

| | | | |
|---|---|---|---|
| Physician/nurse visits | 202.15 (192.73 to 211.57) | 288.2 (271.07 to 305.33) | -86.05 (-105.54 to -66.56) |
| Total | 296.81 (280.74 to 312.88) | 869.97 (814.92 to 925.03) | -573.16 (-630.45 to -515.88) |

CI = Confidence Interval; ESS = Epworth Sleepiness Scale; QALY = Quality-Adjusted Life Years.

Training cost = Average cost per randomized participant of delivering training in terms of salaried time of those delivering the training.

Diagnostic costs = Average cost to the healthcare system per randomized participant of diagnostic testing, utilizing costs reported by trial authors.

Physician/nurse visits = Average cost to the healthcare system per randomized participant of physician or nurse consultations, utilizing costs reported by trial authors.

*Confidence intervals not calculated due to constant cost per participant.

**Table E11. Probabilities (%) of cost-pairs appearing in each cost-effectiveness plane quadrant**

| Study | Quadrant | Meaning | ESS Probability (%) | QALY Probability (%) |
|---|---|---|---|---|
| Chai-Coetzer 2013 | South East | Less expensive, More effective | 67 | 92 |
| | South West | Less expensive, Less effective | 33 | 8 |
| Tarraubella 2018 | South East | Less expensive, More effective | 0 | 81 |
| | South West | Less expensive, Less effective | 100 | 19 |
| Sanchez-Quiroga 2018 | South East | Less expensive, More effective | 19 | 8 |
| | South West | Less expensive, Less effective | 81 | 92 |
| Sánchez-de-la-Torre 2015 | South East | Less expensive, More effective | 0 | 3 |
| | South West | Less expensive, Less effective | 100 | 97 |

ESS = Epworth Sleepiness Scale; QALY = Quality-Adjusted Life Years.

The cost-effectiveness plane compares primary care-based with specialist sleep unit-based OSA management i.e. the descriptions such as “Less expensive” refer to primary care.

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## *5.4. Resultados del objetivo O.3.1*

**Título:** Decrease in sleep quality during COVID-19 outbreak

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# Decrease in sleep quality during COVID-19 outbreak

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**Abstract**

**Purpose:** The COVID-19 outbreak witnessed in the first months of 2020 has led to unprecedented changes in society's lifestyle. In the current study, we aimed to investigate the effect of this unexpected context on sleep.

**Methods:** During the COVID-19 outbreak, we performed an online survey with individuals formerly recruited for validation of the Spanish version of the sleep questionnaire Satisfaction, Alertness, Timing, Efficiency, and Duration (SATED). In the current survey, we asked the participants to complete the previously answered questionnaires including the Pittsburgh Sleep Quality Index (PSQI), a modified version of the Epworth Sleepiness Scale (ESS), and the SATED questionnaire. We also assessed the mood by the Profile of Mood States (POMS) questionnaire.

**Results:** The 71 participants were mostly women (75%) with a mean (±SD)

age of 40.7 ± 11.9 years. Comparing the previous PSQI score to that during the COVID-19 outbreak, we observed worsening sleep quality (5.45 ± 3.14 to 6.18 ± 3.03 points, $p = 0.035$). In parallel, there was an increase in the negative mood ($p = 0.002$). Accordingly, the decrease in sleep quality was substantially correlated with negative mood ($p < 0.001$). There were no differences in the ESS or SATED.

**Conclusions:** The COVID-19 outbreak-associated events correlate with decreased sleep quality in association with an increase in negative mood. Considering the importance of sleep for a healthy life, and in particular for immune function, efforts should be made to improve awareness on this matter and to offer psychological assistance to affected individuals.

**Keywords:** COVID-19, restrictive measures, sleep, mood.

**Abbreviations**

**BMI** Body mass index

**ESS** Modified Epworth Sleepiness Scale

**POMS** Profile of Mood States

**PSQI** Pittsburgh Sleep Quality Index

**SATED** Satisfaction, Alertness, Timing, Efficiency, and Duration

## Introduction

The COVID-19 outbreak witnessed in the first months of 2020 led to unprecedented changes in society's lifestyle. In a tentative to counteract the growing number of positive cases and avoid the health care system collapse, most of the world leaders determined the home confinement as the most effective measure to be followed. In Spain, restrictions on the movement of individuals started on March 14, exceeding two months up to this date (and likely to be extended). As a consequence, the population was compelled to adjust the personal and professional life to this condition, working from home, home teaching their children, and reducing social interaction.

Sleep is an important and highly susceptible behavior within this context. The flexibility in schedules due to social restrainment led to changes in the wake-up time and bedtime. Accordingly, recent studies reported that individuals are waking up and sleeping later during the confinement, possibly influenced by the increased use of digital media near bedtime [1]. Also, reduced exposure to the sunlight, limited activity during the day, and alterations in the food time may lead to dysregulation in the circadian rhythms and, in consequence, may affect sleep [2, 3]. Furthermore, sleep quality is closely related to the mood, which was demonstrably altered during this time [4, 5]. Huang and collaborators (2020) observed a high prevalence of generalized anxiety disorder which seemed to be associated with the time spent focusing on the COVID-19 (≥ 3 hours per day) [6]. In addition, in a study performed during the initial stage of the COVID-19 outbreak in China, 54% of participants rated the psychological impact as moderate or severe and about one-third reported moderate-to-severe anxiety [7]. Accordingly, the few studies evaluating sleep during this period also evaluated anxiety, depression, or stress. Xiao and collaborators

(2020) reported an association between anxiety and poor sleep quality assessed by the Pittsburgh Sleep Quality Index (PSQI) questionnaire [4]. Similarly, poor quality sleep was demonstrably increased in those with depression, anxiety, and stress [1]. However, proper evaluation of the effect of the COVID-19 outbreak on sleep is hindered by the design of the available studies. Considering this, we conducted an online survey from April 28, 2020, to May 12, 2020 (during COVID-19 outbreak) with individuals that had previously answered the same survey (pre-COVID-19 period). The survey included the PSQI, a modified version of the Epworth Sleepiness Scale (ESS), the Satisfaction Alertness Timing Efficiency Duration (SATED), and the Profile of Mood States (POMS) questionnaire.

## Methods

### *Study population*

Our population was composed by part of the individuals recruited as an independent sample aiming to validate the Spanish version of the SATED questionnaire [8]. The participants were older than 18 years of age and considered to be physically and mentally able to participate in the study. The original sample was stratified by sex, age, educational and socioeconomic level to properly represent the general population (for a detailed description, see [8]). This study was approved by the Clinical Research Ethics Committee of the Arnau de Vilanova University Hospital in Lleida (CEIC-1694), and conducted according to the principles outlined by the Declaration of Helsinki.

### *Study design*

The population was first recruited in 2017 as an independent sample to validate the Spanish version of the SATED questionnaire [8] (Fig. 1). Clinical and sociodemographic data were collected, and the participants

completed the PSQI, ESS, SATED, and POMS questionnaires. During the COVID-19 outbreak in Spain, the individuals were contacted by their electronic addresses and asked to complete the previously answered questionnaires. The survey was available for a limited time window (from April 28 to May 12, 2020) and we obtained the answer from 71 individuals. Clinical and sociodemographic data were collected again due to possible changes over the years.

*Clinical and sociodemographic variables*

The following variables were collected: age, sex, educational level, work schedule, physical activity, previous diseases, medication intake, alcohol consumption, smoking, and caffeine-based drinks ingestion. Body mass index (BMI) was calculated as body weight (in kg)/height (in $m^2$).

*Pittsburgh Sleep Quality Index (PSQI)*

The sleep quality was assessed by the PSQI [9]. The questionnaire was composed of 19 questions representing one of the seven components of sleep quality: subjective sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbance, sleep medication intake, and daytime dysfunction. Each component score was rated on a three-point scale, leading to a sum of up to 21 points. A PSQI score >5 indicated a poor sleep quality whereas a PSQI score ≤5 indicated a good sleep quality.

*Modified Epworth Sleepiness Scale (ESS)*

The excessive daytime somnolence was assessed by the ESS [10]. The questionnaire is originally composed of 8 questions to assess the chance of falling asleep during different daily situations. Three questions that were considered inappropriate due to the restrictive measures were excluded. Each question was rated on a three-point scale, in which 0 represented no chance of occurrence, and 3 indicated a high chance of occurrence. The

overall score ranged from 0 to 15 points. Higher scores represented increased daytime somnolence.

*Satisfaction Alertness Timing Efficiency Duration (SATED)*

Sleep health was further assessed by the SATED [8]. The questionnaire was composed of 5 questions representing one of the 5 following sleep-related dimensions: subjective satisfaction, alertness during waking hours, appropriate timing, efficiency, and duration. Each question was rated on a two-point scale, leading to a sum of up to 10 points. Higher scores indicated better sleep health.

*Profile of Mood States (POMS)*

The mood was assessed by the POMS [11]. The questionnaire was composed of 28 questions representing one of the 5 following dimensions: tension (5 questions), depression (6 questions), anger (7 questions), vigor (6 questions), and fatigue (4 questions). Each question was rated on a five-point scale, with 0 representing 'not at all' and 4 indicating 'extremely'. The score of each dimension was the sum of the given rates for each of the corresponding questions. The positive subscale corresponded to 'vigor' and the negative subscale was the sum of tension, depression, anger, and fatigue. The total score was calculated by subtracting the positive subscale from the total of the negative subscale (+100, to avoid negative values). Thus, higher scores indicated a negative mood.

*Statistical analysis*

The means (standard deviation, SD) were estimated for quantitative variables and the absolute and relative frequencies were used for qualitative variables. We compared the questionnaires outcomes between both periods (pre- and during COVID-19 outbreak) using t-test or Wilcoxon rank sum test for paired samples. Furthermore, the relationship

between POMS and PSQI scores during the COVID-19 outbreak was assessed through Spearman's rank correlation coefficient. Finally, the differences in the PSQI components according to the working condition were assessed by linear models. All statistical analyses and data processing procedures were performed using R software, version 3.5.2 (Vienna, Austria).

## Results

*Participants characteristics*

The 71 participants were mostly women (75%) with a mean (±SD) age of 40.7 ± 11.9 years old and a mean (±SD) BMI of 23.0 ± 3.7 $kg.m^{-2}$ (Table 1). Only 1 (1%) individual had been diagnosed with COVID-19 by the time of the survey and no positive case at the same home was reported. The working condition was altered in most of the cases, with 32 (45%) individuals working from home and 12 (17%) unemployed due to the lockdown whilst 16 (23%) remained working at the workplace and 10 (14%) were already unemployed before the COVID-19 outbreak.

*COVID-19 outbreak, sleep, and mood*

According to the PSQI, there was a decrease in sleep quality during this period, demonstrated by a mean (±SD) change of 0.73 ± 3.01 ($p = 0.035$) between the baseline evaluation and that during the COVID-19 outbreak (Table 2). A similar outcome was observed in relation to sleep latency, with a mean (±SD) change of 0.27 ± 0.96 ($p = 0.028$) between the two time-points. Differently, we did not observe changes related to the excessive daytime somnolence and other sleep-related aspects as indicated by the ESS ($p = 0.127$) and SATED ($p = 0.110$), respectively.

The negative mood was significantly increased during the COVID-19 outbreak as demonstrated by a mean (±SD) change of 6.27 ± 14.92 ($p =$

0.002) between the two time-points in the POMS total score (Table 3). Accordingly, there was an increase in the negative subscale with a mean (±SD) change of 5.63 ± 13.88 (p = 0.001) as a result of increases in tension [mean (±SD) change: 1.9 ± 4.38; p = 0.001], depression [mean (±SD) change: 1.17 ± 4.15; p = 0.017] and anger [mean (±SD) change: 2.07 ± 5.88; p = 0.002].

*Correlations between sleep quality and mood*

To evaluate whether the observed decrease in sleep quality was associated with the increase in the negative mood, we investigated the correlations between PSQI and POMS questionnaires (Table 4). There was substantial correlation among POMS total score and different PSQI items such as PSQI total score (corr = 0.55, p < 0.001), subjective sleep quality (corr = 0.49, p < 0.001), sleep latency (corr = 0.31, p = 0.008), sleep duration (corr = 0.33, p = 0.005), sleep medication intake (corr = 0.24, p = 0.040) and daytime dysfunction (corr = 0.49, p < 0.001). Similarly, distinct correlations were observed among PSQI items and the specific dimensions of POMS.

**Discussion**

In the current study, we investigated the influence of the COVID-19 outbreak-associated events on sleep. According to the PSQI, there was a decrease in sleep quality during this period, possibly associated with an increase in sleep latency. In parallel, the mood state evaluation indicated an increase in the score of dimensions representing a negative mood such as tension, depression, and anger. Accordingly, there was substantial correlation between sleep quality and mood states. On the other hand, we did not observe any differences in relation to the daytime somnolence as indicated by the ESS nor on the sleep dimensions assessed by the SATED

questionnaire.

The findings herein presented seem to confirm the available data in the literature. Cellini and collaborators (2020) evaluated 1310 individuals living in the Italian territory and reported a decrease in sleep quality, which was stronger in individuals with higher symptoms of depression, anxiety, and stress [1]. Similarly, Xiao and collaborators (2020) demonstrated that the decrease in sleep quality in individuals confined at home for 14 days in central China was associated with an increase in anxiety and stress [4]. Although those outcomes are headed towards the same direction to the ones observed in this study, proper conclusions were hindered by limitations related to these studies' designs. Here, we compared an evaluation before the COVID-19 outbreak to that during this period, which confirmed a deleterious effect of this context on sleep quality. Accordingly, there was a substantial correlation between sleep-related parameters and mood. The most affected parameter in the PSQI was the sleep latency, which presented a negative correlation with the positive subscale of POMS, i.e., the lack of positive mood appeared to be associated with increased sleep latency. In fact, the PSQI total score presented a positive correlation with all the parameters of POMS that composed the negative subscale, such as tension, depression, anger, and fatigue.

Other factors may have accounted for the observed decrease in sleep quality in addition to the negative mood. Changes in social- and work-related schedules lead to alterations in sleep. We did not observe an influence of the working condition on sleep quality (see Table S1 in the supplemental material), however, recent studies reported that people are waking up and sleeping later during this period [1]. Although this may be due to late chronotype, such situation could be related to the reported increased use of digital media near bedtime associated with the COVID-19 outbreak [1, 12]. In fact, the changes in sleep latency here presented

may be a consequence of excessive screen time at night. Furthermore, the imposed restrictions lead to a decrease in sunlight exposure and physical activity, which are important factors for circadian rhythms maintenance [3, 13, 14]. Accordingly, these behaviors altogether lead to a disruption of circadian rhythms, further aggravating sleep behavior, and mood [15, 16]. Also, such disturbance may affect the immune response [17], body temperature [18], blood pressure [19], metabolism, and energy homeostasis [20].

It is important to address that although the original sample was stratified by sex, age, educational and socioeconomic level to properly represent the general population, our sample was reduced to the individuals who answered the questionnaires during the COVID-19 outbreak. Accordingly, our population was mostly composed of women with a mean age of approximately 40 years. Studies showed that women are more susceptible to worry and to increased psychological burden [21, 22]. In addition, schedules, screen time at night, and the perception of the context may be distinct across the different ages. Thus, the results herein presented should be taken with caution, especially when making generalizations to a broader population. Besides this, this study has some limitations. Considering the influence of age on sleep quality, the three-years of difference between baseline and follow-up evaluations may have affected the sleep quality, in addition to the context of the COVID-19 outbreak. Also, although we have considered alterations in health conditions, changes in medication, differences in food and drink habits during this period, other modifications in lifestyle may have contributed to the observed outcomes. Our study has some strengths as well. Sleep was evaluated by different validated questionnaires. In addition, we investigated the influence of the COVID-19 outbreak-associated events on sleep with a baseline assessment, when the individuals were not under this context.

In summary, we observed a decrease in sleep quality during the COVID-19 outbreak according to the PSQI. In parallel, the mood state evaluation indicated an increase in the scores of dimensions representing a negative mood such as tension, depression, and anger. Accordingly, the decrease in sleep quality was substantially correlated with negative mood. Considering the importance of sleep for a healthy life, and in particular for the immune function, efforts should be made to improve awareness on this matter and to psychologically assist the individuals during this period. These findings unravel a possible facet associated with the restrictive measures, which should be considered in case of future situations.

## Declarations

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### Disclosure statement

The authors declare that no conflict of interests exists.

### Ethics approval

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Clinical Research Ethics Committee of the Arnau de Vilanova University Hospital in Lleida (CEIC-1694).

### Consent to participate

The individuals signed an informed consent form to participate.

