Characteristics and phenotypes of Excessive Daytime Sleepiness

Studies on the general population and sleep apnea patients

Elín Helga Þórarinsdóttir

Thesis for the degree of Philosophiae Doctor

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Supervisors

Thor Aspelund
Christer Janson

Doctoral committee

Helga Ágústa Sigurjónsdóttir
Jóhanna Eyrún Torfadóttir
Samuel T. Kuna

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Einkenni og svipgerð íþyngjandi dagsyfju

Rannsókn á almennu þýði og kæfisvefnssjúklingum

Elín Helga Þórarinsdóttir

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Leiðbeinendur

Thor Aspelund
Christer Janson

Doktorsnefnd

Helga Ágústa Sigurjónsdóttir
Jóhanna Eyrún Torfadóttir
Samuel T. Kuna

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HÁSKÓLI ÍSLANDS

ISBN 978-9935-9699-6-5

ORCID: https://orcid.org/0000-0001-6561-3746

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Ágrip

Inngangur: Íþyngjandi dagsyfja er einkenni sem hefur flókið samband við svefn, lífstíl, andlega- og líkamlega heilsu einstaklinga. Kæfisvefn er algengasti sjúkdómurinn sem veldur dagsyfju. Epworth Syfjuskali (ESS) og er stuttur spurningalisti sem metur líkur á að sofna/dotta og er ESS sú aðferð sem oftast er notuð til að mæla dagsyfju. Veik fylgni er á milli mælinga með ESS og þess hversu oft eða ákaft einstaklingur upplifir syfju. Syfja virðist því ekki vera einsleitt ástand sem unnt er að mæla einungis með "líkum á að dotta", heldur flókið og margþætt einkenni, sem samanstendur af mörgum syfju-tengdum þáttum. Það skortir betri skilning á bæði orsökum og afleiðingum mismunandi þátta huglægrar syfju. Slíkur skilningur gæti stuðlað að þróun á heildstæðari og nákvæmari aðferða við mat á íþyngjandi dagsyfju.

Markmið: Að kanna algengi, sérkenni og fylgni tveggja skilgreininga íþyngjandi dagsyfju bæði meðal almennings og hjá kæfisvefnssjúklingum fyrir og eftir meðferð. Að auki voru skoðuð tengsl margháttaðra mælibreyta í svefni við dagsyfju einkennin.

Efniviður og aðferðir: Tveir þættir íþyngjandi dagsyfju voru metnir; ESS stig (>10 stig skilgreint sem "líklegir til að dotta") og upplifun dagsyfju (≥3 sinnum í viku skilgreint sem að "upplifa dagsyfju"). Þátttakendum var síðan skipt í fjóra syfjuhópa m.t.t. svipgerðar: "ekki syfjaðir", "bara líklegir að dotta", "upplifa bara dagsyfju" og "bæði líklegir að dotta og upplifa dagsyfju". Í grein I voru syfjuhóparnir skoðaðir meðal slembiúrtaks úr almennu þýði einstaklinga 40 ára og eldri sem tóku þátt í faraldsfræðilegri rannsókn á algengi og eðli langvinnrar lungnateppu (e. Burden of Obstructive Lung Disease (BOLD)). Syfjuhóparnir voru bornir saman m.t.t. lýðfræðilegra- og lífsstílsþátta, almennrar heilsu, svefntengdra einkenna, líkum á kæfisvefni og lífsgæða. Í grein II voru syfjuhóparnir kannaðar á meðal sjúklinga með miðlungs-til-alvarlegan kæfisvefn í Íslenska svefnrannsóknarhópnum (e. Icelandic Sleep Apnea Cohort (ISAC)). Algengi og sérkenni syfjuhópanna voru metin við greiningu og aftur 2 árum eftir að meðferð með svefnöndunarvél hófst. Við eftirfylgdina var meðferðarheldni þeirra metin ásamt breytingu á syfju-tengdum einkennum, svefnleysi og lífsgæðum. Þeir sem upplifðu viðvarandi íþyngjandi dagsyfju (voru "líklegir til að dotta" og/eða „upplifa dagsyfju" við greiningu og eftirfylgd) voru bornir saman við þá sem fengu bata. Í grein III voru niðurstöður úr grein II sannreyndar með svipuðum aðferðum og í grein I og II í alþjóðlegum hópi kæfisvefnssjúklinga (e. Sleep Apnea Global Interdisciplinary Consortium (SAGIC)) með miðlungs-til-alvarlegan kæfisvefn. Að lokum, í grein IV, voru svefnbreytur mældar með svefnmælingu (e. polysomnography (PSG)) og bornar saman á milli milli syfjuhópanna meðal sjúklinga með vægan-til-alvarlegan kæfisvefn í SAGIC.

Niðurstöður: Í almenna þýðinu (n=1338, 53% karlar) voru 70.2% „ekki syfjaðir“, 6.7% „bara líklegir til að dotta“, 16.7% „upplifðu bara dagsyfju“ og 6.4% voru “bæði líklegir til að dotta og upplifðu dagsyfju”. Þeir sem voru „bæði líklegir til að dotta og upplifðu dagsyfju” lýstu oftar hrotum, næturstvita og öndunarstoppum í svefni. Þeir sem „upplifði bara dagsyfju“ var oftar með háþrýsting, hjarta- og æðasjúkdóma, sykursýki og einkenni svefnleysis. Einstaklingar í syfjuhópunum tveimur sem “upplifðu dagsyfju” mátu lífsgæði sín marktækt verri en aðrir. Þeir sem voru „bara líklegir til að dotta“ voru líklegri til að lýsa einkennum kæfisvefns (hrotur og öndunarstopp í svefni) en voru að öðru leyti eins og þeir sem voru „ekki syfjaðir“. Á meðal kæfisvefnssjúklinga í ISAC (n=810, 81% karlar) voru 17.7% „ekki syfjaðir“, 7.7% „bara líklegir til að dotta“, 24.7% “upplifðu bara dagsyfju” og 49.9% voru “bæði líklegir til að dotta og upplifðu dagsyfju”. Svipað og hjá einstaklingum í almennu þýði syfjuhóparnir tveir sem “upplifðu dagsyfju” oftar með einkenni svefnleysis og mátu lífsgæði sín verri en einstaklingar öðrum syfjuhópum. Þeir sem “upplifðu bara dagsyfju” voru líklegri til að vera kvöldtýpur. Meðferðarheldni á notkun svefnöndunarvélar var svipuð milli syfjuhópanna. Þeir sjúklingar sem voru “líklegir til að dotta” (með/án að „upplifa dagsyfju) sýndu meiri ávinning af meðferð en aðrir. Við 2ja ára eftirfylgni höfðu 42.3% viðvarandi syfju þrátt fyrir meðferð. Þeir voru með vægari kæfisvefn við greiningu og við eftirfylgd höfðu þeir oftar viðvarandi einkenni kæfisvefns og kvartanir um svefnleysi borið saman við þá sem hafði batnað. Meðal kæfisvefnssjúklinga í SAGIC hópnum (n=2352, 77% karlar) var algengi þess að hafa ESS stig >10 svipað og í ISAC hópnum (57% í SAGIC og 52% í ISAC) en tíðni þess að upplifa dagsyfju ≥3 sinnum á viku var mun lægra (31,3% í SAGIC og 74,7% í ISAC). Á heildina litið studdu niðurstöðurnar í SAGIC hópnum niðurstöður okkar í ISAC. Meðal sjúklinga með vægan-til-alvarlegan kæfisvefn í SAGIC (n= 2097, 68% karlar) höfðu syfjuhóparnir tveir sem voru “líklegir til að dotta” fleiri skipti á klukkustund með öndunarhléum eða minnkaðri öndun (e. apnea-hypopnea index), alvarlegri súrefnisskort mælt með stuðli súrefnismettunarfalls (e. oxygen-desaturation index), lágmarks- og meðalsúrefnismettun og tíma varið <90% í súrefnismettun og vörðu styttri tíma vakandi en þeir sem voru „ekki syfjaðir“ og „upplifðu bara dagsyfju“. Á heildina litið var sambandið milli svefnbreytanna á PSG og syfjuhópanna veikt. Ekki reyndist marktækur munur milli syfjuhópanna á svefnstigum, svefndýpt, tíðni og styrkleika uppvaknana, tíma að sofnun, vökutíma eftir sofnun og hreyfingu útlima í svefni.

Ályktanir: Íþyngjandi dagsyfja er margþætt einkenni. Íþyngjandi dagsyfja metin út frá líkum að dotta annars vegar og hins vegar að upplifa dagsyfju tengjast heilsu, svefni, kæfisvefni og lífsgæðum á mismunandi hátt meðal einstaklinga í almennu þýði og einnig meðal íslenskra kæfisvefnssjúklinga og stórs hóps sjúklinga frá fjölda landa. Eingöngu voru væg tengsl milli margháttaðra mælibreyta í svefni við dagsyfju einkenna.

Lykilorð: Íþyngjandi dagsyfja, Epworth syfjuskali, Basic Nordic Sleep Questionnaire, kæfisvefn, svefnmæling, svefnöndunarvél.

Abstract

Introduction: Excessive daytime sleepiness (EDS) is a symptom that has a complex relationship with a person's sleep and lifestyle as well as their mental and physical health. The most frequently identified medical disorder causing EDS is obstructive sleep apnea (OSA). The Epworth Sleepiness Scale (ESS) is a brief questionnaire that assesses risk of dozing and ESS is the most widely used method to measure sleepiness. There is a weak correlation between the ESS score and measures of how often or how intensely a person experiences a general feeling of sleepiness. This suggests that sleepiness is not a uniform condition that is accurately assessed by the tendency to doze off but a complex symptom comprising multiple components. A better understanding of both the causes and consequences of the different components of subjective sleepiness are needed for the development of a more comprehensive approach when evaluating sleepiness.

Objectives: To examine the prevalence, characteristics and correlation of two subjective EDS measures both among the general population and OSA patients before and after treatment. Also to investigate the association between physiological characteristics during sleep and EDS.