**Consent to publish**

The individuals signed an informed consent form to publish.

**Availability of data and material (data transparency)**

All data support our published claims and comply with field standards.

**Code availability (software application or custom code)**

Not applicable

**Author's contributions:** Adriano Targa: Conceptualization, Methodology, Writing - original draft/review & editing. Iván D. Benítez: Conceptualization, Methodology, Data curation, Formal analysis, Writing - review & editing. Anna Moncusí-Moix: Conceptualization, Methodology, Data curation, Writing - review & editing. Maria Arguimbau: Methodology, Writing - review & editing. Jordi de Batlle: Writing - review & editing. Mireia Dalmases: Conceptualization, Writing - review & editing. Ferran Barbé: Conceptualization, Writing - review & editing.

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**Fig. 1.** Flow chart. ESS, Modified Epworth Sleepiness Scale; POMS, Profile of Mood States; PSQI, Pittsburgh Sleep Quality Index; SATED, Satisfaction Alertness Timing Efficiency Duration.

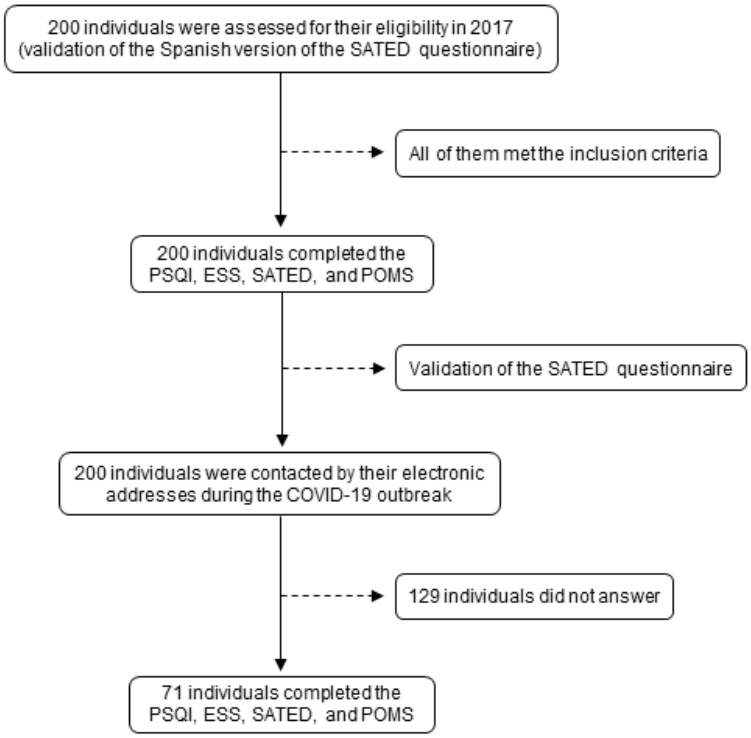

**Table 1.** Characteristics of the participants.

| | **Global** n = 71 *n (%), mean (SD)* |
|---|---|
| ***Sociodemographic data*** | |
| Sex, woman | 53 (75%) |
| Age, years | 40.7 (11.9) |
| BMI, $kg \cdot m^{-2}$ | 23.0 (3.7) |
| Education, years | 9.0 (2.2) |
| ***Health condition*** | |
| Rhinits | 5 (7%) |
| Hypo-thyroidism | 4 (6%) |
| Hypertension | 3 (4%) |
| ***COVID-19*** | |
| Diagnosis | 1 (1%) |
| Hospital admission | 0 (0%) |
| Household cases | 0 (0%) |
| ***Working condition*** | |
| Workplace | 16 (23%) |
| Home working | 32 (45%) |
| Unemployed due to lockdown | 12 (17%) |
| Previously unemployed | 10 (14%) |

BMI, body mass index; n, number; SD, standard deviation.

**Table 2.** COVID-19 outbreak and sleep.

| | **Pre-COVID-19** n = 71 *Mean (SD)* | **COVID-19** n = 71 *Mean (SD)* | **Change** *Mean (SD)* | **p-value** |
|---|---|---|---|---|
| ***PSQI*** | 5.45 (3.14) | 6.18 (3.03) | 0.73 (3.01) | 0.035 |
| Subjective sleep quality | 1.13 (0.67) | 1.20 (0.67) | 0.07 (0.78) | 0.442 |
| Sleep latency | 1.07 (0.90) | 1.34 (0.92) | 0.27 (0.96) | 0.028 |
| Sleep duration | 0.83 (0.61) | 0.72 (0.66) | -0.11 (0.75) | 0.207 |
| Sleep efficiency | 0.34 (0.77) | 0.55 (0.82) | 0.21 (0.91) | 0.090 |
| Sleep disturbance | 1.21 (0.56) | 1.20 (0.43) | -0.01 (0.62) | 0.860 |
| Sleep medication intake | 0.24 (0.73) | 0.35 (0.83) | 0.11 (0.77) | 0.283 |
| Daytime dysfunction | 0.63 (0.68) | 0.83 (0.79) | 0.2 (0.84) | 0.057 |
| ***ESS*** | 6.23 (2.64) | 5.75 (2.99) | -0.48 (2.33) | 0.127 |
| ***SATED*** | 7.25 (1.95) | 7.70 (1.99) | 0.45 (2.44) | 0.110 |

ESS, Modified Epworth Sleepiness Scale; PSQI, Pittsburgh Sleep Quality Index; SATED, Satisfaction Alertness Timing Efficiency Duration; SD, standard deviation.

**Table 3.** COVID-19 outbreak and mood.

| | **Pre-COVID-19** n = 71 *Mean (SD)* | **COVID-19** n = 71 *Mean (SD)* | **Change** *Mean (SD)* | **p-value** |
|---|---|---|---|---|
| ***POMS*** | 107 (17.5) | 113 (17.3) | 6.27 (14.92) | 0.002 |
| Tension | 5.46 (4.35) | 7.37 (4.16) | 1.9 (4.38) | 0.001 |
| Depression | 3.79 (4.52) | 4.96 (3.99) | 1.17 (4.15) | 0.017 |
| Anger | 5.14 (6.39) | 7.21 (5.87) | 2.07 (5.88) | 0.002 |
| Vigor | 12.5 (5.25) | 11.8 (5.31) | -0.63 (5.65) | 0.388 |
| Fatigue | 4.76 (3.61) | 5.25 (3.92) | 0.49 (3.39) | 0.110 |
| Positive subscale | 12.5 (5.25) | 11.8 (5.31) | -0.63 (5.65) | 0.388 |
| Negative subscale | 19.2 (16.3) | 24.8 (15.2) | 5.63 (13.88) | 0.001 |

POMS, Profile of Mood States; SD, standard deviation.

**Table 4.** Correlations between sleep quality and mood.

| | POMS | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | *Tension* | *Depression* | *Anger* | *Vigor* | *Fatigue* | *Positive* | *Negative* | *Total Score* |
| **PSQI** | | | | | | | | |
| *Total score* | 0.44*** | 0.38** | 0.31** | -0.39*** | 0.46*** | -0.39*** | 0.47*** | 0.55*** |
| *Subjective sleep quality* | 0.41*** | 0.31** | 0.34** | -0.31** | 0.42*** | -0.31** | 0.44*** | 0.49*** |
| *Sleep latency* | 0.21 | 0.12 | 0.18 | -0.38** | 0.20 | -0.38** | 0.21 | 0.31** |
| *Sleep duration* | 0.29* | 0.33** | 0.17 | -0.09 | 0.25* | -0.09 | 0.30* | 0.33** |
| *Sleep efficiency* | 0.16 | 0.14 | 0.02 | -0.10 | 0.18 | -0.10 | 0.17 | 0.17 |
| *Sleep disturbance* | 0.26* | 0.15 | -0.01 | -0.05 | 0.23 | -0.05 | 0.18 | 0.17 |
| *Sleep medication intake* | 0.21 | 0.29* | 0.15 | -0.09 | 0.13 | -0.09 | 0.26* | 0.24* |
| *Daytime dysfunction* | 0.27* | 0.34** | 0.30** | -0.47*** | 0.48*** | -0.47*** | 0.39*** | 0.49*** |

*p<0.05, **p<0.01, ***p<0.001. PSQI, Pittsburgh Sleep Quality Index.

**Table S1. Sleep quality and working condition.**

| | **Pre-COVID-19** *Mean (SD)* | **COVID-19** *Mean (SD)* | **Change** *Mean (SD)* | **Estimate** *Mean (SD)* | **p-value** |
|---|---|---|---|---|---|
| ***PSQI (Total score)*** | | | | | |
| Workplace | 5.688 (2.845) | 6.625 (3.462) | 0.937 (3.53) | REF | |
| Unemployed due to lockdown | 4.333 (2.57) | 5.333 (2.674) | 1 (1.907) | -0.587 (1.017) | 0.565 |
| Home working | 5.156 (2.273) | 6.188 (2.845) | 1.031 (3.074) | -0.161 (0.810) | 0.842 |
| Previously unemployed | 7.182 (5.344) | 6.455 (3.446) | -1 (2.981) | -1.163 (1.077) | 0.284 |
| ***Subjective sleep quality*** | | | | | |
| Workplace | 1.063 (0.680) | 1.375 (0.718) | 0.312 (0.793) | REF | |
| Unemployed due to lockdown | 0.833 (0.577) | 1 (0.738) | 0.166 (0.834) | -0.299 (0.246) | 0.230 |
| Home working | 1.188 (0.644) | 1.219 (0.608) | 0.031 (0.739) | -0.197 (0.197) | 0.319 |
| Previously unemployed | 1.4 (0.843) | 1.1 (0.737) | -0.3 (0.823) | -0.387 (0.262) | 0.144 |
| ***Sleep latency*** | | | | | |
| Workplace | 1.063 (0.928) | 1.5 (1.033) | 0.437 (0.963) | REF | |
| Unemployed due to lockdown | 1 (0.738) | 1.417 (1.24) | 0.416 (0.996) | -0.053 (0.321) | 0.867 |
| Home working | 1.063 (0.913) | 1.25 (0.803) | 0.187 (1.03) | -0.250 (0.257) | 0.335 |
| Previously unemployed | 1.2 (1.135) | 1.2 (0.788) | 0 (0.666) | -0.364 (0.339) | 0.286 |
| ***Sleep duration*** | | | | | |
| Workplace | 1.063 (0.573) | 0.937 (0.771) | -0.125 (0.957) | REF | |
| Unemployed due to lockdown | 0.416 (0.514) | 0.333 (0.492) | -0.083 (0.514) | -0.431 (0.257) | 0.098 |

| | | | | | |
|---|---|---|---|---|---|
| Home working | 0.781 (0.42) | 0.75 (0.508) | -0.031 (0.646) | -0.112 (0.197) | 0.572 |
| Previously unemployed | 1.1 (0.994) | 0.7 (0.948) | -0.4 (0.966) | -0.247 (0.255) | 0.336 |
| ***Sleep efficiency*** | | | | | |
| Workplace | 0.375 (0.885) | 0.687 (1.014) | 0.312 (1.352) | REF | |
| Unemployed due to lockdown | 0 (0) | 0.083 (0.288) | 0.083 (0.288) | -0.481 (0.282) | 0.093 |
| Home working | 0.25 (0.568) | 0.562 (0.715) | 0.312 (0.780) | -0.084 (0.224) | 0.708 |
| Previously unemployed | 0.9 (1.287) | 0.6 (0.843) | -0.3 (0.674) | -0.259 (0.301) | 0.393 |
| ***Sleep disturbance*** | | | | | |
| Workplace | 1.125 (0.619) | 1.188 (0.403) | 0.062 (0.573) | REF | |
| Unemployed due to lockdown | 1.083 (0.514) | 1 (0) | -0.083 (0.514) | -0.180 (0.163) | 0.273 |
| Home working | 1.281 (0.522) | 1.281 (0.522) | 0 (0.718) | 0.068 (0.131) | 0.607 |
| Previously unemployed | 1.3 (0.674) | 1.2 (0.421) | -0.1 (0.567) | -0.016 (0.173) | 0.925 |
| ***Sleep medication intake*** | | | | | |
| Workplace | 0.125 (0.5) | 0 (0) | -0.125 (0.5) | REF | |
| Unemployed due to lockdown | 0.5 (1.168) | 0.75 (1.215) | 0.25 (0.621) | 0.534 (0.274) | 0.055 |
| Home working | 0.125 (0.421) | 0.387 (0.843) | 0.25 (0.842) | 0.375 (0.216) | 0.088 |
| Previously unemployed | 0.5 (1.08) | 0.4 (0.843) | -0.1 (0.994) | 0.184 (0.289) | 0.526 |
| ***Daytime dysfunction*** | | | | | |
| Workplace | 0.875 (0.619) | 0.937 (0.997) | 0.062 (0.928) | REF | |
| Unemployed due to lockdown | 0.5 (0.674) | 0.75 (0.621) | 0.25 (0.753) | -0.032 (0.292) | 0.911 |
| Home working | 0.468 (0.621) | 0.75 (0.762) | 0.281 (0.812) | -0.019 (0.237) | 0.933 |
| Previously unemployed | 0.9 (0.875) | 1.1 (0.737) | 0.2 (0.918) | 0.152 (0.304) | 0.618 |

PSQI, Pittsburgh Sleep Quality Index; SD, standard deviation.

## *5.5. Resultados del objetivo O.3.2*

**Título:** Sleep and Circadian Health of Critical COVID-19 Survivors 3 Months After Hospital Discharge

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# Sleep and circadian health of critical COVID-19 survivors three months after hospital discharge

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**Conflicts of interest:** none declared.

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**Abstract**

**Objective:** To evaluate the sleep and circadian rest-activity pattern of critical COVID-19 survivors three months after hospital discharge.

**Design:** Observational, prospective study.

**Setting:** Single-center study.

**Patients:** 172 consecutive COVID-19 survivors admitted to the intensive care unit (ICU) with acute respiratory distress syndrome.

**Interventions:** Seven days of actigraphy for sleep and circadian rest-activity pattern assessment; validated questionnaires; respiratory tests at the 3-month follow-up.

**Measurements and Main results:** The cohort included 172 patients, mostly males (67.4%) with a median [$p_{25}$;$p_{75}$] age of 61.0 [52.8;67.0] years. The median number of days at the ICU was 11.0 [6.00;24.0], and 51.7% of the patients received invasive mechanical ventilation (IMV). According to the Pittsburgh Sleep Quality Index (PSQI), 60.5% presented poor sleep quality three months after hospital discharge, which was further confirmed by actigraphy. Female sex was associated with an increased score in the PSQI (p-value < 0.05) and IMV during ICU stay was able to predict a higher fragmentation of the rest-activity rhythm at the 3-month follow-up (p-value < 0.001). Furthermore, compromised mental health measured by the Hospital Anxiety and Depression Scale was associated with poor sleep

quality (p-value < 0.001).

**Conclusions:** Our findings highlight the importance of considering sleep and circadian health after hospital discharge. Within this context, IMV during the ICU stay could aid in predicting an increased fragmentation of the rest-activity rhythm at the 3-month follow-up. Furthermore, compromised mental health could be a marker for sleep disruption at the post-COVID period.

**Keywords:** Post-COVID, Pittsburgh Sleep Quality Index, actigraphy, intensive care unit, sequelae, acute respiratory distress syndrome.

**Abbreviations**

**6MWT** 6-minute walking test

**6MWD** Predicted 6-minute walked distance

**ARDS** Acute respiratory distress syndrome

**DLCO** Diffusing lung capacity for carbon monoxide

**ESS** Epworth Sleepiness Scale

**HADS** Hospital Anxiety and Depression Scale

**ICU** Intensive care unit

**IMV** Invasive mechanical ventilation

**IS** Interdaily stability

**IV** Intradaily variability

**NIMV** Noninvasive mechanical ventilation

**P** Percentile

**PP-6MWD** Percent predicted 6-minute walked distance

**PSQI** Pittsburgh Sleep Quality Index

**RA** Relative amplitude

**SATED** Satisfaction Alertness Timing Efficiency Duration

**SD** Standard deviation

**TSS** Total severity score

**WASO** Time spent awake after sleep onset

## Introduction

Coronavirus Disease 2019 (COVID-19) affected more than 200 million people worldwide until August 2021. During the acute phase of the disease, approximately 30% of the patients develop severe complications, which increase the risk of hospitalization, intensive care unit (ICU) admission, and death (1). In addition, recent studies report a set of symptoms observed months after hospital discharge including fatigue, joint pain, dyspnea, cough, anxiety, depression, and cognitive impairment, among others (2, 3). While studies investigating the different sequelae in COVID-19 patients are rapidly emerging, a comprehensive evaluation of sleep and circadian rhythms in this context is yet to be performed. Complaints of insomnia and disturbed sleep are often observed, reaching a prevalence of up to 31% (4–6). Nevertheless, all the available findings are based on self-reported assessments. Therefore, additional investigations using validated sleep questionnaires and objective measurements are extremely necessary.

The hospital and particularly the ICU are harmful environments for sleep and circadian health. Accordingly, critically ill patients are exposed to excessive noise and interruptions during the night, unusual feeding schedules, and mistimed artificial light at the detriment of sunlight exposure (7–9). In addition, an appropriate amount of activity during the day and the maintenance of a social routine are often hindered by restrictions related to the hospital context and the health condition of the patients. These factors ultimately lead to poor sleep quality, increased fragmentation of the rest-activity pattern, and decreased synchronization between the endogenous rhythms and the external environment (10, 11). Furthermore, other situations often experienced by critical COVID-19

patients such as depression and anxiety may affect sleep and circadian health (12).

The main objective of this study was to evaluate the sleep and circadian rest-activity pattern of critical COVID-19 survivors three months after hospital discharge. To accomplish this, subjective and objective evaluations were performed using validated questionnaires and wrist actigraphy. We hypothesized that an important number of patients would have compromised sleep and circadian health. We also performed two additional analyses. First, we investigated whether baseline characteristics and ICU-related procedures could predict sleep and circadian outcomes after hospital discharge. Second, we evaluated whether the other sequelae could be associated with sleep and circadian alterations.

## Materials and Methods

*Study population*

This is a prospective, observational, single-center study designed to evaluate the sleep and circadian rest-activity pattern of critical COVID-19 survivors after hospital discharge (Figure S1). Patients were recruited at the Hospital Universitari Arnau de Vilanova-Santa Maria (Lleida, Spain) between March 2020 and April 2021. The inclusion criteria included individuals more than 18 years old who had a confirmed diagnosis of SARS-CoV-2 infection through polymerase chain reaction (PCR), developing acute respiratory distress syndrome (ARDS), and consequently being admitted to the ICU. The exclusion criteria included: 1) patients in palliative care and 2) patients with severe mental and/or physical disability that could prevent the proposed evaluations.

This study was approved by the Medical Ethics Committee of the Hospital Universitari Arnau de Vilanova (Identifier: CEIC-2510) and conducted according to the principles outlined by the Declaration of Helsinki.

Informed consent was acquired for all patients.

*Study design*

Patients recruited at baseline arrived at the Hospital Universitari de Santa Maria (Lleida, Spain) for the medical appointment three months after hospital discharge (Figure 1). A clinical evaluation was performed followed by subjective and objective assessments of sleep and circadian rest-activity pattern. In the sequence, we evaluated respiratory function, mental health, and aerobic capacity.

*Clinical data*

Clinical data were obtained at baseline (ICU stay) and at the clinical evaluation three months after hospital discharge. Age, sex, body mass index (BMI), comorbidities, alcohol consumption, smoking habits, time spent at the ICU, duration of invasive mechanical ventilation (IMV), duration of noninvasive mechanical ventilation (NIMV), hours in prone position, pharmacotherapy, arterial oxygen partial pressure ($PaO_2$) to fractional inspired oxygen ($FiO_2$) ratio, and peripheral oxygen saturation ($SpO_2$) to fractional inspired oxygen ($FiO_2$) ratio were collected at baseline. COVID-19-related symptoms were obtained at the clinical evaluation after hospital discharge.

*Sleep and circadian rest-activity pattern*

Pittsburgh Sleep Quality Index (PSQI)

Sleep quality was assessed by the PSQI. This questionnaire is composed of 19 questions representing one of the seven components of sleep quality: subjective sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbance, sleep medication intake, and daytime dysfunction. Each component score is rated on a three-point scale, leading to a sum of up to 21 points. A PSQI score >5 indicates a poor sleep quality whereas a PSQI score ≤5 indicates a good sleep quality (13, 14).

Epworth Sleepiness Scale (ESS)

Excessive daytime somnolence was assessed by the ESS. This questionnaire is composed of 8 questions to assess the chance of falling asleep during different daily situations. Each question is rated on a three-point scale, in which 0 represents no chance of occurrence, and 3 indicates a high chance of occurrence. The overall score ranges from 0 to 24 points. Higher scores represent increased daytime somnolence (15–17).

Satisfaction Alertness Timing Efficiency Duration (SATED)

Sleep health was further assessed by the SATED. This questionnaire is composed of 5 questions representing one of the following sleep-related dimensions each: subjective satisfaction, alertness during waking hours, appropriate timing, efficiency, and duration. Each question is rated on a two-point scale, leading to a sum of up to 10 points. Higher scores indicate better sleep health (18).

Actigraphy

Recruited patients who arrived for the medical appointment three months after hospital discharge were randomly selected for the objective assessment of sleep and circadian rest-activity pattern through the use of a wrist-mounted actigraph (Actiwatch 2, Philips Respironics) for 7 days. A sleep log was also delivered to be completed during the same period. The following variables were obtained: time in bed (in minutes), total sleep time (in minutes), sleep efficiency (in %, defined as the ratio between total sleep time and the time spent in bed), latency (in minutes, defined as the time spent awake until the first sleep episode while in bed), and WASO (in minutes, defined as the time spent awake after sleep onset). In addition, activity counts of 60-second epochs were obtained, from which different variables associated with the rest-activity rhythm were calculated. The

intradaily variability (IV) represents the fragmentation of the rest-activity rhythm within each 24-h period, indicating whether there are daytime naps and/or nocturnal activity episodes. The interdaily stability (IS) represents the similarity between one 24-hour period and the next, indicating how synchronized the internal rest-activity rhythm is with the different zeitgebers over 7 days of actigraphy. L5 (the mean activity of the five consecutive hours with the lowest activity) and M10 (the mean activity of the ten consecutive hours with the highest activity) were used to calculate the relative amplitude (RA) (M10-L5/M10+L5). The amplitude represents the robustness of the rest-activity rhythm, indicating whether a difference in the magnitude of activity between active and rest phases occurs (19).

Respiratory function

Airway function was measured and represented as previously described (3). The diffusing lung capacity for carbon monoxide (DLCO) was the variable used to represent the respiratory function. Computed tomography (CT) of the chest was performed to evaluate the severity of lung affectation. To quantify this, we calculated the total severity score (TSS). A detailed description of the procedure can be found in (3).

Mental health evaluation

The Hospital Anxiety and Depression Scale (HADS) was used to assess signs of anxiety and depression. This questionnaire consists of a 7-item anxiety subscale and a 7-item depression subscale. Each item is rated on a 3-point scale, leading to a sum of up to 21 points. A score >8 indicates possible anxiety or depression whereas a score ≤8 indicates the opposite (20–23).

Aerobic capacity

The 6-minute walking test (6MWT) was performed to evaluate the aerobic

capacity (24). The traveled distance was compared with reference values. Accordingly, the predicted 6-minute walked distance (6MWD) was calculated based on the following equations: for men, predicted 6MWD = (7.57 x height) - (5.02 x age) - (1.76 x weight) - 309 m; for women, predicted 6MWD = (2.11 x height) - (5.78 x age) - (2.29 x weight) + 667 m (25). Percent predicted 6MWD (PP-6MWD) was calculated using the formula: PP-6MWD = 6MWD/Predicted 6MWD x 100.

*Statistical analysis*

Descriptive statistics were performed to describe sociodemographic and clinical characteristics as well as ICU-related information and post-COVID sequelae. Absolute and relative frequencies were used for qualitative data. The means (standard deviation (SD)) and medians ($25^{th}$ percentile; $75^{th}$ percentile [$p_{25}$;$p_{75}$]) were estimated for quantitative variables with normal and nonnormal distributions, respectively. The normality of the distribution was assessed by the Shapiro-Wilk test.

We evaluated possible associations between baseline characteristics (data obtained during the ICU stay) and sleep/circadian-related data (PSQI score, IV, IS, and RA) collected three months after hospital discharge. PSQI score was chosen based on the observed outcomes and in the clinical relevance of this questionnaire (26). IV, IS, and RA are variables that represent important dimensions of the circadian rest-activity pattern (19). The selection of baseline variables was performed using a relaxed least absolute shrinkage and selection operator (LASSO) model (27, 28). Tenfold cross-validation was carried out to determine the lambda parameter of the LASSO model (29). Lambda was selected as the value that minimized the mean square error. To perform the LASSO analysis, missing values were replaced by the means of the nonmissing values.

We investigated possible associations between sleep/circadian-related data

(PSQI score, IV, IS, and RA) and other sequelae collected three months after hospital discharge. The chosen variables represented different physiological domains that could be associated with sleep and circadian rhythms within this context. These included the depression score (HADS), anxiety score (HADS), DLCO, TSS, PP-6MWD, and other COVID-19-related symptoms (only those with a higher prevalence were included in the analysis). Pearson coefficient tests were performed to assess correlations between variables.

The p-value threshold defining statistical significance was set at <0.05. All statistical analyses were performed using R software, version 4.0.2.

## Results

*Baseline characteristics of the cohort*

The cohort included 172 COVID-19 patients admitted to the ICU. Most of them were males (67.4%) with a median [$p_{25}$;$p_{75}$] age of 61.0 [52.8;67.0] years (Table 1). Different comorbidities were present, including obesity (48.5%), hypertension (47.1%), and diabetes mellitus (22.7%). The patients spent a median number of 23 [14.0;38.2] days at the hospital and 11 [6.00;24.0] days at the ICU, where 51.7% received IMV and 70.9% needed NIMV. Similar characteristics were observed considering only the individuals who performed the actigraphy (Table S1).

*Sleep and circadian rest-activity pattern*

According to the PSQI, most of the patients presented poor sleep quality (60.5%) with a mean (SD) score of 7.09 (4.41) (Table 2). Sleep duration and sleep efficiency were the most affected domains with 73.9% of the patients sleeping less than the recommended hours and 57.5% with a sleep efficiency lower than 85% (30). The objective evaluation of sleep through actigraphy further confirmed these findings, demonstrating that 50.8% of

the patients slept less than 7 hours per night, which was possibly associated with the WASO (Table 3). Accordingly, sleep efficiency was decreased in 55.4% of the patients. The circadian rest-activity pattern presented substantial variability within our sample (Figure S2).

*Other sequelae after hospital discharge*

We evaluated other sequelae including those related to respiratory function, mental health, and aerobic capacity (Table S2). Similar to previous findings (3), 75.4% of patients presented an abnormal DLCO (< 80%) and the mean (SD) distance in the 6MWT was 408 (90.5) meters. Such distance was 87.8% (23.8) of that predicted for healthy individuals after adjusting for sex, age, height, and weight. In relation to mental health, 5.92% of the patients presented abnormal scores for depression and 14.2% for anxiety. Also, the most prevalent symptoms after hospital discharge were muscular fatigue (21.7%) and cough (18.4%). Similar findings were observed considering only the individuals who performed the actigraphy.

*Predictive factors for sleep and circadian outcomes after hospital discharge*

We investigated whether baseline characteristics and ICU-related procedures could predict poor sleep quality and alterations in the circadian rest-activity pattern three months after hospital discharge. We observed that the female sex was associated with an increased score in the PSQI (p-value < 0.05) (Figure 2). Also, the patients that received IMV during the ICU stay presented increased IV at the 3-month follow-up compared to those who did not need this procedure (p-value < 0.001).

*Associations between sequelae after hospital discharge*

We investigated whether sleep and circadian rest-activity pattern were associated with other important sequelae within this context. The analysis

demonstrated a positive correlation between the PSQI score and both anxiety (rho = 0.51, p-value < 0.001) and depression (rho = 0.47, p-value < 0.001) scores obtained with the HADS (Figure S3). No significant correlations were found in relation to the IV, IS, and RA (Figures S4, S5, and S6).

**Discussion**

In the current study, we performed a comprehensive analysis of the sleep and circadian rest-activity pattern of critical COVID-19 survivors three months after hospital discharge. Subjective evaluation using the PSQI revealed a poor sleep quality which was further confirmed by objective evaluation using actigraphy. In addition, female sex was associated with an increased score in the PSQI whilst IMV during the ICU stay were able to predict an increased fragmentation of the rest-activity rhythm three months after hospital discharge. Furthermore, we observed that poor sleep quality was strongly associated with anxiety and depression at the 3-month follow-up.

Recent studies suggest the presence of sleep alterations in COVID-19 patients months after hospitalization. Arnold and collaborators (2020) observed that 24% of 110 consecutive COVID-19 patients reported insomnia three months after hospital admission (4). This number appeared to be higher in another cohort of patients, reaching 31% at 3-4 months postadmission (5). In addition, a recent meta-analysis including 31 studies demonstrated a pooled prevalence of sleeping disturbances in 34% of 5153 COVID-19 patients (31). Nevertheless, all of these findings are based on self-reported assessments. For the first time, through validated questionnaires and an objective evaluation, we demonstrated that a great percentage of COVID-19 patients present poor sleep quality, particularly related to insufficient sleep duration and inappropriate sleep efficiency.

The prevalence of individuals with compromised sleep quality herein observed was higher than that in previous studies, which could be related to differences in the methods used to assess sleep as well as differences among the populations. In fact, our cohort was exclusively composed of critical COVID-19 patients admitted to the ICU whilst the referred studies included patients with different severities. Regardless, our findings reinforce the importance of considering the compromised sleep quality as a component of the post-COVID period, which is of particular interest given the influence of sleep on respiratory and immune function (32–34).

The hospital and particularly the ICU are known for excessive noise and interruptions during the night, unusual feeding schedules, and mistimed artificial light at the detriment of sunlight exposure (7–9). In addition, habitual procedures performed in this environment may account for poor sleep quality and circadian disruption. We observed that IMV during the ICU stay predicted increased fragmentation of the circadian rest-activity rhythm at three months after hospital discharge. This procedure requires the administration of sedative agents that usually affect the sleep structure and circadian rhythms (35, 36). IMV-associated events such as the irregular noradrenergic response and the so-called “biotrauma” may have contributed to altered sleep and circadian rhythms as well (37, 38). Furthermore, given the complex relationship between respiratory function and circadian rhythms (39–41), the respiratory condition of patients submitted to IMV may have been related to increased fragmentation of the rhythm at the 3-month follow-up. Further studies will be necessary to evaluate whether causality between the aforementioned variables is present.

In addition to the characteristics collected at baseline and factors related to the ICU stay, other sequelae may have contributed to alterations in sleep and circadian health at the 3-month follow-up. We observed an association

between poor sleep quality, anxiety, and depression. Such an expected relationship was previously demonstrated in several contexts, including those related to the COVID-19 outbreak (42). However, to our knowledge, the current investigation is the first to confirm this association in COVID-19 patients.

It is important to address some limitations of this study. First, the objective assessment of sleep through actigraphy included a subset of patients randomly selected from the global population. Nevertheless, both groups were similar in relation to the baseline characteristics. Also, the subjective analysis of sleep was corroborated by the actigraphy data. Second, the COVID-19 context prevented a baseline assessment of sleep and circadian health and therefore it was not possible to evaluate whether the patients already had circadian or sleep alterations prior to being hospitalized or infected. Third, it was not possible to establish whether sleep and circadian alterations were consequences of ICU stay or SARS-CoV-2 infection itself. In fact, given the observational design of this study, relationships of causality cannot be confirmed. However, this was beyond the objective of this study. We aimed to evaluate the sleep and circadian health of critical COVID-19 patients after hospital discharge, to highlight the importance of considering these factors in clinical practice. This is the first report presenting a proper characterization of sleep and circadian rest-activity pattern of critical COVID-19 patients through validated questionnaires and an objective assessment. Previous studies were mainly based on self-reported assessments of sleep health and without any evaluation related to circadian function. In addition, with the prospective design and a well-characterized cohort, it was possible to establish potential predictive factors at baseline, including those related to ICU stay, for the adverse outcomes observed after hospital discharge.

## Conclusions

Critical COVID-19 survivors may present poor sleep quality and alterations in the circadian rest-activity pattern three months after hospital discharge. Within this context, female sex could aid in predicting a worse sleep quality whilst IMV during the ICU stay could predict an increased fragmentation of the rest-activity rhythm at the post-COVID period. Furthermore, compromised mental health could be a marker for sleep disruption at the 3-month follow-up.

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**Fig. 1.** Clinical chronology of COVID-19 patients included in the study. The time of hospitalization and time spent at the ICU are represented as median [$p_{25}$;$p_{75}$]. ICU, intensive care unit.