Methods: Two components of EDS were assessed; the ESS score (>10 points defined as having "risk of dozing") and a measure of general sleepiness (feeling sleepy ≥3 times per week defined as "feeling sleepy"). Participants were subsequently categorized into four sleepiness phenotypes: "non-sleepy", "risk of dozing only", "feeling sleepy only" and "both at risk of dozing and feeling sleepy". Paper I assessed the sleepiness phenotypes in a random sample of the general population aged 40 years and above who participated in the Burden of Obstructive Lung Disease (BOLD) study. Sleepiness phenotypes were compared regarding sociodemographic and lifestyle factors, general health, sleep-related symptoms, OSA risk and quality of life. In paper II, the sleepiness phenotypes were explored among OSA patients with moderate-to-severe disease in the Icelandic Sleep Apnea cohort (ISAC). Similarly, as in paper I, the sleepiness phenotypes were assessed and their characteristics compared at time of diagnosis and again after 2 years of positive airway pressure (PAP) treatment. At the 2-year follow-up, their PAP adherence was assessed and changes in symptoms of daytime impairment, insomnia symptoms and quality of life were evaluated. OSA patients experiencing persistent EDS (having "risk of dozing and/or "feeling sleepy" at baseline and follow-up) were compared to those whose sleepiness improved. In paper III, the results from paper II were validated among OSA patients with moderate-to-severe disease in the large international Sleep Apnea Global Interdisciplinary Consortium (SAGIC) cohort using similar methods as in paper I and II. Finally, in paper IV,

polysomnography (PSG) characteristics of the sleepiness phenotypes among OSA patients with mild-to-severe OSA in the SAGIC cohort were assessed and compared.

Results: In the general population (n=1338, 53% males), 70.2% were "non-sleepy", 6.7% reported "risk of dozing only", 16.7% were "feeling sleepy only" and 6.4% had both symptoms. Those "both at risk of dozing and feeling sleepy" had the highest prevalence of snoring, nocturnal sweating, and reporting apneas. Those "feeling sleepy only" more often reported hypertension, cardiovascular disease, diabetes, and insomnia symptoms. Quality of life was poorest among the two phenotypes "feeling sleepy". Those at "risk of dozing only" however had a higher prevalence of OSA symptoms (self-reported apneas and snoring) but were otherwise like the "non-sleepy" subjects. Among OSA patients in ISAC (n=810, 81% males) 17.7% were "non-sleepy", 7.7% were at "risk of dozing only", 24.7% were "feeling sleepy only" and 49.9% reported both symptoms. As in the general population, the two phenotypes "feeling sleepy" had a higher prevalence of insomnia symptoms and reported poorer quality of life. Those "feeling sleepy only" reported the evening chronotype more often. PAP adherence did not differ by baseline sleepiness phenotype, but the two phenotypes with "risk of dozing" showed greater benefits of PAP treatment than "non-sleepy" and "feeling sleepy only" phenotypes. At the 2-year follow-up, 42.3% of PAP users had persistent sleepiness. They had less severe OSA at baseline, more persistent OSA symptoms and more often had symptoms of insomnia than OSA patients in whom sleepiness resolved. Among the OSA patients in the SAGIC cohort (n=2.352, 77% males), the prevalence of having an ESS score >10 was similar to the ISAC cohort (57% vs. 52% respectively) but reporting feeling sleepy ≥3 times per week was not as common as in ISAC (31.3% vs. 74.7% respectively). Overall, the results in the SAGIC cohort supported our findings in the ISAC. Among OSA patients with mild-to-severe disease in SAGIC (n= 2.097, 68% males), the two phenotypes at "risk of dozing" had a higher apnea hypopnea index (AHI) and more severe hypoxemia as measured by the oxygen desaturation index, minimum and average oxygen saturation (SpO_2) and time spent <90% SpO_2 and spent less time awake than "non-sleepy" and "feeling sleepy only" phenotypes. Overall, effect sizes were small. Sleep stages, odds ratio product, frequency and intensity of arousals, sleep latency, wake after sleep onset and limb movement did not differ between sleepiness phenotypes after adjusting for confounders.

Conclusions: EDS is a multifaceted symptom. Defining EDS based on the propensity to doze off and the more general feeling of sleepiness correlates differently with health aspects, sleep, OSA and quality of life among individuals in the general population, in Icelandic OSA patients and in a large group of international OSA patients. Only a weak association was found between EDS and physiological characteristics during sleep.

Keywords: Excessive daytime sleepiness, Epworth Sleepiness Scale, Basic Nordic Sleep Questionnaire, obstructive sleep apnea, polysomnography, positive airway pressure treatment.

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Embarking on a PhD journey is no small feat, and it has been a great adventure that I will never forget. Throughout this journey, there have been both moments of triumph and also times of struggle. I am grateful for both. Hopefully this experience has shaped me into a researcher that can in future confidently bring forward evidence-based science. Along the way towards my PhD, I have had the honor of learning from and collaborating with many outstanding and inspiring individuals. To all of them I'm most sincerely grateful.

First of all, I want to thank my two main supervisors, Christer Janson and Thor Aspelund for their guidance, patience and encouragement throughout my research. Christer's insight into the field of sleep and sleepiness laid the foundation for my PhD when he suggested that we should look at different expressions of daytime sleepiness. His calm demeanor, always looking at the facts, and his kindness have guided me through my PhD and made it enjoyable. His quick answers have also been truly appreciated, often responding to my emails within minutes! Thor Aspelund has also given me unwavering support, encouragement, and supervision. It mattered a lot to me when I realized that he believed in my ability to finish my PhD project. I have been very fortunate to have the opportunity to work with him. His dedication and excellence in research and teaching has been an inspiration.

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I am very privileged in being the daughter of exceptional parents. I would like to thank them both especially. Throughout my studies they have shown their endless support and encouragement. They are both involved in the world of sleep research and through them I got inspired to start my research in the field. Their passion for sleep is admirable

and contagious. My father, Þórarinn Gíslason is a pioneer and a leading expert in sleep. Through sleep research I have gotten to know a whole different side of him that I will always cherish. My mother, Bryndís Benediktsdóttir is my role model in so many ways. As a primary physician (which is also my ultimate goal), she always sees the bigger picture and reminds me to think about the clinical implication of my work. Asking, is this useful in our everyday work with patients? I am forever grateful for her guidance, both in research and life. I also want to thank my siblings: my fun and caring little sister Lísbet Guðný, my big brother (the only one in the family with any business knowledge) Gísli Hrafn, and my clever and thoughtful big sister Hulda Rósa, who has shared with me her recent experience of writing and defending her PhD.

Finally, I want to thank my husband, Gísli Árni Gíslason for his unwavering belief in me and coming up with the "brilliant" suggestion of me finishing my PhD while on maternity leave. To be honest, at first, I wasn't sure if it was a realistic idea, but with his encouragement and "just do it" attitude, I decided to go for it. Writing this PhD would not have been possible without his support, going on an extended paternity leave, taking care of our three children, coping with me during stressful times and listening to my endless talk about my research. I also want to extend my heartfelt thanks to my wonderful parents-in-law, Dýrleif Eydís and Gísli Steinarr for always being there to help. Taking care of the kids and cooking my favorite, kjötsúpa, when I have been busy and tired. To my children, Þórarinn, Eiríkur Steinarr and Dýrleif Ósk, I want to thank you for always reminding me of what is most important in life – you are my everything.

Reykjavík, 2023

Elín Helga Þórarinsdóttir

Contents

List of Abbreviations

AASM: American Academy of Sleep Medicine

AHI: Apnea Hypopnea Index

BDNF: Brain-Derived Neurotrophic Factor

BMI: Body Mass Index

BNSQ: Basic Nordic Sleep Questionnaire

BOLD: Burden of Obstructive Lung Disease

COPD: Chronic Obstructive Pulmonary Disease

CVD: Cardiovascular Disease

DIS: Difficulties Initiating Sleep

DM: Diabetes Mellitus

DMS: Difficulties Maintaining Sleep

EDS: Excessive Daytime Sleepiness

EEG: Electroencephalography

EMA: Early Morning Awakenings

EMG: Electromyogram

EOM: Electrooculogram

ESS: Epworth Sleepiness Scale

FEV1: Forced Expiratory Volume in 1 second

FVC: Forced Vital Capacity

HSAT: Home Sleep Apnea Test

HTN: Hypertension

ICSD-3: International Classification of Sleep Disorders, third edition

IL-6: Interleukin 6

ISAC: Icelandic Sleep Apnea Cohort

KSS: Karolinska Sleepiness Scale

MAP-index: Multivariable Apnea Prediction Index

minSaO2: Minimum Oxygen Saturation

MSLT: Multiple Sleep Latency Test

MWT: Maintenance of Wakefulness Test

nGER: Nocturnal Gastroesophageal Reflux

NREM: Non-Rapid Eye Movement

ODI: Oxygen Desaturation Index

ORP: Odds Ratio Product

OSA: Obstructive Sleep Apnea

PAP: Positive Airway Pressure

PSG: Polysomnography

PVT: Psychomotor Vigilance Task

QOL: Quality of Life

REM: Rapid Eye Movement

RLS: Restless Legs Syndrome

SAGIC: Sleep Apnea Global Interdisciplinary Consortium

SCN: Suprachiasmatic nuclei

SD: Standard Deviation

SSS: Stanford Sleepiness Scale

SWS: Slow Wave Sleep

TNF-alpha: Tumor Necrosis Factor alpha

List of Figures

List of Tables

List of Original Papers

This thesis is based on the following original publications, which are referred to in the text by their Roman numerals:

I. Thorarinsdottir, E. H., Bjornsdottir, E., Benediktsdottir, B., Janson, C., Gislason, T., Aspelund, T., Kuna, S. T., Pack, A. and Arnardottir, E. S. (2019). Definition of excessive daytime sleepiness in the general population: Feeling sleepy relates better to sleep-related symptoms and quality of life than the Epworth Sleepiness Scale score. Results from an epidemiological study. *Journal of Sleep Research, 28*(6), e12852. doi:10.1111/jsr.12852

II. Thorarinsdottir, E. H., Janson, C., Aspelund, T., Benediktsdottir, B., Juliusson, S., Gislason, T., Kuna, S. T., Pack, A. I. and Keenan, B. T. (2022). Different components of excessive daytime sleepiness and the change with positive airway pressure treatment in patients with obstructive sleep apnea: Results from the Icelandic Sleep Apnea Cohort (ISAC). *Journal of Sleep Research, 31*(3), e13528. doi:10.1111/jsr.13528

III. Thorarinsdottir, E. H., Gislason, T., Pack, A. I., Kuna, S. T., Penzel, T., Han, F., Li, Q. Y., Cistulli, P. A., Magalang, U. J., McArdle, N., Singh, B. and Keenan, B. T. (2022). Evaluation of excessive daytime sleepiness in obstructive sleep apnea across international sleep centers. *Sleep*. doi:10.1093/sleep/zsac271

IV. Thorarinsdottir, E. H., Pack, A. I., Gislason, T., Kuna, S. T., Penzel, T., Li, Q. Y., Cistulli, P. A., Magalang, U. J., McArdle, N., Singh, B., Janson, C., Aspelund, T., Younes, M., de Chazal, P., Tufik, S. and Keenan, B. T. Polysomnographic characteristics of excessive daytime sleepiness phenotypes in obstructive sleep apnea: Results from the international Sleep Apnea Global Interdisciplinary Consortium (SAGIC). Submitted for publication in Sleep.