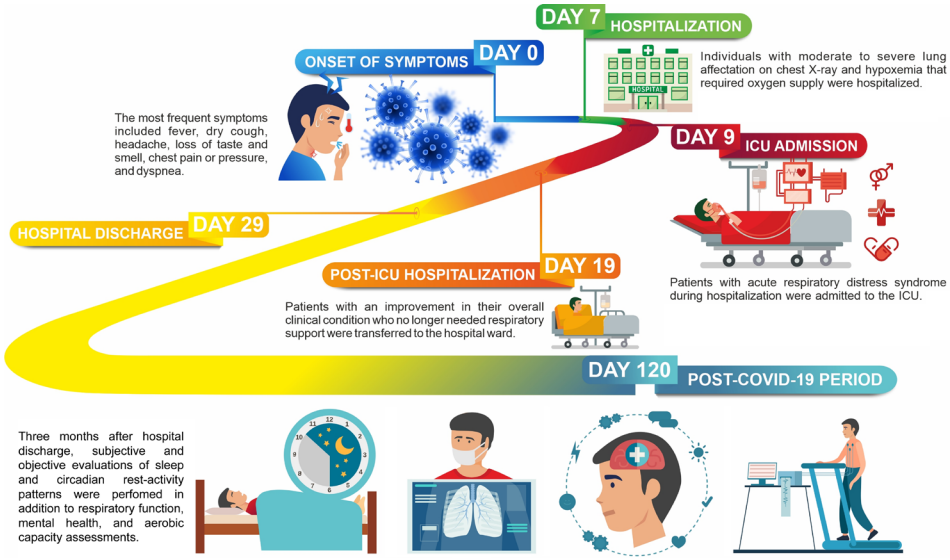

**Fig. 2.** Predictive factors for poor sleep quality and increased fragmentation of the circadian rest-activity rhythm after hospital discharge. t-test was performed to assess correlations between the variables. The p-value threshold defining statistical significance was set at <0.05. PSQI, Pittsburgh Sleep Quality Index.

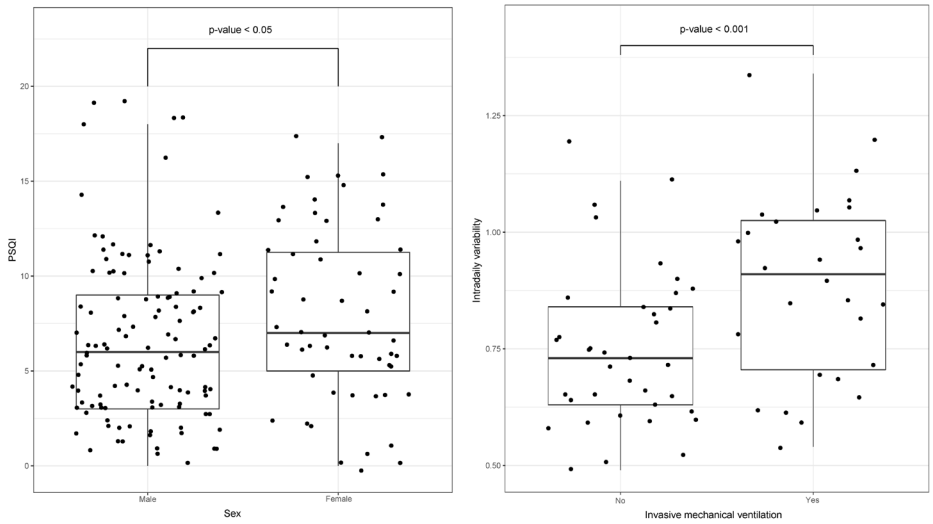


**Table 1.** Baseline characteristics of the cohort.

| **Characteristics** | **Global**<br>n = 172 |
|---|---|
| **Sociodemographic data** | |
| Sex, male | 116 (67.4%) |
| Age, years | 61.0 [52.8;67.0] |
| BMI, $kg \cdot m^{-2}$ | 29.8 [26.8;34.2] |
| **Habits** | |
| Tobacco | |
| Current smoker | 7 (4.07%) |
| Former smoker | 72 (41.9%) |
| Non-smoker | 93 (54.1%) |
| Chronic alcohol abuse | 6 (3.49%) |
| **Comorbidities** | |
| Obesity | 83 (48.5%) |
| Hypertension | 81 (47.1%) |

| | |
|---|---|
| Diabetes mellitus | 39 (22.7%) |
| Chronic lung disease | 10 (5.81%) |
| **Hospital stay** | |
| Days | 23.0 [14.0;38.2] |
| **ICU stay** | |
| Days | 11.0 [6.00;24.0] |
| Minimum $PaO_2$ to $FiO_2$ ratio | 110 [84.0;168] |
| ***Procedures*** | |
| Mechanical ventilation | |
| Invasive | 89 (51.7%) |
| Days | 16.0 [9.00;26.0] |
| Non-invasive | 122 (70.9%) |
| Days | 3.00 [1.00;5.00] |
| Prone position | 84 (48.8%) |
| Prone position, hours | 41.0 [24.0;73.0] |
| ***Pharmacotherapy*** | |
| Antibiotics | 142 (82.6%) |
| Corticosteroids | 153 (89.0%) |
| Tocilizumab | 108 (63.2%) |
| Hydroxychloroquine | 55 (32.0%) |
| Remdesivir | 25 (14.5%) |

Qualitative and quantitative data are represented as n (%) and median [$p_{25}$;$p_{75}$], respectively. BMI, body mass index; $FiO_2$, fractional inspired oxygen; ICU, intensive care unit; n, number; p, percentile; $PaO_2$, arterial oxygen partial pressure. Missings: obesity, 1; minimum $PaO_2/FiO_2$, 6; prone position, hours, 7; tocilizumab, 1.

**Table 2.** Sleep questionnaires.

| **Questionnaires** | **Global**<br>n = 172 |
|---|---|
| **PSQI** | 7.09 (4.41) |
| Good sleep quality | 68 (39.5%) |
| Poor sleep quality | 104 (60.5%) |
| ***Subjective sleep quality*** | 1.12 (0.79) |
| Very good | 33 (19.2%) |
| Fairly good | 97 (56.4%) |

| | |
|---|---|
| Fairly bad | 31 (18.0%) |
| Very bad | 11 (6.40%) |
| ***Sleep latency*** | 1.14 (1.10) |
| ≤ 15 min | 64 (37.2%) |
| 16-30 min | 49 (28.5%) |
| 31-60 min | 30 (17.4%) |
| > 60 min | 29 (16.9%) |
| ***Sleep duration*** | 1.41 (1.10) |
| > 7 hours | 45 (26.2%) |
| 6-7 hours | 50 (29.1%) |
| 5-6 hours | 39 (22.7%) |
| < 5 hours | 38 (22.1%) |
| ***Sleep efficiency*** | 1.08 (1.15) |
| ≥ 85% | 73 (42.4%) |
| 75-84% | 46 (26.7%) |
| 65-74% | 19 (11.0%) |
| < 65% | 34 (19.8%) |
| ***Sleep disturbance*** | 0.97 (0.62) |
| Not during past month | 32 (18.6%) |
| Less than once a week | 116 (67.4%) |
| Once or twice a week | 21 (12.2%) |
| Three or more times a week | 3 (1.74%) |
| ***Sleep medication intake*** | 0.78 (1.29) |
| Not during past month | 125 (72.7%) |
| Less than once a week | 1 (0.58%) |
| Once or twice a week | 5 (2.91%) |
| Three or more times a week | 41 (23.8%) |
| ***Daytime dysfunction*** | 0.60 (0.86) |
| Never | 104 (60.5%) |
| A few times | 40 (23.3%) |
| Sometimes | 21 (12.2%) |
| A lot of times | 7 (4.07%) |
| **ESS** | 6.12 (3.77) |
| **SATED** | 7.54 (2.16) |

**Table 3.** Actigraphy.

| **Variables** | **Global** n = 65 |
|---|---|

| | |
|---|---|
| ***Sleep*** | |
| Total sleep time (TST), hour | 6.98 [6.33;7.67] |
| *> 9 hours* | 3 (4.62%) |
| *7-9 hours* | 29 (44.6%) |
| *< 7 hours* | 33 (50.8%) |
| Time in bed (TIB), hour | 8.38 [7.73;9.10] |
| Sleep efficiency (SE), % | 84.6 [81.0;88.3] |
| *≥ 85%* | 29 (44.6%) |
| *75-84%* | 29 (44.6%) |
| *< 75%* | 7 (10.8%) |
| Latency, min | 10.0 [5.00;18.0] |
| *≤ 30 min* | 57 (87.7%) |
| *31-45 min* | 6 (9.23%) |
| *> 45 min* | 2 (3.08%) |
| Arousals, number | 25.5 (7.07) |
| WASO, min | 51.0 [39.0;66.0] |
| *0-20 min* | 1 (1.54%) |
| *21-40 min* | 17 (26.2%) |
| *≥ 40 min* | 47 (72.3%) |
| ***Rest-activity rhythm*** | |
| Interdaily stability (IS) | 0.59 (0.13) |
| Intradaily variability (IV) | 0.81 (0.19) |
| Relative amplitude (RA) | 0.89 [0.85;0.93] |
| M10 | 238 [170;315] |
| L5 | 12.2 [8.46;19.6] |

Qualitative data are represented as n (%). The means (SD) and medians [$p_{25}$;$p_{75}$] were estimated for variables with normal and non-normal distributions, respectively. L5, the mean activity of the five consecutive hours with less activity; n, number; M10, the mean activity of the ten consecutive hours with more activity; p, percentile; SD, standard deviation; WASO, wake after sleep onset.

**Sleep and circadian health of critical COVID-19 survivors three months after hospital discharge**

**Supplementary material**

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**Figure S1.** Flowchart of the study.

**Figure S2.** Representative actograms of critical COVID-19 survivors.

**Figure. S3.** Correlations between sleep and other sequelae after hospital discharge.

**Figure. S4.** Correlations between fragmentation of the circadian rest-activity rhythm and other sequelae after hospital discharge.

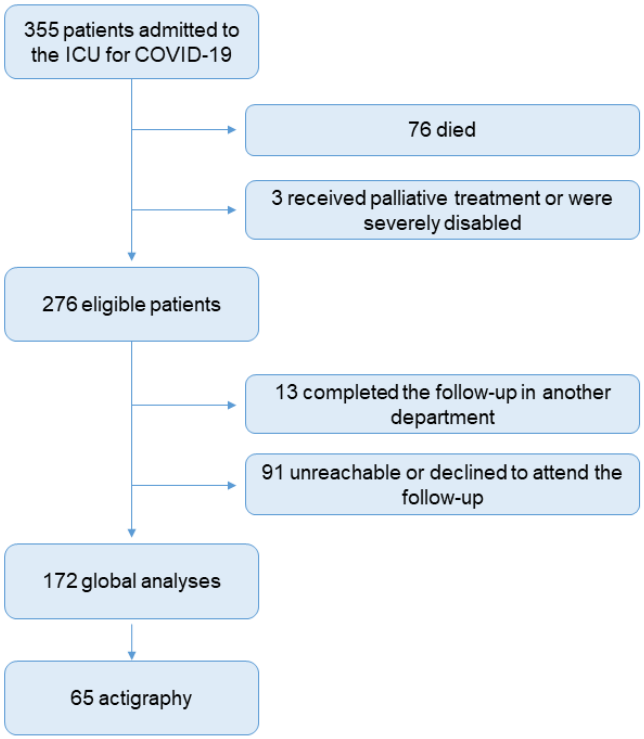
**Figure S5.** Correlations between amplitude of the circadian rest-activity rhythm and other sequelae after hospital discharge.

**Figure S6.** Correlations between stability of the circadian rest-activity rhythm and other sequelae after hospital discharge.

**Table S1.** Baseline characteristics of the cohort (actigraphy).

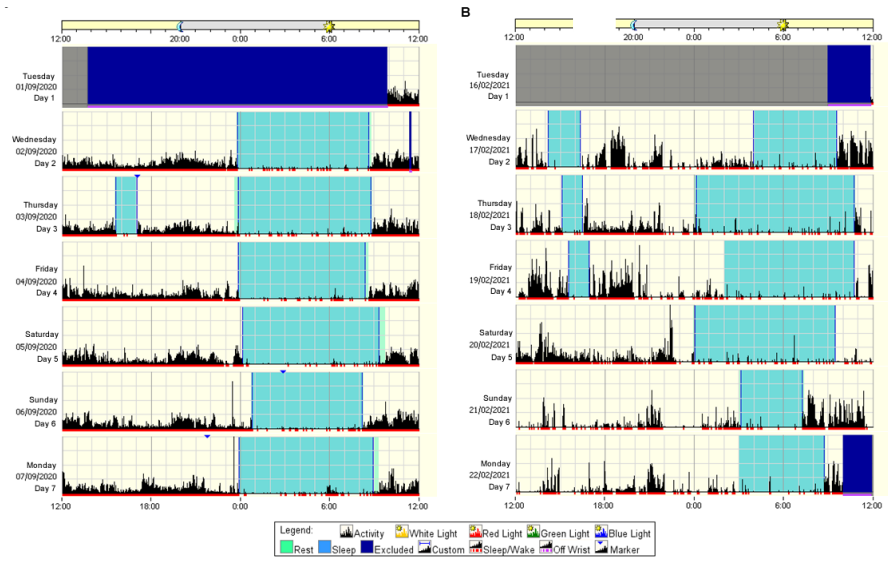
**Table S2.** Other sequelae after hospital discharge.

**Figure S1.** Flowchart of the study.



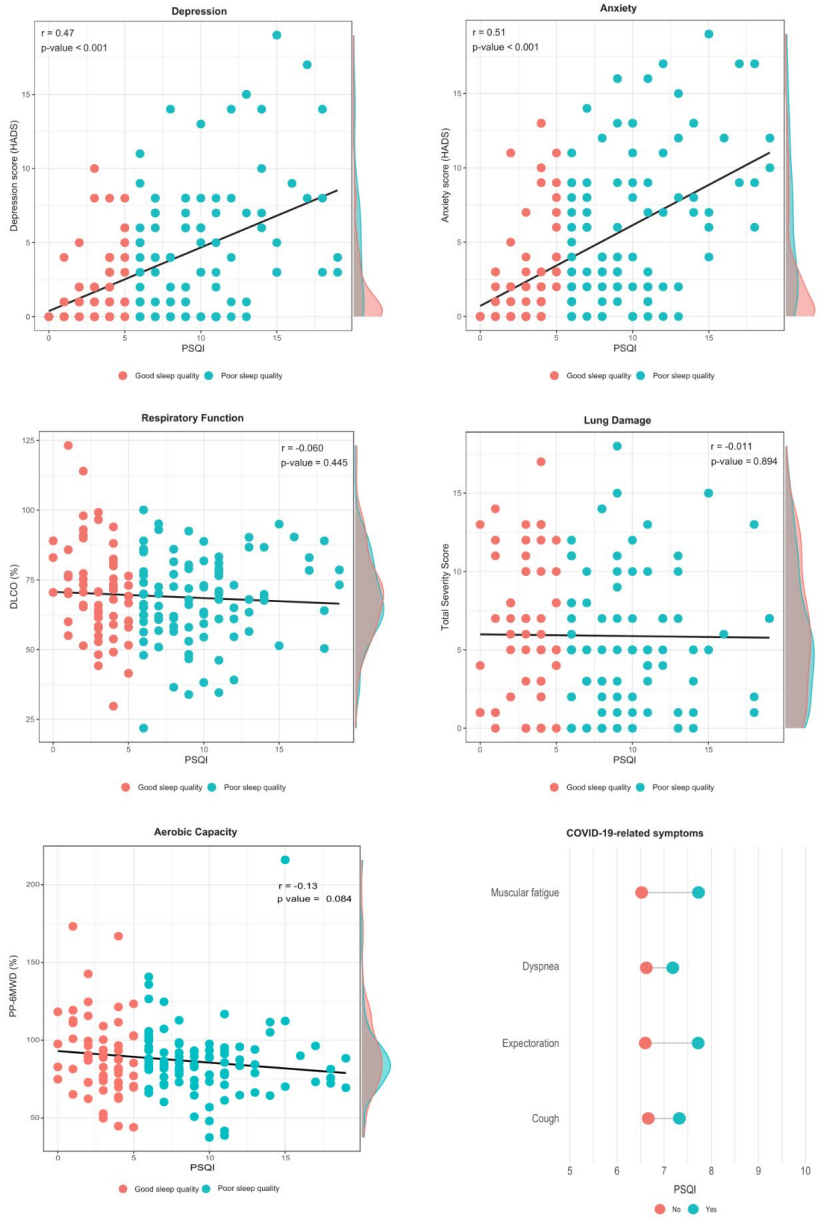

ICU, intensive care unit.

**Figure S2.** Representative actograms of critical COVID-19 survivors.




The left panel represents a patient with appropriate interdaily stability, intradaily variabily, and relative amplitude; The right panel represents a patient with decreased interdaily stability, increased intradaily variabily, and decreased relative amplitude.

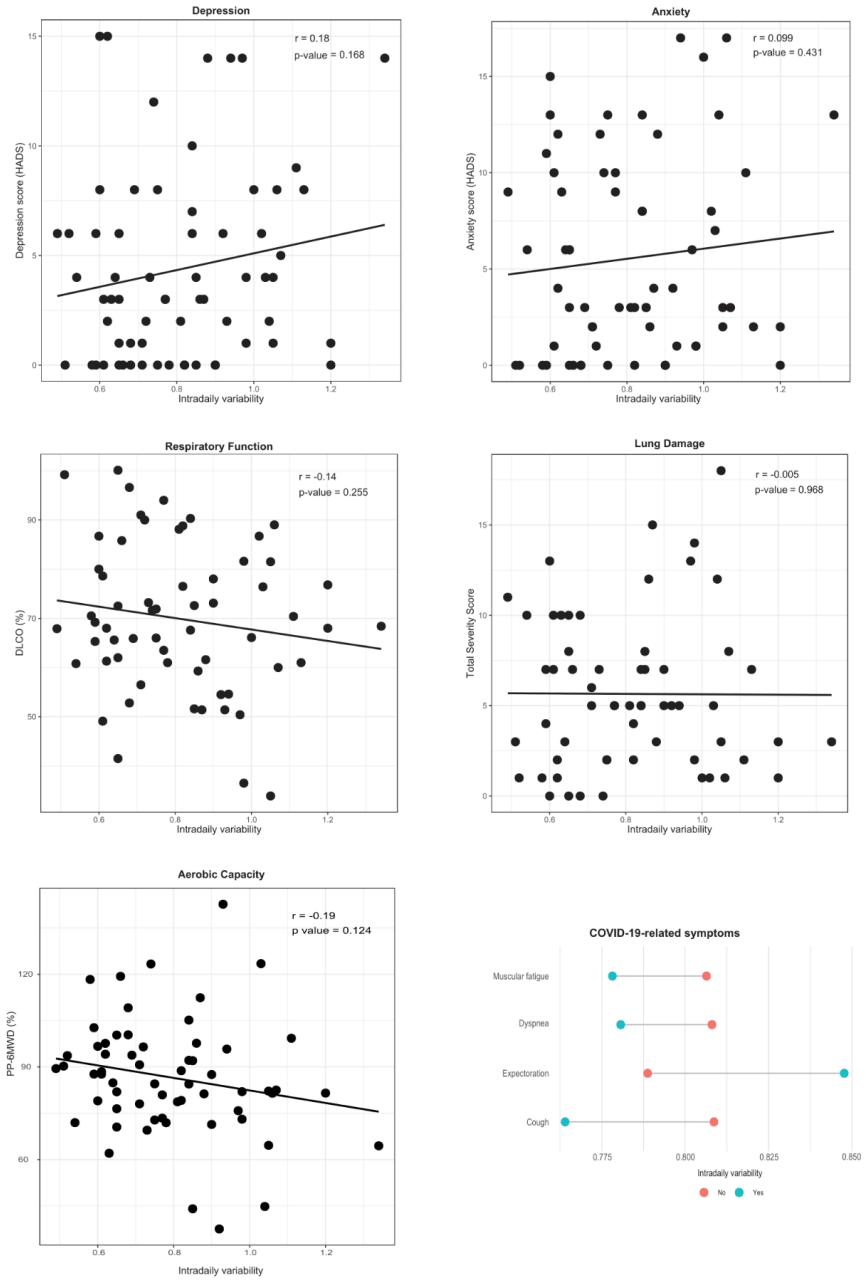
**Figure. S3.** Correlations between sleep and other sequelae after hospital discharge.




Pearson coefficient tests were performed to assess correlations between variables. The PSQI score according to the COVID-19-related symptoms are represented by the mean. The p-value threshold defining statistical

significance was set at <0.05. No statistical significance was observed in relation to the COVID-19-related symptoms. DLCO, diffusing lung capacity for carbon monoxide; HADS, Hospital Anxiety and Depression Scale; PP-6MWD, percent predicted 6-minute walked distance; PSQI, Pittsburgh Sleep Quality Index.

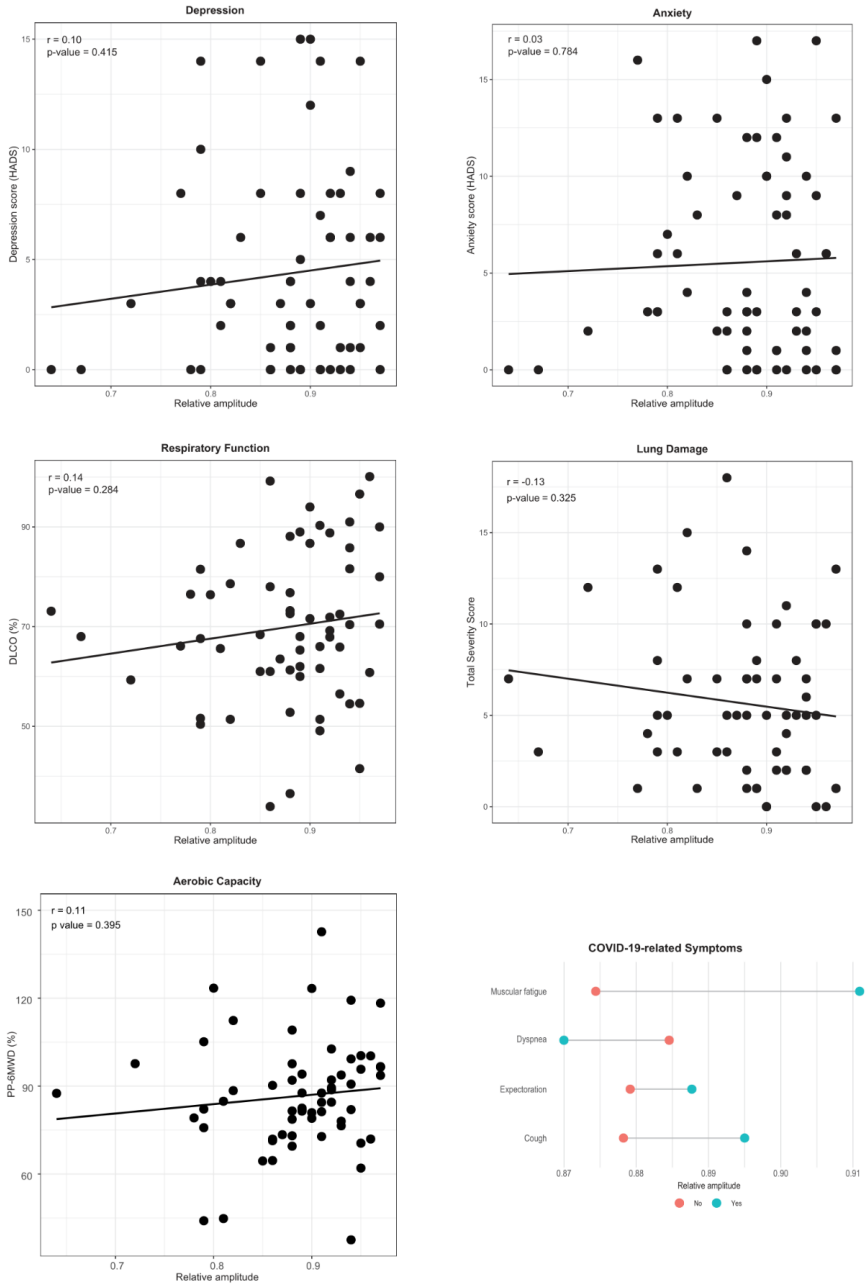
**Figure. S4.** Correlations between fragmentation of the circadian rest-activity rhythm and other sequelae after hospital discharge.




Pearson coefficient tests were performed to assess correlations between variables. The intradaily variability values according to the COVID-19-

related symptoms are represented by the mean. The p-value threshold defining statistical significance was set at <0.05. No statistical significance was observed in relation to the COVID-19-related symptoms. DLCO, diffusing lung capacity for carbon monoxide; HADS, Hospital Anxiety and Depression Scale; PP-6MWD, percent predicted 6-minute walked distance.

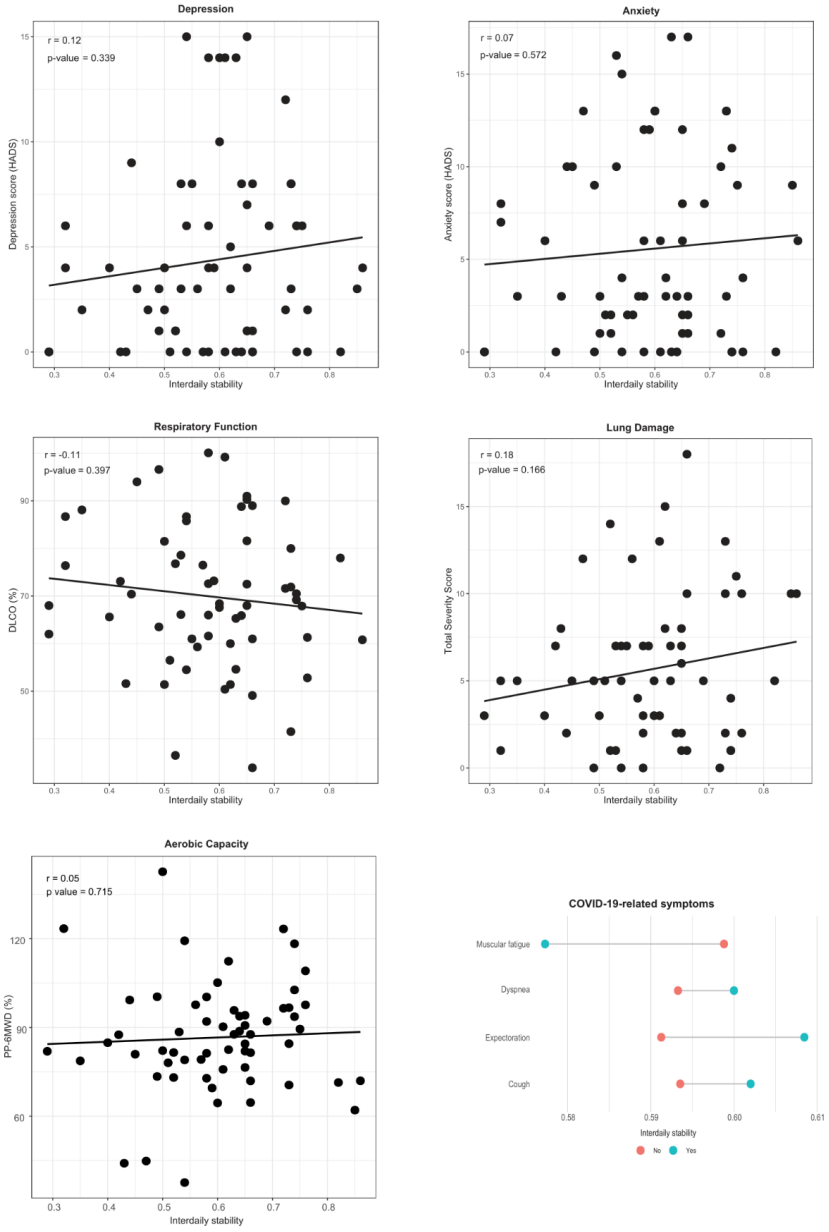
**Figure S5.** Correlations between amplitude of the circadian rest-activity rhythm and other sequelae after hospital discharge.




Pearson coefficient tests were performed to assess correlations between variables. The relative amplitude values according to the COVID-19-

related symptoms are represented by the mean. The p-value threshold defining statistical significance was set at <0.05. No statistical significance was observed in relation to the COVID-19-related symptoms. DLCO, diffusing lung capacity for carbon monoxide; HADS, Hospital Anxiety and Depression Scale; PP-6MWD, percent predicted 6-minute walked distance.

**Figure S6.** Correlations between stability of the circadian rest-activity rhythm and other sequelae after hospital discharge.




Pearson coefficient tests were performed to assess correlations between variables. The interdaily stability values according to the COVID-19-related symptoms are represented by the mean. The p-value threshold

defining statistical significance was set at <0.05. No statistical significance was observed in relation to the COVID-19-related symptoms. DLCO, diffusing lung capacity for carbon monoxide; HADS, Hospital Anxiety and Depression Scale; PP-6MWD, percent predicted 6-minute walked distance.

**Table S1.** Baseline characteristics of the cohort (actigraphy).

| Characteristics | Global<br>n = 65 |
|---|---|
| **Sociodemographic data** | |
| Sex, male | 40 (61.5%) |
| Age, years | 61.0 [53.0;66.0] |
| BMI, $kg \cdot m^{-2}$ | 29.2 [27.0;33.0] |
| **Habits** | |
| Tobacco | |
| Current smoker | 4 (6.15%) |
| Former smoker | 30 (46.2%) |
| Non-smoker | 31 (47.7%) |
| Chronic alcohol abuse | 3 (4.61%) |
| **Comorbidities** | |
| Obesity | 27 (42.2%) |
| Hypertension | 34 (52.3%) |
| Diabetes mellitus | 15 (23.1%) |
| Chronic lung disease | 6 (9.23%) |
| **Hospital stay** | |
| Days | 20.0 [12.0;39.0] |
| **ICU stay** | |
| Days | 8.00 [5.00;20.0] |
| Minimum $PaO_2$ to $FiO_2$ ratio | 138 [94.0;211] |
| ***Procedures*** | |
| Mechanical ventilation | |
| Invasive | 28 (43.1%) |
| Days | 18.5 [13.0;29.5] |
| Non-invasive | 48 (73.8%) |
| Days | 2.00 [1.00;4.00] |

| | |
|---|---|
| Prone position | 30 (46.2%) |
| Prone position, hours | 44.0 [30.5;77.5] |
| ***Pharmacotherapy*** | |
| Antibiotics | 56 (86.2%) |
| Corticosteroids | 65 (100%) |
| Tocilizumab | 47 (72.3%) |
| Hydroxychloroquine | 17 (26.2%) |
| Remdesivir | 17 (26.2%) |

Qualitative and quantitative data are represented as n (%) and median [$p_{25}$;$p_{75}$], respectively. BMI, body mass index; $FiO_2$, fractional inspired oxygen; ICU, intensive care unit; n, number; p, percentile; $PaO_2$, arterial oxygen partial pressure. Missings: obesity, 1; minimum $PaO_2/FiO_2$, 5; prone position, hours, 7.

**Table S2.** Other sequelae after hospital discharge.

| | **Global** | **Actigraphy** |
|---|---|---|
| | n = 172 | n = 65 |
| ***Respiratory evaluation*** | | |
| DLCO, mL/min/mm Hg | 69.1 (16.0) | 69.9 (15.1) |
| *< 60%* | 39 (24.7%) | 13 (21.3%) |
| *60-79%* | 81 (51.3%) | 32 (52.5%) |
| *≥ 80%* | 38 (24.1%) | 16 (26.2%) |
| Distance (6MWT), m | 408 (90.5) | 395 (85.1) |
| *Percent predicted 6MWD, %* | 87.8 (23.8) | 86.6 (18.7) |
| TSS score | 5.00 [2.00;8.75] | 5.00 [2.00;8.00] |
| ***Mental health evaluation*** | | |
| Depression score (HADS) | 2.00 [0.00;6.00] | 3.00 [1.00;6.00] |
| *Normal (0-7)* | 143 (84.6%) | 50 (76.9%) |
| *Borderline abnormal (8-10)* | 16 (9.47%) | 8 (12.3%) |
| *Abnormal (11-21)* | 10 (5.92%) | 7 (10.8%) |

| | | |
|---|---|---|
| Anxiety score (HADS) | 3.00 [1.00;8.00] | 3.00 [1.00;10.0] |
| *Normal (0-7)* | 126 (74.6%) | 42 (64.6%) |
| *Borderline abnormal (8-10)* | 19 (11.2%) | 10 (15.4%) |
| *Abnormal (11-21)* | 24 (14.2%) | 13 (20.0%) |
| ***COVID-19-related symptoms*** | | |
| Cough | 28 (18.4%) | 10 (16.4%) |
| Expectoration | 25 (16.4%) | 13 (21.3%) |
| Dyspnea | | |
| *0* | 74 (49.7%) | 26 (42.6%) |
| *1* | 42 (28.2%) | 20 (32.8%) |
| *2* | 28 (18.8%) | 13 (21.3%) |
| *3* | 4 (2.68%) | 1 (1.64%) |
| *4* | 1 (0.67%) | 1 (1.64%) |
| Fever | 1 (0.66%) | 0 (0%) |
| Asthenia | 1 (0.66%) | 1 (1.64%) |
| Muscular fatigue | 33 (21.7%) | 11 (18.0%) |

Qualitative data are represented as n (%). The means (SD) and medians [$p_{25}$;$p_{75}$] were estimated for variables with normal and non-normal distributions, respectively. 6MWD, 6-minute walked distance; 6MWT, 6-minute walking test; DLCO, diffusing capacity for carbon monoxide; HADS, Hospital Anxiety and Depression Scale; n, number; p, percentile; SD, standard deviation; TSS, total severity score. Missings (global): DLCO, 14; HADS, 3; dyspnea, 23; other COVID-19-related symptoms, 20. Missings (actigraphy): DLCO, 4; dyspnea, 4; other COVID-19-related symptoms, 4.