Declaration of Contribution

Below is a declaration of contribution to each paper on which this thesis is based.

Paper I: The idea that the Epworth Sleepiness Scale is an insufficient marker of daytime sleepiness came originally some 30 years ago from Prof. Christer Jansson, Uppsala. He helped with the preparation of data and together with Prof. Thor Aspelund advised me (EHT) on the calculations. They critically advised and helped EHT who was mainly responsible for drafting the paper. Co-authors revised the paper and contributed with suggestions with further analysis and wording.

Paper II: EHT designed the study with PhD mentor Samuel T. Kuna and co-authors Allan I. Pack, Brendan Keenan and Thorarinn Gislason. The statistical work was done by EHT with help from statistician Brendan Keenan during weekly meetings. EHT drafted the manuscript and co-authors revised the paper for important intellectual content. EHT participated in all revisions of the paper.

Paper III: EHT analyzed the data in co-operation with statistician Brendan Keenan. EHT wrote the manuscript in collaboration with all co-authors. Additional analyses were done by EHT according to reviewers' comments in the publication process.

Paper IV: The design of the study was outlined by Allan I. Pack and Brendan Keenan and modulated during weekly meetings with other co-authors. The statistical work was done by EHT in consultation with statistician Brendan Keenan in weekly meetings and Thor Aspelund. EHT wrote the manuscript in collaboration with all co-authors.

1 Introduction

Sleepiness is the feeling of a need to sleep and the desire to do so and, as such, sleepiness is a normal part of the sleep-wake cycle. Through the centuries, sleepiness has not been associated with adverse health aspects, but mainly related to laziness, or lack of motivation. In the Icelandic Sagas, the settlement of Iceland by the Norse in the 9th and 10th centuries is described in considerable detail in the Book of Settlements (Landnámabók). More than 3,000 people and 1,400 settlements are described, and it provides a detailed account of settlers' names, where they settled and information about their families and their descendants. Landnámabók is originally from the late 11th or early 12th century, but it has been preserved in versions from the 13th and 14th centuries. According to it, Hallsteinn the son of Þórólfur settled in Þorskafjörður at Hallsteinsnes. He had, previously, on a Viking raid in Scotland, enslaved men, whom he took with him to Iceland. According to the story, he sent his slaves to islands in Breiðafjörður to extract salt. When he later visited the islands, he found his slaves asleep in the middle of the day and decided to execute them. The name of these islands – Svefneyjar, which translates to "Sleep Islands" in English, is unusual and has not been given to other islands. The story about the destiny of the sleepy slaves is more than 1,000 years old. If this story is true, the fate of these Scottish slaves is probably the first Icelandic description of deaths related to daytime sleepiness.

In the late 1960s, scientist-clinicians began to recognize the importance of sleep for health and the association between excessive daytime sleepiness (EDS) and life-threatening medical conditions (Shepard et al., 2005). With the growing body of scientific literature on the causes and consequences of EDS, specific methods for detecting and measuring sleepiness were urgently needed but proved to be difficult to develop. Because sleepiness is subjective in nature, many factors can influence the experience and perception of sleepiness, making it difficult to measure, quantify and define universal standards of what is considered EDS. Differentiating between related terms like feeling tired, fatigued, not feeling rested, or having low energy, has also proved difficult as they are often used interchangeably when describing daytime impairment in general. Wording has become clearer and today sleepiness refers to the sensation of wanting to sleep, where one's eyelids may droop, or a subject may even doze off (American Academy of Sleep Medicine, 2014). Tiredness or fatigue, on the other hand, refers to feeling physically or emotionally exhausted or sleepy without necessarily feeling the need to sleep (Moncrieff and Fletcher, 2007; Pigeon et al., 2003; Shen et al., 2006). These different expressions of daytime impairment have, however, been found to be closely related and physicians still have challenges distinguishing between the different terms (Chervin, 2000). Moreover, studies have

demonstrated that fatigue, tiredness and not feeling rested share the same risk factors as sleepiness; lack of sleep, poor health, depression, use of medications and a sedentary lifestyle, making it in some cases near impossible to distinguish between them (Dukes et al., 2021; Le Bon et al., 2000; Ruggles and Hausman, 2003; Shen et al., 2006). How these different expressions of daytime impairment relate to sleep, health and quality of life impairment are not yet clear. This is of special concern to clinicians who evaluate individuals for EDS as it is a major symptom of many sleep disorders and used to prioritize patients for further diagnosis and treatment. EDS affects all tasks that require vigilance, memory, and executive functioning, and can have serious consequences for the individual itself and the public by increasing accidents in the workplace, reducing work performance, lowering productivity, and decreasing quality of life (Leger and Stepnowsky, 2020). Recently, EDS was named one of the top five main causes of motorway accidents leading to injuries (Federal Roads Office (FEDRO), 2022) and many reports have found EDS behind serious and costly accidents (Mitler et al., 1988; Mullins et al., 2014). Furthermore, in a recent study conducted by Li et al. (2021) EDS was found to be associated with a nearly two-and-a-half times greater chance of cardiovascular mortality, making it a more powerful predictor of cardiovascular mortality than some well-established risk factors like hypertension, obesity and a sedentary lifestyle. Since screening for EDS, using specific questions and questionnaires, is simple, inexpensive and could potentially help prevent accidents, reduce mortality and increase quality of life, there is an urgent need for having a better understanding of the nature of self-reported EDS and this is the aim of this thesis. The chapters below describe some basic information on the definition, physiology, causes, epidemiology, and assessment of EDS.

1.1 Definition of EDS

Currently, there are several definitions of EDS being used, but there is no consensus on the precise definition of what constitutes sleepiness (compared to other complaints of daytime impairment), or the specific threshold at which it becomes excessive (Martin et al., 2023). The International Classification of Sleep Disorders, third edition (ICSD-3), defines EDS as "the inability to maintain wakefulness and alertness during the major waking episodes of the day, with sleep occurring unintentionally or at inappropriate times almost daily for at least three months" (American Academy of Sleep Medicine, 2014). In general, when sleepiness becomes overwhelming or persistent, disrupting the person's daily activities and functioning, it is referred to as EDS (M. M. Ohayon, 2012).

1.2 Physiology of sleep and sleepiness

1.2.1 Measurements of normal sleep by polysomnography

Sleep has been defined as a "reversible behavioral state of perceptual disengagement and unresponsiveness from the environment" (Kryger, 2022). Sleep and wake can be measured objectively by polysomnography (PSG). On electroencephalography (EEG) brain activity changes when moving from wakefulness to sleep (**Figure 1**). Sleep can be categorized into two main stages: non-rapid eye movement (NREM) and rapid eye movement (REM) sleep, which is evaluated for every 30-second time domain (epoch) on the PSG (Nayak and Anilkumar, 2023).

Wake is characterized by the presence of alpha activity in 50% or more of the epoch, most prominent in the occipital channel (**Figure 1a**). When falling asleep, the low-voltage fast EEG pattern of wakefulness typically transitions into slower frequencies as sleep progresses through NREM sleep stages 1 (N1), 2 (N2) and 3 (N3). Sleep stage N1 is characterized by a reduction in alpha waves (**Figure 1b**). N2, includes spindles and K-complexes (**Figure 1c**), and N3, features a rise in the amplitude and regularity of delta rhythm (**Figure 1d**). N3 sleep is also known as slow-wave sleep (SWS). When entering stage REM sleep, low chin muscle tone in conjugation with rapid eye movements and relatively low-voltage, mixed frequency EEG are seen (**Figure 1e**) (Nayak and Anilkumar, 2023).

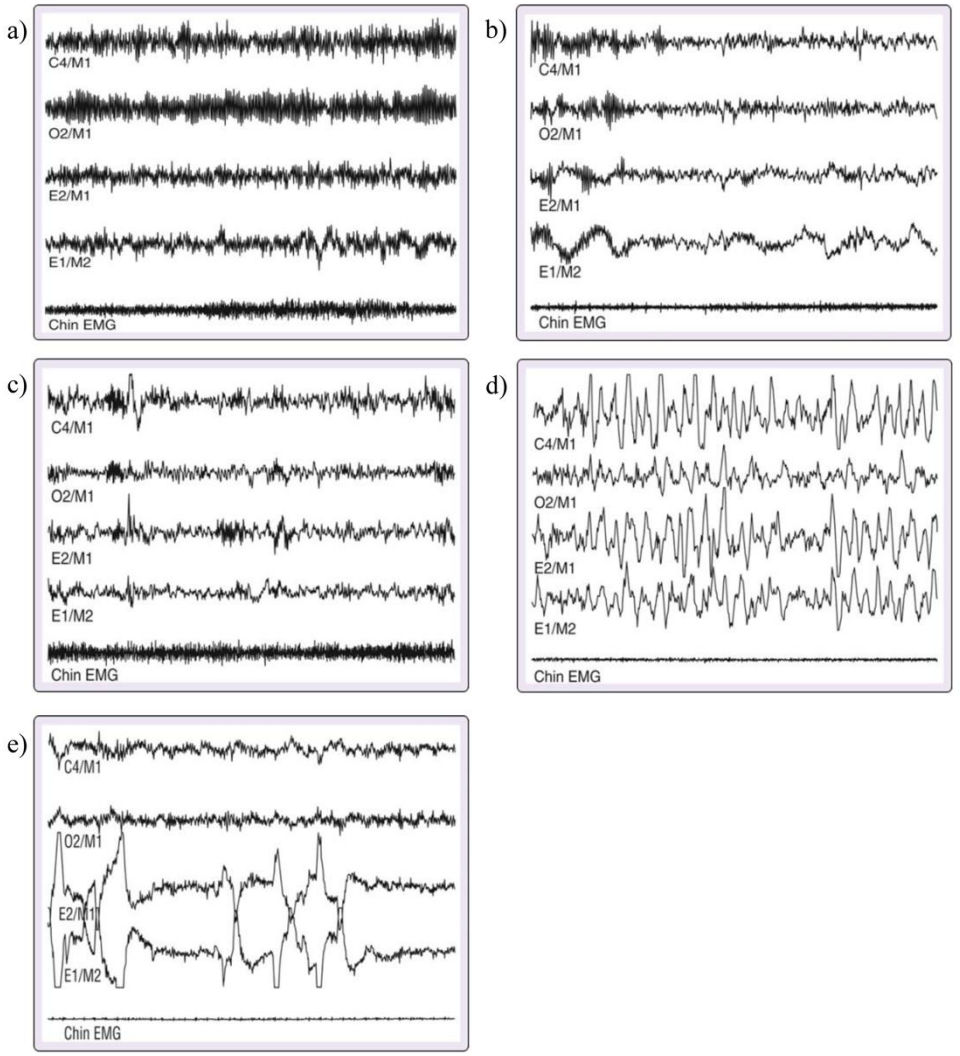

Figure 1. Brain activity (electroencephalogram, EEG) during wakefulness and sleep. C4/M1 = Right central EEG referenced to left mastoid, E2/M1 = right eye (outer canthus) referenced to left mastoid, E1/M2 = left eye (outer canthus) referenced to right mastoid, EMG = electromyogram a) Wake b) NREM sleep stage N1. c) NREM sleep stage N2, d) NREM sleep stage N3. e) REM sleep. From Principles and Practice of Sleep Medicine (Kryger, 2022), with permission from publisher.

Throughout the night, sleep progresses through several distinct cycles of NREM and REM sleep. In healthy adults, each cycle typically lasts between 90 and 120 minutes, with around 4 to 5 cycles occurring during an 8-hour night of sleep. In the first half of the night, NREM sleep makes up the majority of sleep, while the second half of the night is characterized by a higher proportion of REM sleep (**Figure 2**) (Kryger, 2022).

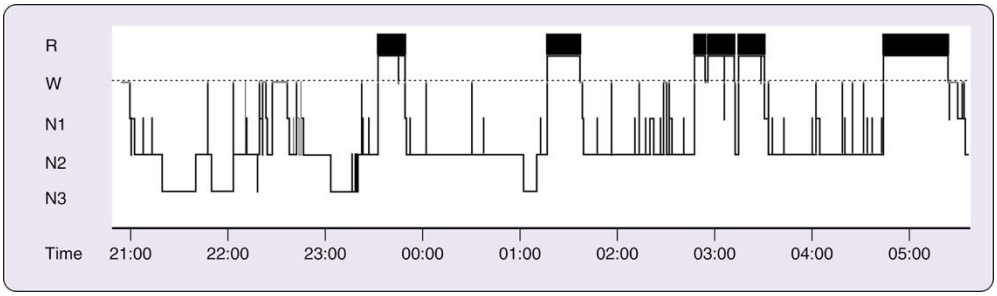

Figure 2. A normal hypnogram showing the progression of the sleep stages across the night. N1, N2 and N3 represent NREM sleep stages 1, 2, 3 respectively. R = REM sleep, W = Wakefulness. From Principles and Practice of Sleep Medicine (Kryger, 2022), with permission from publisher

1.2.2 Regulation of sleep and wakefulness

The regulation of the timing, duration and quality of sleep and wakefulness involves the combined action of two processes: the homeostatic process for sleep and the circadian rhythm for arousal (**Figure 3**) (Borbely, 1982).

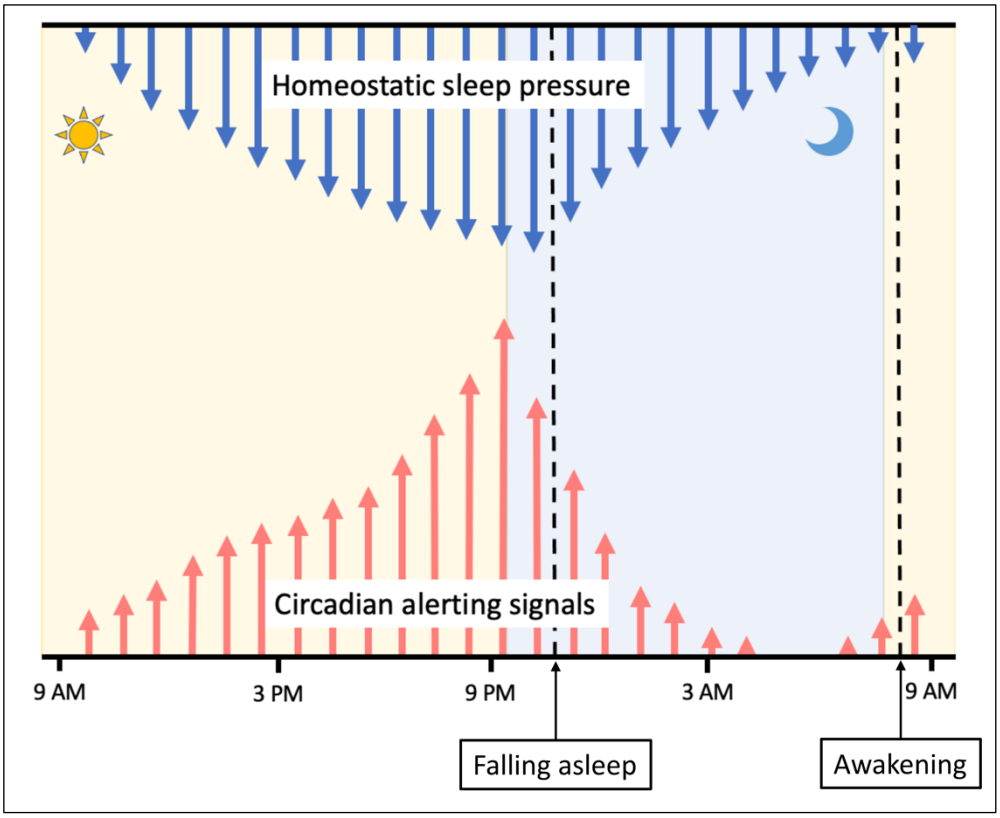

Figure 3. The proposed interaction between the homeostatic drive for sleep (blue) and the circadian drive for arousal (red) in regulating of sleep, wake and alertness level.

1.2.2.1 The homeostatic process

The homeostatic process for sleep or "sleep pressure" is theorized as a pressure that decreases alertness. Sleep pressure accumulates during time awake and dissipates during sleep. Sleep pressure is determined both by the length of wakefulness and the sleep quality of the previous sleep cycle. When sleep is initiated after a long episode of wakefulness, homeostatic sleep pressure facilitates deep sleep (SWS) and continuous, long episodes of sleep (Borbely, 1982; Daan et al., 1984; Franken et al., 1991; McCauley et al., 2009). Homeostatic sleep pressure is to some extent regional and use-dependent, it builds up and dissipates fastest in areas that are most active during the day (Rusterholz and Achermann, 2011). Several substances have been reported to play a role in mediating the dynamics of the homeostatic process, including adenosine, tumor necrosis factor (TNF)-alpha and brain-derived neurotrophic factor (BDNF) (**Figure 4**) (Porkka-Heiskanen, 2013).

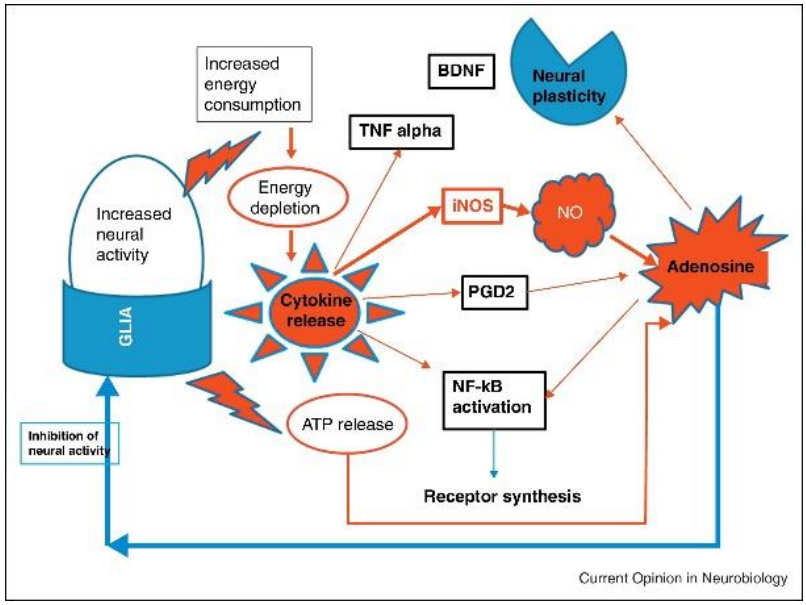

Figure 4. Mediators in the regulation of sleep homeostasis. Figure from (Porkka-Heiskanen, 2013), pages 799-805 (Figure 1), with permission from publisher.