## *5.6. Resultados del objetivo O.3.3*

**Título:** Sleep and circadian health 6 months after critical COVID-19 disease

**Autores:** Adriano D. S. Targa, Iván D. Benítez, Jessica González, Gerard Torres, Sally Santisteve, Rafaela Vaca, Olga Minguez, Maria Aguilà, Paola Carmona, Anna Moncusí-Moix, Clara Gort-Paniello, Gonzalo Labarca, Jesús Caballero, Carme Barberà, Antoni Torres, David de Gonzalo-Calvo, Ferran Barbé

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# Sleep and circadian health six months after critical COVID-19 disease

*To the Editors:*

Coronavirus disease 2019 (COVID-19) and the development of acute respiratory distress syndrome (ARDS) are often related to hospitalization and/or intensive care unit (ICU) admission, a context that leads to several sequelae[1].

We evaluated 172 critical COVID-19 survivors and observed that 60.5% presented with poor sleep quality three months after hospital discharge, with a remarkable fragmentation of the circadian rest-activity pattern, which was predicted by the use of invasive mechanical ventilation (IMV) during ICU stay[2]. Nevertheless, long-term evaluations of sleep within this context are scarce and mainly based on self-reported symptom questionnaires, while the assessment of circadian function is yet to be performed[3]. Hence, we aimed to investigate the sleep and circadian health of critical COVID-19 survivors six months after hospital discharge. Additional analyses were also performed to identify possible predictors for sleep and circadian alterations at the 6-month follow-up and to evaluate possible correlations with mental health.

Consecutive patients were prospectively recruited during the ICU stay. The inclusion criteria comprised individuals more than 18 years old, who developed ARDS and had a confirmed diagnosis of SARS-CoV-2 infection. A clinical evaluation was performed at the first and second medical appointments (3 and 6 months after hospital discharge), followed by subjective assessments of sleep (Pittsburgh sleep quality index [PSQI] and Epworth sleepiness scale [ESS]). Additionally, the patients were randomly selected for objective evaluation of sleep and circadian rest-activity pattern through the use of a wrist-mounted actigraph (Actiwatch 2, Philips

Respironics) for 7 days. Participants' mental health was assessed with the Hospital Anxiety and Depression Scale (HADS).

Absolute and relative frequencies describe qualitative data while means (standard deviation (SD)) and medians (25th percentile; 75th percentile [$p_{25}$;$p_{75}$]) were estimated for quantitative variables with normal and non-normal distributions, respectively. Changes between 3-6 months of follow-up were evaluated using paired t-test. Linear regression models were performed to identify baseline predictors (age, sex, body mass index [BMI], comorbidities, time spent at the hospital, time spent in the ICU, IMV, noninvasive mechanical ventilation [NIMV], prone position, and pharmacotherapy) of sleep quality (PSQI) and circadian function at the 6-month follow-up. Circadian function was represented by the interdaily stability (IS, indicates the synchronization between the endogenous rhythms and the external cues), intradaily variability (IV, indicates the fragmentation of the rhythms within each 24-h period), and relative amplitude (RA, indicates the robustness of the rhythms)[4]. The associations between sleep/circadian function and mental health were assessed using Pearson coefficient tests. R statistical software version 4.0.1 (R Foundation for Statistical Computing) was used for the analyses.

The cohort was composed of 145 patients (66.9% males), with a median [$p_{25}$;$p_{75}$] age of 62.0 [56.0;68.0] years and a BMI of 29.3 [26.2; 33.0] $kg \cdot m^{-2}$ (Table 1). The most frequent comorbidities were hypertension (53.8%) and obesity (44.4%). The median length of hospital stay was 24.0 [15.0; 38.0] days, from which 14.0 [6.00; 27.0] were spent in the ICU, and where 60.7% of the patients required IMV. The subset of 75 patients randomly selected for the objective evaluation presented similar characteristics. According to the PSQI, 48.3% of the cohort presented with poor sleep quality at the 6-month follow-up, which was confirmed by the objective analysis (Table 2). Sleep duration was the most affected component. Based

on the ESS, 11.1% of the patients presented with daytime somnolence six months after hospital discharge. In relation to the circadian rest-activity pattern, there was substantial variability among the sample, especially concerning the fragmentation of the rhythm.

There was a slight improvement in sleep between the 3-6-month follow-ups, demonstrated by a mean (95% CI) change of -0.73 (-1.30 to -0.16) in the PSQI (Figure 1). Such improvement was higher among those patients who presented with poor sleep quality three months after hospital discharge, with a mean change of -1.71 (-2.59 to -0.82). No significant difference between the investigated time points was observed in relation to the ESS and the circadian rest-activity pattern.

Additional analyses revealed that higher BMI at baseline was associated with worse sleep quality and increased fragmentation of the rest-activity rhythm at the 6-month follow-up with effect sizes (SD) of 0.184 (0.082) ($p < 0.05$) and 0.252 (0.110) ($p < 0.05$), respectively. Similarly, time spent in hospital, time spent in the ICU, and the use of IMV predicted an increased fragmentation of the rhythm with respective effect sizes of 0.536 (0.189) ($p < 0.01$), 0.271 (0.112) ($p < 0.01$), and 0.473 (0.228) ($p < 0.05$). Correlation analysis revealed a positive relationship between worse sleep quality and both symptoms of anxiety ($r = 0.51$) ($p < 0.001$) and depression ($r = 0.57$) ($p < 0.001$) at 6-month follow-up.

Previous studies reveal that COVID-19 patients present with compromised sleep quality in the short term[2]. Nevertheless, long-term evaluations within this context are scarce and no assessment of the circadian function has been performed. In non-COVID-19-related ARDS survivors, short-term poor sleep quality is also reported and the circadian rest-activity pattern is remarkably unstable, fragmented, and less robust compared to community-dwelling adults[5,6]. To our knowledge, this is the first study presenting a proper characterization of sleep and circadian health of COVID-19

patients in the long term, which is also relevant to long-term evaluations of ARDS patients.

Our analysis showed that the BMI at baseline predicted both sleep quality and circadian health at the 6-month follow-up. Obesity, sleep, and circadian health present a complex relationship. On the one hand, poor sleep quality and increased fragmentation of the rest-activity rhythm are associated with greater rates of weight gain[7,8]. On the other, erratic eating times and increased neck circumference usually related to obesity may enhance the risk of circadian disruption and incidence of obstructive sleep apnea[9].

The length of stay in hospital and ICU, and the use of IMV also predicted fragmentation of the circadian rest-activity rhythm. The hospital environment is well known for its detrimental effects on sleep and circadian rhythms due to mistimed artificial light, interruptions during the night, and unusual eating schedules. Also, pharmacological treatments within this context and the use of IMV are related to several sleep and circadian-related sequelae[10].

This study has some limitations. First, given the context of COVID-19, it was not possible to perform a baseline evaluation of sleep and circadian function, preventing the identification of possible sleep and circadian alterations prior to hospitalization or SARS-CoV-2 infection. Second, with the study's observational design, it is not possible to establish relationships of causality between predictive factors and outcomes as well as between the correlated sequelae. The evaluation of causality among the variables of interest was beyond the objectives of the study.

In summary, our findings reveal that sleep and circadian alterations are maintained in COVID-19 survivors who developed ARDS and were admitted to the ICU. Within this context, characteristics such as BMI, time spent in the hospital and ICU, and the use of IMV during the ICU stay

could aid in the prediction of ongoing adverse outcomes related to sleep and circadian rest-activity rhythm. Altogether, this highlights the importance of considering the sleep and circadian health of critical patients in the longer term.

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**Short title:** COVID-19, sleep and circadian health

**Keywords:** ARDS, COVID-19, Critical Care Medicine, Respiratory Neurobiology, Sleep, Sleep disorders, Circadian Health

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**Conflict of Interest:** None declared

**Data Availability Statement:** The data that support the findings of this study are available from the corresponding author upon reasonable request.

**Human Ethics Approval Declaration:** This study was approved by the Medical Ethics Committee of the Hospital Universitari Arnau de Vilanova (Identifier: CEIC-2510) and conducted according to the principles outlined by the Declaration of Helsinki. Informed consent was acquired for all patients.

**Abbreviations:** ARDS Acute respiratory distress syndrome, BMI Body mass index, COVID-19 Coronavirus disease 2019, ESS Epworth Sleepiness Scale, HADS Hospital Anxiety and Depression Scale, ICU Intensive care unit, IMV Invasive mechanical ventilation, IS Interdaily stability, IV Intradaily variability, NIMV Noninvasive mechanical ventilation, OSA Obstructive sleep apnea, PSQI Pittsburgh Sleep Quality Index, RA Relative amplitude, SARS-CoV-2 Severe acute respiratory syndrome coronavirus 2.

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**Figure 1.** Evolution of sleep quality and circadian rest-activity pattern between 3-6-month follow-up. The red background indicates worsening from 3-6-month follow-up and the blue background indicates an improvement between these time-points. The black dots indicate good sleep quality (PSQI ≤5) at the 3-month follow-up while green dots indicate poor sleep quality (PSQI >5) at the same time-point. Only the patients with available data in both time-points (3 and 6-month follow-up) were included in this analysis. The p-value threshold defining statistical significance was set at <0.05. PSQI, Pittsburgh Sleep Quality Index.

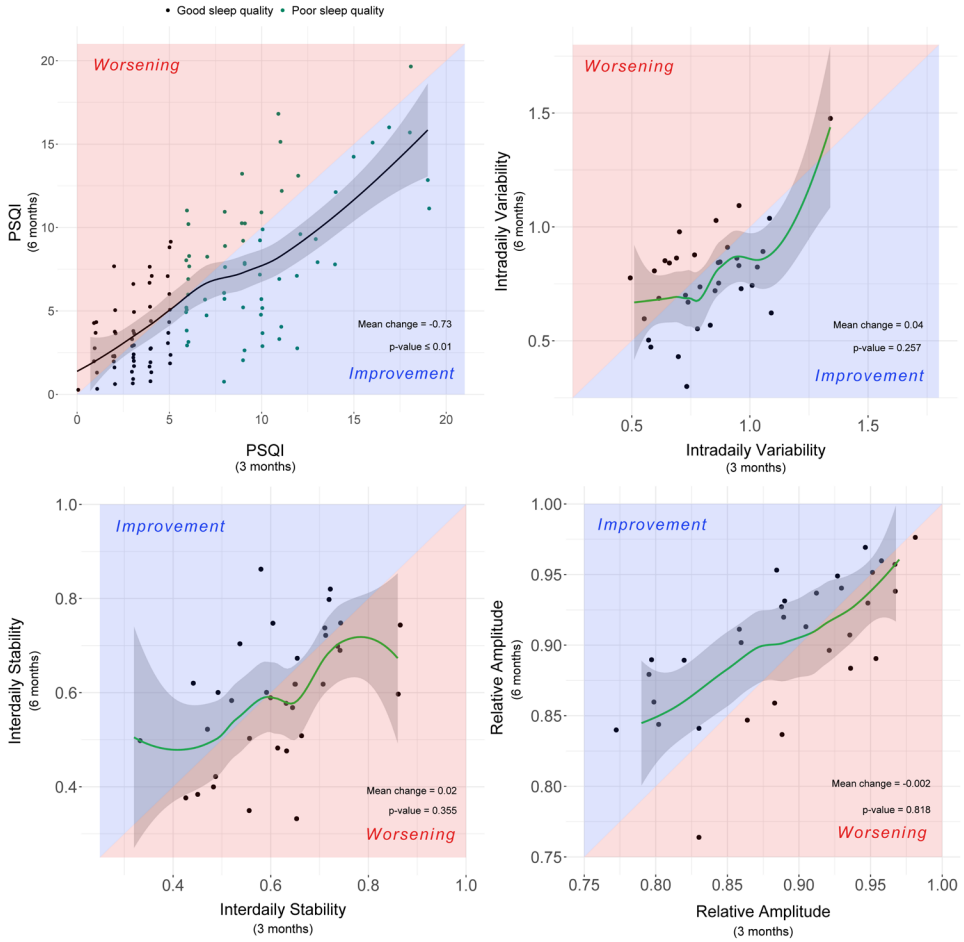

**Table 1.** Baseline characteristics of the cohort.

| | **Global** n = 145 | **With actigraphy** n = 75 | **Without actigraphy** n = 70 | **p-value** |
|---|---|---|---|---|
| **Sociodemographic data** | | | | |
| Sex, male | 97 (66.9%) | 50 (66.7%) | 47 (67.1%) | 1.000 |
| Age, years | 62.0 [56.0;68.0] | 62.0 [55.0;67.0] | 63.5 [56.5;70.0] | 0.173 |
| BMI, $kg \cdot m^{-2}$ | 29.3 [26.2;33.0] | 30.2 [27.6;34.7] | 28.1 [25.7;31.2] | 0.017 |
| **Habits** | | | | |
| Tobacco | | | | 0.182 |
| Current | 4 (2.76%) | 1 (1.33%) | 3 (4.29%) | |
| Former | 71 (49.0%) | 42 (56.0%) | 29 (41.4%) | |
| Non-smoker | 70 (48.3%) | 32 (42.7%) | 38 (54.3%) | |
| Chronic alcohol abuse | | | | 0.356 |
| Current | 4 (3.03%) | 1 (1.43%) | 3 (4.84%) | |
| Former | 3 (2.27%) | 3 (4.29%) | 0 (0.00%) | |
| Non-alcohol abuse | 125 (94.7%) | 66 (94.3%) | 59 (95.2%) | |
| **Comorbidities** | | | | |
| Hypertension | 78 (53.8%) | 40 (53.3%) | 38 (54.3%) | 1.000 |
| Obesity | 64 (44.4%) | 39 (52.0%) | 25 (36.2%) | 0.083 |
| Diabetes mellitus | 37 (25.5%) | 18 (24.0%) | 19 (27.1%) | 0.808 |
| Asthma | 12 (8.28%) | 5 (6.67%) | 7 (10.0%) | 0.670 |
| COPD | 6 (4.14%) | 3 (4.00%) | 3 (4.29%) | 1.000 |
| **Hospitalization** | | | | |
| Duration, days | 24.0 [15.0;38.0] | 25.0 [14.5;37.0] | 24.0 [15.0;39.5] | 0.719 |
| Before ICU admission, days | 1.00 [0.00;2.00] | 1.00 [0.00;2.50] | 0.50 [0.00;2.00] | 0.332 |
| After ICU discharge, days | 8.00 [5.00;12.0] | 8.00 [5.00;12.5] | 8.00 [5.25;12.0] | 0.800 |
| **ICU stay** | | | | |
| Duration, days | 14.0 [6.00;27.0] | 13.0 [6.00;26.0] | 14.0 [8.00;26.8] | 0.304 |
| ***Procedures*** | | | | |
| Mechanical ventilation | | | | |
| Invasive | 88 (60.7%) | 41 (54.7%) | 47 (67.1%) | 0.172 |
| Days | 14.5 [8.00;27.0] | 18.0 [11.0;31.0] | 13.0 [7.00;25.0] | 0.096 |
| Non-invasive | 99 (68.3%) | 50 (66.7%) | 49 (70.0%) | 0.801 |
| Days | 3.00 [1.00;5.00] | 3.00 [2.00;5.00] | 3.00 [1.00;5.00] | 0.747 |

| | | | | |
|---|---|---|---|---|
| Prone position | 83 (57.6%) | 41 (55.4%) | 42 (60.0%) | 0.697 |
| Hours | 44.5 [24.0;81.2] | 40.0 [21.2;67.8] | 68.0 [29.0;98.0] | 0.048 |
| ***Pharmacotherapy*** | | | | |
| Antibiotics | 118 (84.9%) | 63 (86.3%) | 55 (83.3%) | 0.802 |
| Corticosteroids | 127 (90.1%) | 67 (90.5%) | 60 (89.6%) | 1.000 |
| Hydroxychloroquine | 48 (33.1%) | 30 (40.0%) | 18 (25.7%) | 0.099 |
| Interferon beta | 26 (19.7%) | 18 (25.7%) | 8 (12.9%) | 0.104 |
| Lopinavir/ritonavir | 47 (32.4%) | 29 (38.7%) | 18 (25.7%) | 0.137 |
| Remdesivir | 27 (18.6%) | 19 (25.3%) | 8 (11.4%) | 0.053 |
| Tocilizumab | 84 (57.9%) | 39 (52.0%) | 45 (64.3%) | 0.184 |
| **Post-COVID** | | | | |
| First visit, days | 96.0 [85.0;107] | 96.5 [87.2;108] | 96.0 [84.2;106] | 0.878 |
| Second visit, days | 201 [186;221] | 197 [185;214] | 208 [186;227] | 0.189 |
| Time between visits, days | 109 [91.0;132] | 104 [91.0;119] | 112 [97.2;136] | 0.005 |

Qualitative data are represented as n (%). The medians [p25;p75] were estimated for quantitative variables. BMI, body mass index; COPD, chronic obstructive pulmonary disease; ICU, intensive care unit; n, number; p, percentile. Missings: antibiotics, 6; chronic alcohol abuse, 13; corticosterioids, 4; interferon beta, 13; obesity, 1; prone position, 1.