Adenosine is a purine nucleoside that accumulates during wakefulness and when it reaches a certain concentration, it is believed to inhibit neural activity in areas of the brain that promote wakefulness and activate sleep-promoting neurons located near the basal forebrain (Porkka-Heiskanen et al., 1997; Saper et al., 2005). Consistent with this hypothesis are studies reporting that adenosine levels in brain regions increase with prolonged wakefulness and decline with sleep and when administrating adenosine antagonists (e.g. caffeine) there is a potential increase in alertness (for review see (Porkka-Heiskanen et al., 2002)).

1.2.2.2 The circadian process

In opposition and independent of the homeostatic sleep pressure that promotes sleepiness is the circadian process that mainly promotes wakefulness and is responsible for regulating the timing of sleep (Borbely, 1982). Circadian rhythm follows a roughly 24-hour cycle, endogenously controlled by the suprachiasmatic nuclei (SCN) in the hypothalamus (**Figure 5**). The circadian signals are transmitted from the SCN via the paraventricular nuclei (PVN), intermediolateral nucleus of the spinal cord, and the superior cervical ganglion to the pineal gland, which secretes the nocturnal hormone melatonin (Borjigin et al., 2012).

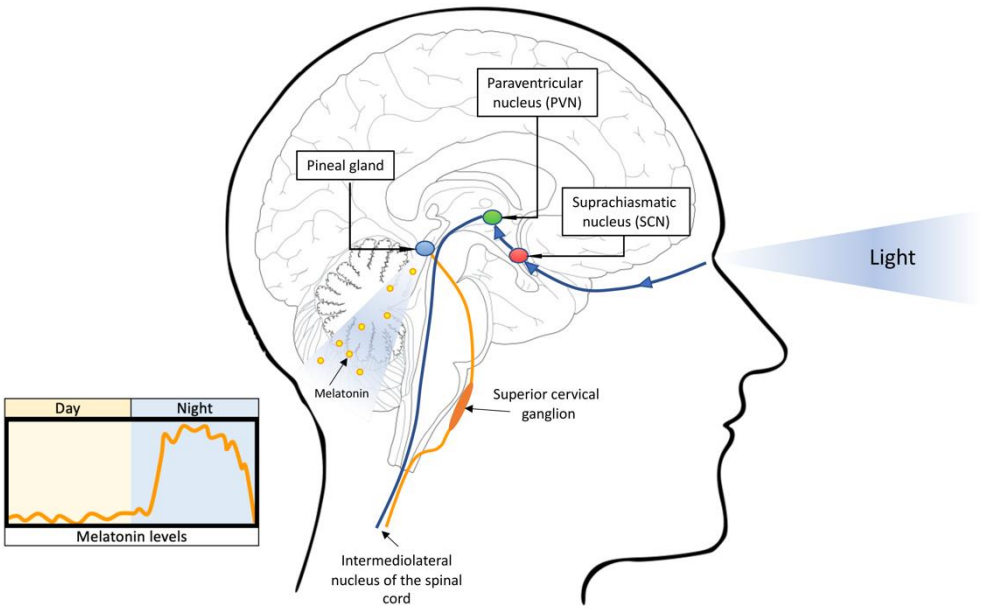

Figure 5. The neuronal circuit that controls pineal rhythmicity in producing melatonin.

The circadian drive for wakefulness increases gradually during the day, reaching its peak in the early evening, and then rapidly decreases around the onset of melatonin secretion at the beginning of the night (Dijk and Archer, 2009). Later in the night, the circadian process actively promotes sleep, especially REM sleep. Genetic variations of circadian rhythms have been identified (Jones et al., 2016; Zhang et al., 2011). Chronotype, also known as morningness-eveningness, is an individual characteristic that reflects a preference for functioning at different times of the day. Three chronotypes are distinguished: morning, neither and evening types (**Figure 6**).

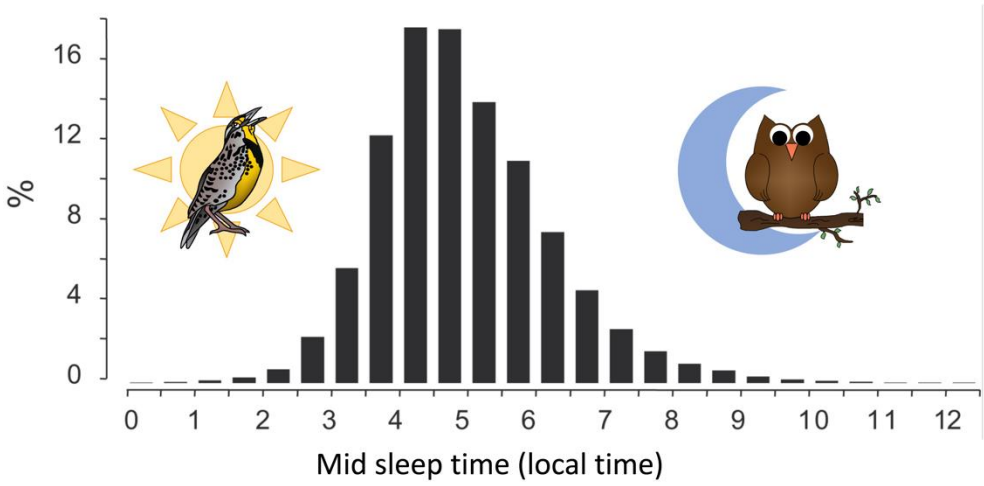

Figure 6. Distribution of chronotypes as assessed by mid sleep time on free days (local time) corrected for age, gender and sleep-debt accumulated during the work-week. The histogram is by (Roenneberg et al., 2007).

Chronotype is influenced by several factors, including individual characteristics such as age and gender (Adan et al., 2012), environmental factors like variations in light and dark and geographical location (Randler and Rahafar, 2017) and social factors like school and work schedules and lifestyle choices (Leonhard and Randler, 2009).

1.2.2.3 Interaction between the homeostatic and circadian processes in controlling levels of sleepiness

Throughout the day, the increase in homeostatic sleep pressure is balanced by the gradual increase in the circadian drive for wakefulness. During sleep, the sleep pressure dissipates, and this change is countered by circadian decrease. Hence, the homeostatic and circadian processes are thought to interact to control levels of alertness/sleepiness and promote nocturnal sleep (**Figure 3**) (Dijk and Czeisler, 1994).

1.3 Determinants of EDS

EDS is a symptom that has a complex relationship with a person's sleep and behavior as well as their mental and physical health. Commonly, EDS is a consequence of insufficient sleep duration, poor sleep quality and/or sleeping in desynchrony with the biological clock (Owens et al., 2014). Of sleep disorders that cause EDS, obstructive sleep apnea (OSA) is the most commonly diagnosed condition (M. M. Ohayon, 2012). EDS has also been related to several medical and psychiatric conditions as well as being a consequence of medication (Perez-Carbonell et al., 2022). In fact, EDS is often the result of multiple factors within the same individual.

1.3.1 Interaction between duration, timing and quality of sleep on levels of sleepiness

The duration of sleep required for individuals to feel rested and alert is highly variable and under strong genetic control (Kocevska et al., 2021). The National Sleep Foundation recommends 7 to 9 hours of sleep for young adults and 7 to 8 hours of sleep for adults aged 65 years and older (Hirshkowitz et al., 2015). These guidelines are corroborated by evidence that suggests that individuals who sleep within these durations typically exhibit better cognitive, mental, and physical health and experience a better quality of life than those who sleep for shorter or longer periods (Hirshkowitz et al., 2015). There is, however, a great individual difference in how sleepy one feels with extended periods of waking and what impact sleep deprivation has on performance (Van Dongen et al., 2003). Inter-individual variability in sleep needs implies that there is no "magic number" for the ideal duration of sleep (Chaput et al., 2018). Adequate sleep duration is therefore often defined as the amount of sleep that enables an individual to remain fully awake, alert, and capable of maintaining normal levels of performance throughout the day without experiencing EDS.

In addition to sleep duration, sleep timing and quality can also have significant influence on sleepiness levels (Ferrara and De Gennaro, 2001; Roenneberg et al., 2007). Individuals with evening chronotypes and shift workers are particularly susceptible to sleeping in desynchrony with the biological clock (Boivin et al., 2022; Roenneberg et al., 2007). Such misalignment can affect sleep and daytime functioning leading to acutely disrupted daytime sleep, reduction of total sleep, build-up of sleep pressure and excessive day and nocturnal sleepiness (Garde et al., 2009; Kazemi et al., 2016). Sleep quality is a complex concept that encompasses several factors, such as sleep latency (the amount of time it takes to fall alseep), the number and duration of awakenings during sleep, the proportion of time spent in each stage of sleep and how refreshed one feels upon waking up. Sleep quality can be assessed subjectively by questionnaires and objectively by PSG (Fabbri et al., 2021; McCarter et al., 2022). A large number of awakenings on PSG have been found to be associated with reports of poor sleep quality, whereas longer durations of REM sleep are associated with good sleep quality (Della Monica et al., 2018).

1.3.2 Medical disorders, medications and EDS

The relationship between sleepiness and health is complex and is influenced by many factors. Insufficient sleep and decreased sleep quality are perhaps the most common cause of EDS in patients with medical illnesses (Lee-Chiong, 2006). Sleepiness can also result from medication side-effects used to manage these illnesses and coexisting sleep disorders such as OSA. However, these factors are often not considered when examining the correlation between sleepiness and medical disorders.

Sleepiness is commonly associated with sleep disorders of which OSA is the most common disorder to cause sleepiness. The association between OSA and EDS is discussed separately (see chapter 1.4.3). Others include narcolepsy, idiopathic hypersomnia and restless legs syndrome (Perez-Carbonell et al., 2022). EDS has also been associated with various medical disorders and conditions such as obesity, pregnancy, cardiovascular diseases, respiratory disorders, diabetes, metabolic disorders, musculoskeletal diseases, chronic pain, urological symptoms, renal disorders and diseases with sensory and neurological impairments (Asplund, 1996; Bixler et al., 2005; Bock et al., 2022; M. M. Ohayon et al., 1997; Olszowka et al., 2021; Sarberg et al., 2016; Vgontzas et al., 1998). According to a longitudinal study, factors such as insomnia, anxiety, depression, and smoking were found to be the most significant predictors of incident EDS (Theorell-Haglow et al., 2015). Furthermore, in a recent prospective study of a representative sample of US adults, EDS was independently associated with a two-and-a-half-fold increase in the risk of cardiovascular mortality even after adjusting for sociodemographic factors, comorbidities, cardiovascular risk factors, sleep duration, and sleep disorders (J. G. Li et al., 2021). Overall, the association of EDS with poor general health is demonstrated by a significant relationship between the number of co-existing medical disorders and the prevalence of EDS (Stroe et al., 2010).

Several medications, including both prescription and over-the-counter drugs, have been known to cause EDS as a side effect. These include benzodiazepines, antihistamines, sedative antidepressants, opioids, antiepileptics, dopaminergics and antihypertensives (Perez-Carbonell et al., 2022). Side effects of medications are an important cause of EDS in patients with multimorbidity as these patients are often at increased risk for sedative side effects due to polypharmacy, organ dysfunction and advanced age (Pagel, 2009; Van Gastel, 2022).

1.3.3 Obstructive sleep apnea

1.3.3.1 Definition, prevalence and risk factors

OSA is a medical disorder characterized by repeated breathing cessation (apnea) or reduction (hypopnea) due to partial or complete collapse of the upper airway during sleep. These episodes are brief (lasting for tens of seconds) and can occur multiple times per hour, leading to intermittent hypoxemia, hypercapnia, and frequent arousals from sleep (Dempsey et al., 2010). The apnea-hypopnea index (AHI) is generally used to assess the severity of OSA and is based on the number of apnea and hypopnea events per hour of sleep. An AHI of less than 5 is considered normal, while an AHI between 5-15 is classified as mild, 15-30 as moderate, and above 30 as severe OSA (Heinzer et al., 2015; White, 1995). OSA is an established health concern. In the general population, 22% of men and 17% of women have an AHI >5 and 6% of men

and 4% of women have OSA in conjugation with EDS (Franklin and Lindberg, 2015). Factors that have been reported to increase the risk of developing OSA include being male, aging, obesity, anatomical abnormalities (such as having a small pharyngeal size due to fatty tissue in the neck), smoking, a family history of OSA, and respiratory control instability during sleep (Krishnan et al., 2014; Punjabi, 2008).

1.3.3.2 Symptoms and diagnosis

The most common symptoms of OSA include EDS, snoring, gasping or choking during sleep, nocturnal sweating, nocturnal gastroesophageal reflux (nGER), nocturia, waking up with a headache, sore throat and dry mouth (Myers et al., 2013). Among clinical OSA patients, women have been found to be more likely to report subjective sleepiness than men (Ye et al., 2009). OSA is associated with a number of comorbidities, including hypertension, cardiovascular diseases, type 2 diabetes (Paschou et al., 2022), depression and cognitive decline (Vanek et al., 2020).

To confirm a diagnosis of OSA, a sleep study is required. Sleep studies for OSA are classified into four levels of complexity, with type 1 being the most comprehensive, involving a full in-laboratory PSG that includes measures of airflow, respiratory effort, oxygen saturation, electrocardiogram (ECG), EEG, electrooculogram (EOM), and EMG to allow for accurate sleep staging (**Table 1**) (Kryger, 2022). However, OSA is commonly diagnosed using a type 3 study or a home sleep apnea test (HSAT), an unattended portable recording measuring at least 4 signals, including airflow, two respiratory effort channels and pulse oximetry, but not sleep staging.

Table 1. Variables commonly recorded during the different types of sleep studies

	Type of sleep study			
	Type 1	Type 2	Type 3	Type 4
Channels (n)	≥ 7	≥ 7	≥ 4	≤ 2
Measurements	EEG EOG EMG ECG Air flow Respiratory effort Pulse oximetry	EEG EOG EMG ECG Air flow Respiratory effort Pulse oximetry	ECG Airflow Two respiratory effort channels Pulse oximetry Peripheral arterial tonometry	Pulse oximetry Air flow or chest movement
Body position	Observed or objective	Possible	Possible	No
Leg movement	Yes	Optional	Optional	No
Attended	Yes	No	No	No
Intervention	Possible	No	No	No

Abbreviations: EEG: Electroencephalogram, EOG: Electrooculogram, EMG: Electromyogram, ECG: Electrocardiogram

1.3.3.3 Pathophysiology of OSA and EDS

EDS is a cardinal symptom of OSA and an important factor when considering treatment (Patil et al., 2019). The intermittent hypoxemia and sleep fragmentation are generally thought to cause EDS in OSA patients (Deegan and McNicholas, 1995). There is, however, a great interindividual difference in sleepiness levels among OSA patients and it has been reported that less than 50% of patients diagnosed with moderate-to-severe disease have EDS (Rey de Castro and Rosales-Mayor, 2013; Shao et al., 2019; Ulander et al., 2022; Ye et al., 2014). When individuals randomly selected from the general population are screened for OSA, the majority of those with an AHI ≥ 5 do not have EDS (Arnardottir et al., 2016; Gottlieb et al., 1999). Furthermore, in a study involving 394 hypertensive primary care patients under 65 years of age who had undergone PSG, it was found that obesity, snoring, apneas, long sleep duration, and male gender were the most accurate predictors of OSA. However, the study did not observe any significant difference in EDS between patients with and without OSA, even when defining OSA as having at least moderate disease (AHI ≥15).

In order to gain a better understanding of the underlying mechanisms behind EDS in individuals with OSA, several studies have examined the association between PSG markers and EDS in OSA. While many studies have found that a higher AHI and more severe hypoxemia as measured by ODI, minimum oxygen saturation (SpO2) and hypoxic burden are associated with subjective sleepiness in OSA patients (Chen et al., 2011; Gottlieb et al., 1999; Jacobsen et al., 2013; Kapur et al., 2005; Mediano et al., 2007; Ulander et al., 2022) these associations are generally weak and not consistently found across studies (Prasad et al., 2018; Sharkey et al., 2013). Other studies have suggested that the presence of EDS in OSA patients may be due to worse sleep quality caused by arousals associated with obstructive events. In this regard, higher sleep efficiency, shorter sleep latency and a higher arousal index and microarousal index have been associated with sleepiness in OSA (Goncalves et al., 2004; Guilleminault et al., 1988; Oksenberg et al., 2010; Prasad et al., 2018; Punjabi et al., 1999; Shao et al., 2019; Sun et al., 2012). Additionally, studies have found significant difference in sleep architecture where sleepy OSA patients have increased "light sleep", indicated by a higher proportion of NREM sleep stage N1 and a decrease in SWS and REM compared to non-sleepy subjects (Deegan and McNicholas, 1995; Punjabi et al., 1999; Shao et al., 2019). However, this is not supported by other studies (Jacobsen et al., 2013; Kapur et al., 2005; Rey de Castro and Rosales-Mayor, 2013). The exact mechanism behind how OSA causes EDS is therefore poorly understood.

Futhermore, the intermittent hypoxemia and sleep fragmentation associated with OSA have both been found to stimulate cell and molecular responses that generate systemic inflammation (Prasad et al., 2018). Cytokines TNF-alpha and interleukin-6 (IL-6) are elevated in OSA patients with EDS compared with those without EDS, indicating that systemic inflammation might have a role in producing sleepiness (Bravo Mde et al.,

2007). Other studies have found that the known co-morbidities of OSA, such as hypertension and cardiovascular disease are mainly associated with the combination of OSA and EDS (Kapur et al., 2008). Therefore, inflammation has been proposed as a link between EDS, OSA and cardiovascular disease and hypertension (Imani et al., 2020; Vgontzas et al., 2000).

1.3.3.4 Treatment and persistent sleepiness

Positive airway pressure (PAP) treatment during sleep has been demonstrated as the most effective treatment for moderate-to-severe OSA (Kushida et al., 2006), improving symptoms of sleepiness and increasing quality of life, both in the short and long terms (Giles et al., 2006; Kawahara et al., 2005; Lindberg et al., 2006). Despite its effectiveness in treating moderate-to-severe OSA, not all patients experience symptom improvement with PAP treatment and studies have shown that 12-55% of OSA patients still report persistent EDS even with adherence to PAP therapy. Studies have found that persistent sleepiness with PAP is associated with more sleepiness at baseline and less severe OSA (Gasa et al., 2013; Koutsourelakis et al., 2009; Pepin et al., 2009) but there is also evidence in mice that the long-term intermittent hypoxemia seen in OSA may cause permanent brain injury with persistent sleepiness as a result of neuronal injury of wake promoting regions of the brain (Alchanatis et al., 2004). In an Australian review (Chapman et al., 2016), persistent sleepiness was attributed to comorbid conditions of OSA, such as diabetes and obesity, rather than OSA itself.

1.4 Assessment of sleepiness

Epidemiological studies on EDS face a well-known challenge due to the varying definitions and usage of many different instruments, both subjective and objective, to measure EDS. Some commonly used measures of EDS are discussed below and summarized in **Table 2**.

Table 2. Frequently used tools for assessing Excessive Daytime Sleepiness

Tool	**Measurement**	Cut-off value suggestive of EDS
Objective		
Mean Sleep Latency Test (Littner et al., 2005)	Ability to fall asleep during 20 minute nap sessions	Sleep latency ≤ 8 min
Maintenance of wakefulness test (Doghramji et al., 1997; Littner et al., 2005)	Ability to stay awake for 40 minute sessions	Sleep latency ≤ 19 min
Psychomotor vigilance task (Thomann et al., 2014)	Sustained attention and vigilance (i.e., reaction time, lapses in attention)	N/A*
Subjective		
Epworth Sleepiness Scale (M. Johns and Hocking, 1997; M. W. Johns, 1991)	Usual risk of dozing in daily situations in recent times	Score >10
The Basic Nordic Sleep Questionnaire (M. Partinen and Gislason, 1995)	Frequency of sleepiness during the week for the past three months	Feeling sleepy ≥3 times per week
Stanford Sleepiness Scale (Carskadon and Dement, 1981; Hoddes et al., 1972; Hoddes et al., 1973)	Degree of sleepiness at a moment in time	Score >3**
Karolinska Sleepiness Scale (Akerstedt and Gillberg, 1990; Shahid et al., 2012)	Degree of sleepiness at a moment in time	Score ≥7***

* No standard cut-off but individuals with EDS exhibit slower reaction times, more inconsistent reaction times during the task, and longer and more frequent lapses (reaction time >500ms).
** A 7-point Likert scale ranging from 1 to 7, with higher scores indicating greater sleepiness.
*** A 9 point Likert scale ranging from 1 to 9, with higher scores indicating greater sleepiness. Abbreviations; EDS: Excessive Daytime Sleepiness; N/A: not applicable.