**Table 2.** Sleep and circadian rest-activity pattern.

| **Questionnaires** | n = 145 |
|---|---|
| **PSQI** | 6.20 (4.25) |
| Good sleep quality | 75 (51.7%) |
| Poor sleep quality | 70 (48.3%) |
| ***Subjective sleep quality*** | 1.13 (0.78) |
| Very good | 27 (18.6%) |
| Fairly good | 80 (55.2%) |
| Fairly bad | 30 (20.7%) |
| Very bad | 8 (5.52%) |
| ***Sleep latency*** | 0.98 (1.02) |
| ≤ 15 min | 59 (40.7%) |
| 16-30 min | 47 (32.4%) |
| 31-60 min | 22 (15.2%) |
| > 60 min | 17 (11.7%) |
| ***Sleep duration*** | 1.14 (1.08) |
| > 7 hours | 54 (37.2%) |
| 6-7 hours | 38 (26.2%) |
| 5-6 hours | 32 (22.1%) |
| < 5 hours | 21 (14.5%) |
| ***Sleep efficiency*** | 0.89 (1.07) |
| ≥ 85% | 72 (49.7%) |
| 75-84% | 37 (25.5%) |
| 65-74% | 16 (11.0%) |
| < 65% | 20 (13.8%) |
| ***Sleep disturbance*** | 0.77 (0.64) |
| Not during past month | 50 (34.5%) |
| Less than once a week | 78 (53.8%) |
| Once or twice a week | 17 (11.7%) |
| Three or more times a week | 0 (0%) |
| ***Sleep medication intake*** | 0.77 (1.29) |
| Not during past month | 106 (73.1%) |
| Less than once a week | 2 (1.38%) |
| Once or twice a week | 2 (1.38%) |
| Three or more times a week | 35 (24.1%) |
| ***Daytime dysfunction*** | 0.52 (0.76) |
| Never | 90 (62.1%) |
| A few times | 37 (25.5%) |
| Sometimes | 15 (10.3%) |
| A lot of times | 3 (2.07%) |
| **ESS** | 5.61 (3.69) |
| **Actigraphy** | n = 75 |

| | |
|---|---|
| ***Total sleep time (TST), hour*** | 6.98 [6.45;7.66] |
| > 9 hours | 1 (1.33%) |
| 7-9 hours | 36 (48.0%) |
| < 7 hours | 38 (50.7%) |
| ***Time in bed (TIB), hour*** | 8.37 [7.49;9.06] |
| ***Sleep efficiency (SE), %*** | 84.4 [79.5;88.2] |
| ≥ 85% | 36 (48.0%) |
| 75-84% | 30 (40.0%) |
| < 75% | 9 (12.0%) |
| ***Latency, min*** | 12.0 [6.00;21.5] |
| ≤ 30 min | 67 (89.3%) |
| 31-45 min | 3 (4.00%) |
| > 45 min | 5 (6.67%) |
| ***Arousals, number*** | 23.2 [18.9;29.5] |
| ***WASO, min*** | 48.0 [34.0;62.5] |
| 0-20 min | 4 (5.33%) |
| 21-40 min | 21 (28.0%) |
| > 40 min | 50 (66.7%) |

Qualitative data are presented as n (%). The means (SD) and medians [p25;p75] were estimated for quantitative data with normal and non-normal distributions, respectively. ESS, Epworth Sleepiness Scale; n, number; p, percentile; PSQI, Pittsburgh Sleep Quality Index; SD, standard deviation; WASO, wake after sleep onset.

# *6. Discusión*

Los resultados obtenidos en las investigaciones realizadas respaldan las hipótesis planteadas en la tesis (sección 2). Las hipótesis contrastadas son un reflejo de una investigación multidimensional del sueño poblacional, abordando temas como la salud del sueño y factores sociales que afectan a la calidad de sueño. Aunque la investigación tiene como eje central el sueño, se ha considerado necesario una discusión específica para cada perspectiva incluida en la presente tesis. Por lo tanto, esta sección se divide en subsecciones que permitan una lectura lineal de la discusión, respetando la independencia de cada uno de los temas tratados.

En resumen, la tesis presenta resultados que demuestran la utilidad del cuestionario SATED para la medición de la salud del sueño. Además, se describe una asociación entre la salud del sueño y el estado de salud global individuo, siendo la asociación de magnitud comparable a otros hábitos saludables. En relación a la gestión de patologías del sueño prevalentes como la AOS, se demuestra que el manejo de los pacientes en el ámbito de atención primaria es una estrategia de gestión coste-efectiva en comparación con el manejo de rutina habitual en unidad especializada. Finalmente, se constata que la COVID-19 redujo la calidad del sueño en la población general, debido al contexto social de la pandemia, y en aquellos pacientes que superaron enfermedad grave por COVID-19. A continuación, se presenta las discusiones específicas para cada bloque de investigación trabajado en la tesis.

## *6.1. Salud del sueño*

La presente tesis incluye una investigación centrada en la traducción y adaptación cultural del cuestionario SATED al español, así como la evaluación de sus características psicométricas (Objetivo O.1.1). En una

primera fase, se observó consistencia tanto en las traducciones realizadas por diversos profesionales como en la retrotraducción del cuestionario a la lengua inglesa. En una segunda fase, los resultados mostraron propiedades psicométricas adecuadas del cuestionario. SATED mostró fiabilidad, con valores altos de consistencia interna (alfa de Cronbach 0.77) y una correlación de 0.93 en la prueba de test-retest. Además, obtuvo una correcta validación de criterio y constructo, mostrando alta correlación con cuestionarios de referencia y obteniendo resultados consistentes en el análisis factorial exploratorio (AFE) y confirmatorio (AFC). El AFE mostró la estructura subyacente de un solo factor y el AFC respaldó la validación de su estructura en una población independiente. Finalmente, la viabilidad del cuestionario fue favorable, ya que fue fácil e inteligible y requirió aproximadamente 1 minuto para completarse. Así, esta validación del SATED ha demostrado propiedades psicométricas satisfactorias, constituyendo la primera herramienta validada en español para la medición de la salud del sueño.

Existen estudios, previos a la presente investigación, de validación de cuestionarios de salud del sueño: el Sleep Health Scale (SHS) (138) y el Sleep Health Index (SHI) (24). El SHS es un cuestionario similar al SATED que incorpora una dimensión añadida de regularidad del sueño, y que fue validado en población portuguesa. Igual que en el SATED, el AFE resultó en un único factor e incluye cinco categorías para evaluar cada ítem. Contrariamente, la dimensión relativa a la eficiencia mostró ser irrelevante para este factor. Además, existen diferencias en el método de la cuantificación de la puntuación global del cuestionario, usando en este caso una puntuación de 0 a 5 para cada ítem. Nuestro estudio presenta ciertas ventajas sobre la validación del SHS. A diferencia de SHS, SATED fue validado en una muestra diseñada para garantizar la representatividad

de la población general, en este caso de Catalunya. Este tipo de muestreo garantiza la correcta evaluación en la población objetivo. Un punto a favor del cuestionario SHS es la incorporación de la dimensión de regularidad. La valoración del comportamiento regular sobre el horario de acostarse y/o despertarse podría ser un elemento importante en la definición de la salud de sueño (139). Otra herramienta para la medición de la salud del sueño es el cuestionario SHI, propuesto por National Sleep Foundation (24). Este cuestionario incluye 12 ítems relativos a la duración, calidad y trastornos del sueño. De la misma forma que SATED, SHS demostró alta fiabilidad en una muestra de representatividad poblacional. Sin embargo, no se realizó un estudio exhaustivo de validación de criterio, correlacionando la herramienta únicamente con estado de salud, estrés y la valoración sobre la satisfacción de la vida. Esta herramienta, en comparación con la versión validada de SATED, tiene mayor complejidad. Esto dificulta las adaptaciones culturales a otros idiomas y disminuye la factibilidad de ser aplicado en estudios epidemiológicos. Como resultado adicional, cabe destacar que las versiones validadas de SATED en español se incorporaron a todas las oleadas de la ESCA en el período 2020-2023.

Una vez lograda la validación del cuestionario, se llevó a cabo un estudio con el propósito de evaluar la asociación de la salud del sueño con el estado general de salud de las personas. Además, la magnitud de esta asociación fue comparada con otros aspectos del estilo de vida, como la alimentación, la actividad física, el tabaquismo y el consumo de alcohol (Objetivo O.1.2). Los resultados del estudio revelaron una asociación significativa entre una salud del sueño deficiente y una peor percepción del estado de salud general. Además, esta asociación mantuvo su magnitud después de ajustar por factores sociodemográficos, el número de comorbilidades y otros hábitos saludables.

El creciente conocimiento sobre cómo los hábitos saludables de higiene del sueño influyen en la salud ha posicionado al sueño como un componente esencial en la promoción del bienestar. Por ejemplo, en 2010, la American Heart Association definió el constructo de salud cardiovascular (140). En este manuscrito, se incluyeron siete determinantes fundamentales para la optimización y la preservación de la salud cardiovascular (alimentación, actividad física, consumo de nicotina, peso y niveles lípidos en sangre, glucosa en sangre y presión arterial). En la actualidad, la American Heart Association ha actualizado este estamento para incluir el sueño como el octavo factor esencial para la promoción de salud cardiovascular (141). Este hecho refleja la creciente consideración del sueño como elemento fundamental de la salud global del individuo. Sin embargo, es importante destacar que este estamento propone la evaluación del sueño únicamente mediante su duración diaria. Los hallazgos de esta tesis sugieren que una correcta evaluación de la salud del sueño implica considerar sus diferentes dimensiones, como la satisfacción, la alerta, el horario, la somnolencia y la duración. Esta perspectiva holística puede proporcionar una imagen más precisa del impacto del sueño en la salud global del individuo.

En conclusión, hemos llevado a cabo un estudio que abarca la traducción, adaptación cultural y evaluación de las características psicométricas del cuestionario SATED. Los resultados respaldan la validez del cuestionario en la evaluación de la salud del sueño. Estos hallazgos ponen a disposición de la comunidad científica el primer cuestionario para una evaluación de la salud de sueño en español. Este cuestionario emerge como una herramienta esencial para abordar la creciente necesidad de evaluar la salud del sueño en la población, lo que a su vez facilita la creación de estrategias de salud orientadas a promover una higiene del sueño adecuada.

Asimismo, los resultados sobre la relación entre la calidad del sueño y el estado general de salud del individuo contribuyen al creciente conocimiento de que la higiene del sueño constituye un pilar fundamental para el bienestar del individuo.

### *6.2. Manejo del paciente con sospecha de AOS*

Otra perspectiva incluida en la presente tesis fue la optimización de la gestión de patologías del sueño altamente prevalentes como la AOS. Para ello, se llevó a cabo un metaanálisis con datos individualizados de estudios que comparan el modelo de gestión de pacientes con sospecha de AOS basado en atención primaria con el tradicional, basado en unidades especializadas. Este metaanálisis de datos individuales ofrece el nivel más elevado de evidencia, demostrando que la gestión de la AOS en atención primaria no solo se equipara en términos de efectividad a la atención en unidades especializadas, sino que también puede resultar en ahorros económicos significativos. Las diferencias de somnolencia diurna entre los grupos no fueron superiores a la diferencia mínima clínicamente relevante, la cual fue previamente establecida (142) en dos puntos en la escala de Epworth (109). No se observaron diferencias clínicamente relevantes en los resultados secundarios incluidos en el estudio, aunque cabe resaltar una tendencia a una mayor reducción de la presión arterial diastólica en los pacientes manejados en atención primaria. Por el contrario, el abordaje de pacientes en atención primaria demostró ser una estrategia eficiente, generando un ahorro medio por paciente de 399,49 euros tras el diagnóstico, tratamiento y seguimiento.

A pesar de que la efectividad en el manejo de pacientes con AOS es a menudo evaluada a través de la somnolencia diurna, no podemos pasar por alto el efecto de la AOS sobre la presión arterial (109), especialmente

durante las horas nocturnas. Además, un reciente estudio señala a parámetros nocturnos de presión arterial como indicadores de riesgo cardiovascular a largo plazo (143). La experiencia de los médicos de atención primaria en este campo podría constituir un elemento crucial en la gestión de estos pacientes, permitiendo la evaluación de otros aspectos fundamentales de su salud, como es el caso de la presión arterial. Nuestro estudio mostró una reducción media de 1.9 (3.20 a 0.57) mmHg en comparación con la unidad especializada en sueño. Esta diferencia, estadísticamente significativa, se aproxima considerablemente al umbral de relevancia clínica establecida (144). Aunque no se logre una diferencia de impacto clínico significativo, los resultados sugieren la necesidad de planificar nuevos estudios que prioricen la presión arterial como un resultado principal, con el propósito de esclarecer cualquier posible diferencia en el control de la presión arterial entre ámbitos clínicos.

En respuesta a problemas de carga asistencial, otras especialidades médicas han establecido vías clínicas que han facilitado el manejo exitoso de pacientes con enfermedades crónicas como el asma, la enfermedad pulmonar obstructiva crónica y la diabetes por parte de médicos de atención primaria. Además, los hallazgos de nuestro estudio revelaron una reducción en los costes en el ámbito de la atención primaria, a pesar de los gastos adicionales para la capacitación de los médicos de esta unidad. Estos costes se vieron compensados por los ahorros generados en términos de pruebas diagnósticas y consultas médicas. Uno de los principales objetivos de los sistemas de salud es mejorar la salud de la población mediante la identificación de estrategias coste-efectivas. En este contexto, son numerosos los estudios que muestran resultados que invitan a explorar la integración de atención primaria en el manejo de pacientes con sospecha de AOS (145). Aunque los resultados de nuestro estudio son sólidos entre

los países incluidos, es posible que las diferencias organizativas en cada sistema de salud requieran diseños específicos para lograr una gestión coste-efectiva de estos pacientes. Actualmente, ya existen ejemplos de implementación de la gestión de estos pacientes en el ámbito de primaria. Un ejemplo destacable es la iniciativa implementada por el sistema de salud nacional de Australia en 2018, la cual permitió a los médicos de atención primaria solicitar pruebas domiciliarias de AOS sin requerir una revisión previa por parte de un especialista (146,147). Esta medida estuvo respaldada por un programa de capacitación y educación sobre AOS diseñado para los profesionales de la atención primaria (147). Esta estrategia ha sido rigurosamente evaluada y en la actualidad constituye el enfoque diagnóstico principal para la AOS en Australia.

De manera similar, se está produciendo una transformación en la forma en que se maneja la AOS en países europeos, donde los tiempos de espera para acceder a la atención especializada son extensos debido a la cantidad de pacientes que requieren evaluación y seguimiento de la AOS (148,149). Un ejemplo es el Reino Unido, que ha sugerido incrementar la formación en la interpretación de estudios de poligrafía en el hogar (148,149) destinada al personal de atención primaria.