1.4.1 Objective tests

Objective tests for assessment of EDS include the Multiple Sleep Latency Test (MSLT), the Maintenance of Wakefulness Test (MWT), and the Psychomotor Vigilance Task (PVT) (Doghramji et al., 1997; Littner et al., 2005; Thomann et al., 2014). The MSLT measures a patient's propensity to fall asleep while the MWT assesses the ability to stay awake. PVT on the other hand assesses sleepiness indirectly as the ability to maintain a consistent level of attention and reaction time. Overall, these methods of objectively measuring sleepiness are time consuming and costly and not practical in routine monitoring or screening for EDS.

1.4.2 Subjective tests

Subjective or self-reported measures of sleepiness include the Epworth Sleepiness Scale (M. W. Johns, 1991), Basic Nordic Sleep Questionnaire (BNSQ) (M. Partinen and Gislason, 1995), Stanford Sleepiness Scale (SSS) (Hoddes et al., 1972; Hoddes et al., 1973) and Karolinska Sleepiness Scale (KSS) (Akerstedt and Gillberg, 1990; Shahid et al., 2012).

The ESS is the far most widely used questionnaire to assess sleepiness in research and clinically (Martin et al., 2023). The ESS is a self-administered questionnaire that was developed by Dr. Murray Johns over 30 years ago. The ESS consists of eight questions, each of which asks the person to rate the likelihood of dozing off or falling asleep in different situations, such as while sitting and watching TV, or while lying down to rest (see Appendix 1). Each question is rated on a scale of 0 to 3, with 0 indicating "would never doze" and 3 indicating "high chance of dozing". The total score ranges from 0-24, with higher scores indicating more daytime sleepiness. The ESS is easily administered and can be completed within a few minutes. The ESS score is generally considered to indicate EDS if the total score is greater than 10 (M. Johns and Hocking, 1997; M. W. Johns, 1991). Studies have shown that several factors such as age, ethnicity, gender, and BMI can influence ESS scores. For instance, African Americans reported higher ESS scores than Caucasians in a study on insomnia (Sanford et al., 2006), while being Maori in New Zealand was associated with higher ESS scores than being non-Maori (Gander et al., 2005). In OSA patients with at least moderate disease (AHI>15), the highest ESS scores were seen in Hispanic and Caucasian obese males and the lowest in non-obese females and non-obese Caucasian males (Hesselbacher et al., 2012). Chervin et al. found that male gender had greater influence on the ESS score than on MSLT or measures of OSA severity (Chervin and Aldrich, 1999). Another study by Ulander et al (2013) investigated how age and gender affected responses to each of the eight items on the ESS and found that older individuals tended to score lower on items 2 (watching TV) and item 4 (as a passenger in a car for an hour without a break) and higher on item 8 (in a car, while stopped for a few minutes in traffic). Meanwhile, men generally scored higher than women on item 3 (sitting inactive in a

public place). The differences seen in the ESS scores might therefore not only reflect the individual's level of sleepiness but also age and gender-related differences in exposures to the situations listed in the ESS.

The Basic Nordic Sleep Questionnaire (BNSQ) is a self-reported measure of sleep-related complaints and insomnia symptoms (M. Partinen and Gislason, 1995) (see Appendix 2). It was developed as a brief and easy-to-use tool to assess insomnia and sleep-related complaints in the general population. The BNSQ is widely used in sleep studies published in the Nordic countries and consists of 16 questions that assess different aspects of sleep, including difficulty falling asleep, difficulty staying asleep, early morning awakenings, non-restorative sleep, sleepiness and overall sleep satisfaction. Each item is rated on a 5-point scale, where the options range from never to almost every night. In the BNSQ, individuals are asked how often per week they feel sleepy (question nr. 9). This question is commonly used to assess general feeling of sleepiness (rather than the risk of dozing off as measured by the ESS) and has been shown to correlate with variables that contribute to EDS, such as snoring (Young et al., 1993) and OSA severity (Fedson et al., 2012; Young et al., 1996; Young et al., 1993). If subjects experience daytime sleepiness three or more times per week they are usually considered to have EDS (Hara et al., 2004; Janson et al., 1995; Kallin et al., 2018).

The SSS and KSS both assess sleepiness at a moment in time (Akerstedt and Gillberg, 1990; Hoddes et al., 1972; Hoddes et al., 1973). The SSS uses a 7-point Likert scale, with 1 indicating feeling active, vital, alert or wide awake and 7 indicating that sleep is imminent and dream-like thoughts have already begun. Scores greater than 3 have been associated with sleep debt (Carskadon and Dement, 1981). Similarly, the KSS uses a 9-point Likert scale, with scores ranging from 1 (extremely alert) to 9 (extremely sleepy and struggling to stay awake), to assess an individual's level of sleepiness at a moment in time. A score of 7 or higher has been associated with physiological signs of sleepiness, as determined by EEG and electrooculography (Akerstedt and Gillberg, 1990). The SSS and KSS only measure sleepiness at a moment in time and therefore are influenced by recent sleep patterns and time of day.

1.5 Epidemiology

1.5.1 Prevalence

Several well-conducted studies have examined the prevalence of EDS in the general population. In a summary of 24 studies conducted from 1976 to 1997, Partinen and Hublin found the prevalence of EDS to be a wide range of 0.3% to 36.0% across studies (M. Partinen, Hublin C., 2000). However, they noted that the variation in prevalence depended on the population sampled and the questions asked. Studies that reported EDS rates of under 3% generally focused on hypersomnia or "sleeping too much," while the prevalence of "falling asleep during the daytime or experiencing

frequent sleep attacks" ranged from 5-10% in young to middle-aged individuals and 20-30% in older adults. Finally, the prevalence of "perceived sleepiness" ranged from 10 to 15%.

A few large epidemiological studies have estimated the prevalence of EDS in general population samples in more recent years (see **Table 3**). Studies have found that 13% to 30% of individuals from the general population report significant "risk of dozing" (ESS score >10) and 6.7% to 26% report frequently "feeling sleepy", although the definition of "frequent" varied somewhat between studies (see **Table 3**).

Table 3. Prevalence of excessive daytime sleepiness in general population studies

Study	Sample size	Age, y	Measure	Prevalence, %
Studies using Epworth Sleepiness Scale				
Bicester, United Kingdom (Stradling et al., 2000)	1084	25-65	ESS>10, %	Men = 13, Women = 16
Sleep Heart Health Study (Baldwin et al., 2004)	6440	>40	ESS>10, %	Men = 30, Women = 21
Wisconsin Sleep Cohort Study (Young et al., 1993)	3328	30-60	ESS>10, %	Men = 24, Women = 23
Warsaw-MONICA (Zielinski et al., 1999)	1186	38-67	ESS>10, %	Total sample = 26
Australian commercial drivers (Howard et al., 2004)	2342	16-71	ESS>10, %	Total sample = 24
Studies measuring frequency of feeling sleepy				
Sleep Heart Health Study (Baldwin et al., 2004)	6440	>40	Feeling sleepy frequently or almost always	Men = 13.0, Women = 14
Bambui, Brazil (Hara et al., 2004)	1066	≥18	Feeling sleepy ≥3 days/week for the past year associated with problems	Men = 10, Women = 21
Warsaw-MONICA (Zielinski et al., 1999)	1186	38-67	Feeling sleepy often or always	Total sample = 26
Japan general population (Liu et al., 2000)	3030	≥20	Feeling sleepy often or always	Total sample = 14.9
Finnish Twin Study (Hublin et al., 1996)	11.354	33-60	Feeling sleepy daily	Men = 6.7, Women = 11.0
RHINE II study (Lindberg et al., 2017)	10.854	26-54	Feeling drowsy in the daytime ≥3 days/week	Men = 18.4, Women = 23.8

1.5.2 Gender and age difference

Several studies have shown a significant difference in EDS prevalence between the genders (Baldwin et al., 2004; Hara et al., 2004; Lindberg et al., 2017). However, results are inconsistent as to whether men or women have a higher prevalence of EDS. There is some evidence that men and women may report sleepiness in different ways (Baldwin et al., 2004; Chervin and Aldrich, 1999; Whitney et al., 1998). In the Sleep Heart Health study men were significantly more likely to have an abnormal ESS score (ESS score >10) compared to women (30% vs. 21% respectively, $p<0.001$, see **Table 3** (Baldwin et al., 2004). However, in the same cohort, women were more likely to report feelings of being unrested during the day compared to men (21% vs. 15% respectively, $p<0.001$). In contrast, the question regarding daytime sleepiness (feeling sleepy frequently or almost always) was not significantly associated with gender (13% in men and 14% in women). Sleepiness is more common in adolescents than in children and adults (Campbell et al., 2017). Some studies show that EDS increases with age, affecting up to one-third of those aged ≥80 years (Hayley et al., 2014).

1.6 The complexity of EDS

Currently, the ESS is the far most widely used tool to measure sleepiness. The original paper on the ESS by Johns (M. W. Johns, 1991) has over 4,500 citations on PubMed (as of March 2023), which reflects the importance of the ESS as a tool for assessing EDS. In clinic, primary physicians use the ESS to take important decisions, such as when considering whether to reinstate driving licenses, refer individuals for an OSA screening and in monitoring effects of OSA treatment (Bonsignore, Randerath, et al., 2021; Epstein et al., 2009; Lieberman, 2009). In sleep clinics, the ESS is used to prioritize OSA patients for treatment and assess response to treatment as EDS poses a danger to both personal and public safety (Bioulac et al., 2017).