En líneas generales, el diagnóstico y tratamiento de la AOS no revisten una alta complejidad; no obstante, existen circunstancias en las cuales se precisan conocimientos profundos acerca de la patología. En los ensayos incorporados en este metaanálisis, se excluyeron a pacientes con comorbilidades graves (como insuficiencia cardíaca avanzada, neoplasias o tumores activos, trastornos psiquiátricos activos y enfermedades pulmonares severas), así como aquellos con otros trastornos del sueño y/o que hubieran recibido tratamiento con CPAP previamente. Es esencial

reconocer la importancia de las unidades de sueño especializadas para abordar casos de esta patología que presenten un alto nivel de complejidad. En este sentido, se hace imprescindible establecer canales de comunicación efectivos entre la atención primaria y las unidades especializadas en sueño, como requisito fundamental para una gestión integral y eficaz de los pacientes con AOS.

En conclusión, este metaanálisis de datos individualizados proporciona el nivel más alto de evidencia sobre la no inferioridad de la efectividad del manejo de pacientes con sospecha de AOS en atención primaria, además de reducir el coste por paciente. Es esencial llevar a cabo investigaciones en el campo de los servicios de salud para definir los enfoques más idóneos en la implementación de estos descubrimientos.

### *6.3. Cambio en la calidad del sueño en periodo de pandemia por COVID-19*

La presente tesis incluye un estudio en el que se evalúa el impacto de la pandemia por COVID-19 sobre la calidad del sueño de la población (Objetivo O.3.1). Según los resultados del Índice de Calidad del Sueño de Pittsburgh (PSQI), se observó una reducción en la calidad del sueño durante este periodo. Asimismo, al evaluar el estado de ánimo, se observó un incremento en las puntuaciones de dimensiones que reflejan estados emocionales negativos, como tensión, depresión e irritabilidad. En consecuencia, encontramos una conexión sólida entre la calidad del sueño y las dimensiones del estado emocional. Sin embargo, no detectamos diferencias en relación a la somnolencia diurna mediante la escala de Epworth (109).

Los hallazgos presentados parecen confirmar los resultados de otras investigaciones. Por ejemplo, Cellini y colaboradores evaluaron a 1310

individuos que vivían en el territorio italiano y reportaron una disminución en la calidad del sueño, que fue más pronunciada en personas con síntomas más elevados de depresión, ansiedad y estrés (117). De manera similar, Xiao y colaboradores (2020) demostraron que la disminución en la calidad del sueño en personas confinadas en casa durante 14 días en China central se asoció con un aumento en la ansiedad y el estrés (150). Aunque estos resultados apuntan en la misma dirección que los observados en el presente estudio, limitaciones en el diseño de estas investigaciones obstaculizaron la obtención de conclusiones precisas. El estudio incluido en la tesis comparó una evaluación de la calidad del sueño durante el periodo de pandemia con una evaluación previa a su inicio, lo cual confirmó un cambio de la calidad del sueño en este periodo.

Como se ha destacado anteriormente, el estado anímico puede ser un factor determinante de la calidad del individuo. En nuestro estudio, la puntuación total del PSQI presentó una correlación positiva con todos los parámetros de la subescala negativa del POMS como la tensión, la depresión, la ira y la fatiga. Específicamente, el parámetro más afectado en el PSQI fue la latencia del sueño, que además presentó una correlación con el estado anímico medido por la subescala positiva del POMS (151).

Más allá del estado anímico, existen otros factores que podrían haber contribuido en la disminución de la calidad del sueño, por ejemplo, los cambios en los horarios sociales y laborales. Aunque en nuestro estudio no se observó una asociación entre condición laboral y calidad del sueño, otros estudios han mostrado que las personas se despertaban y dormían más tarde durante este periodo de pandemia. Además, las restricciones impuestas han llevado a una disminución en la exposición a la luz solar y a la actividad física, factores importantes para el mantenimiento del ritmo

circadiano (152,153). En consecuencia, se podría observar una exacerbación de las alteraciones de sueño y de un estado de ánimo negativo (154,155).

El sueño es un elemento importante para la salud, y en particular para la función inmunológica y salud mental. Promocionar la higiene del sueño en el contexto sociales como los generados en la pandemia por COVID-19 pueden ser una iniciativa que permita mejorar la calidad de vida de la población y prevenir desarrollo de patologías de mayor gravedad, tales como depresión e infecciones severas. El conocimiento adquirido sugiere la necesidad de esfuerzos para mejorar la conciencia sobre este tema y brindar asistencia psicológica a las personas durante periodos futuros de restricciones sociales.

Es importante señalar que, aunque la muestra obtenida en nuestro estudio fue estratificada por sexo, edad, nivel educativo y socioeconómico para representar adecuadamente a la población general, nuestra muestra se redujo a las personas que respondieron los cuestionarios durante el periodo de pandemia. En consecuencia, nuestra población estaba compuesta en su mayoría por mujeres con un promedio de edad de 40 años, limitando así la representatividad poblacional. Por lo tanto, nuestros resultados deben ser interpretados con precaución, especialmente al generalizar a una población más amplia. La principal fortaleza del estudio fue contar con una evaluación del sueño previa a la pandemia, cuando los individuos no estaban bajo este contexto.

En resumen, observamos una disminución en la calidad del sueño durante el periodo de pandemia por COVID-19 según la puntuación del cuestionario PSQI. Paralelamente, la evaluación del estado de ánimo indicó un aumento en las puntuaciones de las dimensiones que representan

un estado de ánimo negativo, como la tensión, la depresión y la ira. En consecuencia, la disminución en la calidad del sueño presentó una correlación sustancial con el estado de ánimo negativo. Estos resultados siguieren que, en contextos de restricciones sociales, la calidad del sueño podría ser un elemento importante para preservar la calidad de vida de los individuos.

### *6.4. Secuelas del sueño en pacientes ingresados en UCI por COVID-19*

La presente tesis incluyó un análisis exhaustivo de la calidad del sueño de pacientes ingresados en unidades de cuidados intensivos por COVID-19 en el periodo posthospitalario (Objetivo O.3.2 y O.3.3). Esta evaluación fue realizada, por primera vez, mediante cuestionarios validados y mediciones objetivas del sueño en estos pacientes. La evaluación subjetiva mediante el PSQI reveló una mala calidad del sueño en el 60.5% de los pacientes a los tres meses de seguimiento, el cual fue confirmado con una evaluación objetiva mediante actigrafía. Particularmente, la duración y la eficiencia fueron los parámetros más afectados. En este punto temporal, la calidad de sueño correlacionó con niveles de ansiedad y depresión de los pacientes. La evaluación a los seis meses de seguimiento mostró una mejora significativa de la media de calidad del sueño de los pacientes, aunque la mala calidad del sueño persistió en el 48.3% de los pacientes. Consistentemente, la correlación entre la calidad del sueño y los niveles de ansiedad y depresión, que se identificó a los tres meses de seguimiento, se mantuvo en la evaluación efectuada a los seis meses de seguimiento.

Otros estudios recientes sugieren la presencia de alteraciones en el sueño en pacientes de COVID-19 meses después de la hospitalización. En el estudio de Arnold et al. (156) se observó que un 24% de los 110 pacientes incluidos con COVID-19 reportaron insomnio a los tres meses después del

alta hospitalaria. Este porcentaje pareció ser superior en otra cohorte de pacientes, llegando al 31% de los pacientes a los tres meses después del alta hospitalaria (157). La prevalencia de individuos con calidad de sueño comprometida observada en el presente estudio fue mayor que la de los estudios comparativos, lo cual podría estar relacionado con diferencias en los métodos utilizados para la evaluación del sueño, así como diferencias entre las poblaciones. Cabe resaltar que, a excepción del nuestro, todos los estudios comparativos se han basado en evaluaciones llevadas a cabo por herramientas no validadas. Asimismo, la cohorte incluida en la tesis estuvo compuesta exclusivamente por pacientes COVID-19 admitidos en UCI, mientras que los estudios mencionados incluyeron pacientes con diferentes grados de severidad. De hecho, las UCI son conocidas por el exceso de ruido e interrupciones durante la noche, horarios de alimentación inusuales, luz artificial desfasada o sedaciones e intervenciones invasivas como ciertas modalidades de ventilación (158–160). Estudios previos han demostrado que estos factores, asociados al periodo de hospitalización, se asocian al riesgo de trastornos de sueño tras el alta hospitalaria (124).

Después de la publicación del presente estudio, se llevó a cabo una investigación que evaluó la calidad del sueño en pacientes que habían ingresado en UCI por COVID-19 (161). Según el cuestionario PSQI, un 75% de los pacientes mostraron alteraciones del sueño a los tres meses de seguimiento. La principal limitación del estudio fue el pequeño tamaño muestral con el que se realizó la estimación.

En lo que respecta a la calidad de sueño a largo plazo (seis meses), los hallazgos indican que un porcentaje elevado de pacientes (48.3%) sigue experimentando una calidad de sueño deficiente. Otras investigaciones han evaluado la calidad del sueño en pacientes que estuvieron ingresados en

UCI, por causas no COVID-19, en el mismo periodo temporal de seis meses de seguimiento (124). Particularmente, un estudio observacional con 179 pacientes ingresados en UCI, sugiere una persistencia de la alteración del sueño en un 57% de los pacientes a los seis meses de seguimiento (130). Existen diferencias entre dicho estudio y el nuestro. El estudio mencionado incluyó a pacientes con diversos diagnósticos, siendo pacientes con patología cardiovascular la más predominante. En contraste, nuestro análisis incluye exclusivamente a pacientes ingresados por COVID-19. Es importante señalar que los pacientes con patología cardiovascular tienen un riesgo elevado de sufrir trastornos respiratorios durante el sueño (162), lo cual podría explicar la mayor tasa de persistencia observada en el estudio comparativo. A pesar de las discrepancias en las estimaciones entre los estudios, ambos concuerdan en que la persistencia de una calidad de sueño deficiente tras seis meses de seguimiento es un fenómeno frecuente en pacientes ingresados en la UCI, siendo estas superiores a la tasa estimada en población adulta (163).

La disrupción del sueño en estos pacientes puede tener implicaciones importantes en la fase de recuperación de la enfermedad. Las consecuencias a corto plazo de la alteración del sueño incluyen sobreactivación del sistema simpático, angustia emocional, trastornos del estado de ánimo y otros problemas de salud mental y cognitivos (23). Existe una relación bidireccional entre las alteraciones del sueño y la salud mental (164).

Por lo tanto, la alteración del sueño podría dificultar la recuperación del comprometido estado mental de estos pacientes. Un sueño deficiente podría dificultar la recuperación del proceso inflamatorio mediante la alteración de citoquinas pro- y antiinflamatorias que limita el correcto

funcionamiento del sistema inmune (165), afectando la recuperación y aumentando el riesgo de los pacientes a nuevas infecciones. Estas razones nos permiten hipotetizar que la alteración del sueño puede ser un factor de riesgo añadido que impida una correcta recuperación de la salud mental y física de los pacientes ingresados en UCI por COVID-19.

Aunque existen estudios previos que respaldan la hipótesis acerca de una relación causal entre enfermedades críticas que requieren un ingreso en UCI y las secuelas en el sueño, es importante resaltar que, debido al enfoque observacional del presente estudio, no podemos establecer conclusiones definitivas acerca de la causalidad. Se requerirá llevar a cabo investigaciones adicionales con diseños específicos para poder evaluar de manera más precisa si existe una verdadera relación causal entre las variables que se mencionan.

En resumen, un alto porcentaje de pacientes supervivientes a COVID-19 crítico presentan mala calidad del sueño a corto y medio plazo. Aunque se evidencia una mejoría a los seis meses de seguimiento en comparación con el período de tres meses, es importante destacar que un considerable número de pacientes aún informa una calidad de sueño deficiente en este punto temporal. Estos hallazgos refuerzan la importancia de identificar y tratar las alteraciones del sueño en fase postaguda de pacientes críticos por COVID-19.

### *6.5. Implicaciones en la sociedad*

Los resultados obtenidos en la tesis tienen importantes implicaciones para la sociedad contemporánea. La sociedad debe continuar uniendo fuerzas para promover la higiene del sueño como un componente esencial de la salud individual y poblacional. Aunque en la comunidad científica y clínica se reconoce la importancia del sueño para el bienestar individual,

se necesitan estrategias efectivas para difundir este conocimiento a todos los estratos sociales. La promoción del sueño debería recibir la misma consideración que otras prácticas saludables, como la alimentación y la actividad física. Asimismo, surge la necesidad de realizar evaluaciones del patrón de sueño en la población con el objetivo de diseñar estrategias de promoción de la higiene del sueño adaptadas a grupos sociales específicos. Además, llevar a cabo estas evaluaciones de manera periódica permitiría identificar nuevas dinámicas sociales que puedan tener un impacto negativo en la calidad del sueño.

Por otra parte, la alta prevalencia de trastornos del sueño requiere la implementación de nuevas estructuras organizativas en el ámbito de la salud. Con este propósito, resulta fundamental la participación activa del sector de atención primaria en la detección, tratamiento y seguimiento de los pacientes afectados por alteraciones del sueño. En consecuencia, se hacen imprescindibles iniciativas por parte del sistema nacional de salud, tales como la formación de profesionales de atención primaria, la creación de canales de comunicación con especialistas en medicina del sueño y el desarrollo de nuevos protocolos para la identificación y manejo de los diversos trastornos del sueño. A modo de ejemplo, la presente tesis incluye una propuesta de gestión coste-efectiva para manejar a pacientes con sospecha de AOS en atención primaria.

Otra implicación significativa que se desprende de la tesis es la importancia de anticipar los períodos de trastorno en el patrón de sueño a nivel poblacional, como los que hemos experimentado durante la pandemia de COVID-19. Esto posibilitaría la implementación de medidas que contrarresten el impacto negativo de situaciones excepcionales en la calidad del sueño de la sociedad. Además, es esencial tener en cuenta tanto

el sueño como la salud mental al tomar decisiones relacionadas con las restricciones sociales y otras medidas.

Por último, los resultados de nuestras investigaciones subrayan la importancia de identificar y abordar las alteraciones del sueño en pacientes que han sobrevivido a la COVID-19 en estado crítico. Dada la potencial relevancia del sueño en el proceso de recuperación de los pacientes que han estado hospitalizados en unidades de cuidados intensivos, debería ser considerada como una posible secuela y ser monitorizada y tratada adecuadamente. Esta idea debería ser confirmada en nuevos estudios científicos futuros que evalúen si el tratamiento de las alteraciones del sueño en estos pacientes puede mejorar su recuperación tanto a nivel físico como psicológico.

En resumen, la sociedad debería tomar consciencia de la importancia del sueño en la salud y la enfermedad, y se deberían impulsar estrategias basadas en la medición, evaluación y gestión de la salud del sueño a nivel individual y poblacional.

# *7. Conclusiones*

A lo largo de los trabajos incluidos en esta tesis se ha estudiado el sueño desde múltiples perspectivas, proporcionándose una visión amplia del sueño en la salud y en la enfermedad. Los resultados han puesto de manifiesto la importancia de que la sociedad y todos sus organismos relacionados con la salud asuman el sueño como un elemento esencial para la salud global del individuo. A continuación, se enumeran las principales conclusiones de la tesis según la perspectiva de estudio planteada.

En relación a la salud de sueño:

1. El cuestionario SATED es una herramienta útil para la medición de la salud del sueño a nivel poblacional.
2. La sólida asociación entre la salud global y la salud del sueño sugiere que la higiene del sueño es fundamental para la promoción del bienestar integral del individuo.

Respecto al manejo de pacientes con sospecha de AOS:

3. La gestión de pacientes con sospecha de AOS en el ámbito de atención primaria se muestra como una estrategia coste-efectiva en comparación a su gestión en unidades especializadas en sueño.

Respecto a la calidad del sueño en periodo de pandemia COVID-19:

4. La existencia de pérdida de calidad del sueño y salud mental en periodos de restricciones sociales pone de manifiesto la necesidad de diseñar estrategias en salud que anticipen estos escenarios y activen medidas preventivas.
5. El impacto sobre el sueño debería ser considerado al decidir sobre medidas de restricciones sociales.

Respecto a la calidad de sueño en paciente crítico por COVID-19:

1. Un alto porcentaje de pacientes críticos por COVID-19 experimentan alteraciones en fase posthospitalaria, siendo estas persistentes a medio plazo.
2. La solida asociación de las alteraciones del sueño con la salud mental

de los pacientes críticos por COVID-19 sugiere que su identificación y tratamiento podría mejorar la recuperación psicológica de los pacientes.

## *8. Otros artículos con resultados colaterales*

Durante el desarrollo de esta tesis, el doctorando ha participado en la publicación de otros trabajos relacionados con la temática de la tesis. A continuación, se presenta un listado de las referencias asociadas a cada uno de estos artículos científicos.

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