However, when using only the ESS to measure sleepiness, it is assumed that there is a linear relationship between the level of sleepiness and risk of dozing (**Figure 7**). This would mean that the more sleepiness an individual experiences, the higher the risk of dozing during activities that require wakefulness, such as driving, sitting and reading, and when attending a meeting. Sleepiness then increases in a linear fashion, from no sleepiness at all to the most extreme, where it is assumed that the individual has a very high likelihood of dozing or is asleep. This implies that sleepiness is a unidimensional symptom and the risk of dozing off equals EDS.

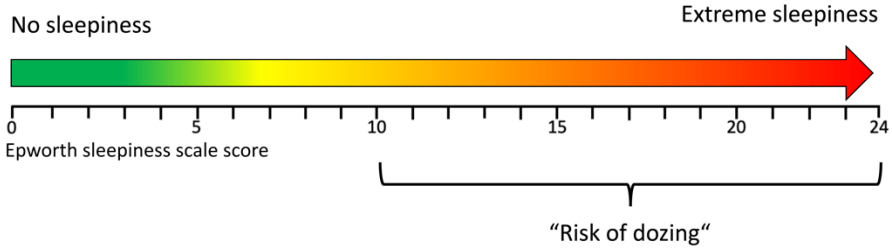

Figure 7. The assumed linear relationship between the Epworth Sleepiness Scale (ESS) score and level of sleepiness when relying only on the ESS.

In clinical practice and in research there have been concerns of how accurately the ESS measures sleepiness and identifies those with significant impairment. In primary care, it is not uncommon for clinicians to encounter patients who express significant sleepiness that severely affects their daytime functioning and quality of life, but they are not likely to doze off. If only the ESS is used to measure their sleepiness they will be characterized as non-sleepy. This symptom has been speculated to be another thing entirely, separate from sleepiness and called various names such as tiredness, fatigue, having low energy, or not being rested (Pigeon et al., 2003; Shen et al., 2006). Consequently, as these individuals are not identified as having EDS, they might also not be considered as having higher risk EDS-related consequences, such as accidents, work-related errors or mortality. On the other hand, there are also individuals that fall asleep easily at any time of the day and they do so by choice. These naps do not interfere with their daily activities, quality of life or functioning but as they have a high propensity for falling asleep the ESS might identify them as having EDS. The ESS might therefore not be a reliable method by which to measure their sleepiness.

Only a few studies have investigated the association between the general feeling of sleepiness/fatigue/tiredness (which needs not manifest as sleep) and the "risk of dozing" as measured by the ESS score >10 (Adams et al., 2016; Baldwin et al., 2004; Kim and Young, 2005; Pilcher et al., 2003; Pilcher et al., 2000). In general, the results suggest that the association between the two are weak and they identify different individuals as having problematic daytime impairment (most often called EDS). For example, in a study of 826 randomly selected, community dwelling men aged 40 years and older, 12.6% had significant risk of dozing (ESS score >10) and 30.4% had general sleepiness/tiredness/fatigue (e.g. daytime sleepiness or impairment that does not necessarily result in dozing) (Adams et al., 2016). Of those having a general feeling of sleepiness/tiredness/fatigue, 75.3% had an ESS score of ≤ 10 and would therefore not be identified as having significant EDS if only the ESS was used. Furthermore, the two different definitions related differently to outcome measures;

feeling sleepy/tired/fatigued without having risk of dozing (ESS score ≤10) was significantly associated with OSA severity and short sleep whereas having risk of dozing was associated with depression and nocturia. This indicates that the "risk of dozing" does not identify all of those with EDS and that feeling sleepy/tired/fatigued is also important when assessing OSA patients for significant daytime impairment. This is supported by studies that have shown that OSA subjects not only report sleepiness but commonly report other related terms like feeling tired, fatigued and having low energy (Chervin, 2000). If they are treated with PAP, not only do the symptoms of sleepiness get better but they also get improvements in feeling tired, fatigued and having low energy (Chotinaiwattarakul et al., 2009). These findings highlight the complexity of EDS, indicating that it is not a unidimensional symptom but rather a symptom with multiple components that is closely related to other symptoms of daytime impairment (**Figure 8**).

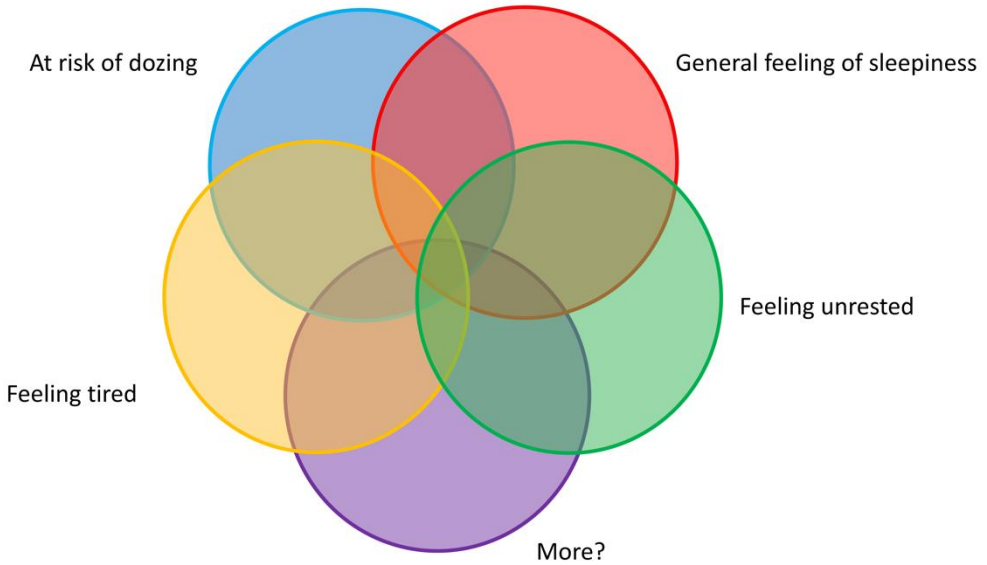

Figure 8. A schematic figure showing how "risk of dozing" and "general feeling of sleepiness" might represent components of a larger, multifaceted phenomenon of daytime impairment.

What exactly these different components could be is not yet clear but might include a propensity to fall asleep, such as "risk of dozing", the more general feeling of sleepiness, and even related terms, such as feeling tired, unrested, fatigue and having low energy. This would then imply that sleepiness is not merely the increased propensity to fall asleep and a simple reflection of lack of sleep but part of a larger multifaceted phenomenon of daytime impairment which could have similar causes,

such as OSA, lack of sleep and poor mental and physical health. This is of a special concern to clinicians, researchers and health authorities who use self-reported scales to assess sleepiness. Due to the limited information on how these different components of daytime impairment are related to underlying causes and consequences, such as risk of accidents, it is currently unclear which specific components need to be assessed when evaluating patients, for instance, in the context of determining their fitness to drive. Therefore, there is a need for a better understanding of the concept of self-reported sleepiness and its relationship to other symptoms of daytime impairment, sleep, health and quality of life for a fuller understanding of sleepiness and for new, improved tools to be developed. Given the high prevalence of OSA in society and its association with EDS, individuals with OSA are a feasible group for EDS studies. Additionally, as PAP treatment is effective in improving EDS among OSA patients, studying EDS in OSA can provide valuable insight into the underlying mechanisms of EDS.

2 Aims

The overall aim of this study was to investigate the complexity of subjective sleepiness, both among individuals in the general population and among well-defined cohorts of patients with OSA, by assessing the potential causes and consequences of two components of EDS. The well-established ESS questionnaire was used to estimate the "risk of dozing" and the question "Do you feel sleepy during the day?", from the Basic Nordic Sleep Questionnaire, to reflect the more general feeling of sleepiness. We aimed to examine the prevalence of EDS based on these two components and their correlation to sociodemographic variables, general health, sleep-related symptoms, symptoms of daytime impairment, short sleep, chronotype and quality of life. The change in these two components of EDS were estimated following OSA treatment. Among OSA patients, the PSG characteristics of these sleepiness components were further assessed. The specific aims of the four resulting papers were as follows:

Paper I: The aims of the study were:

a) To compare the prevalence and association of the two EDS components in a general population sample from Reykjavik and Uppsala

b) To examine differences in general health characteristics, quality of life, sleep-related symptoms and risk of OSA between the two components of EDS

Paper II: The aims of the study were:

a) To investigate the prevalence and characteristics of the two EDS components in untreated OSA patients from the Icelandic Sleep Apnea Cohort (ISAC)

b) To examine if there was a difference in response to PAP treatment depending on baseline assessment of sleepiness components.

c) To investigate the characteristics of those with persistent EDS (by either definition) despite PAP treatment

Paper III: The aims of the study were:

a) To verify the findings of paper II in a large, multicenter, international cohort of Sleep Apnea Global Interdisciplinary Consortium (SAGIC)

Paper IV: The aims of the study were:

a) To investigate the PSG characteristics of the different components of EDS among untreated OSA patients in the large, international cohort of SAGIC

3 Materials and Methods

3.1 Study cohorts

The research described in this thesis is based on results from three study cohorts.

3.1.1 General population cohort

The general population sample used in paper I were individuals that participated in The Burden of Obstructive Lung Disease I (BOLD, www.boldstudy.org) initiative in Reykjavik, Iceland and Uppsala, Sweden. The BOLD study is an international, multicenter study aiming to estimate the global burden of chronic obstructive pulmonary disease (COPD) (Buist et al., 2007). The study included a random selection of individuals aged 40 years and above from the general population, identified through national registries of inhabitants. The response rates were 81.8% in Reykjavik and 62.2% in Uppsala, resulting in the participation of 1,366 individuals (52% male) – 765 from Reykjavik and 601 from Uppsala. Paper I utilized data from questionnaires, body measurements, and spirometry tests. Each study site received ethical approval from their respective local ethical committee (National Bioethics Committee of Iceland: 04-080; Regional Ethical Review Board in Uppsala: 2006/146), and written informed consent was obtained from all participants.

3.1.2 Icelandic Sleep Apnea Cohort (ISAC)

In Paper II, the clinical cohort of OSA patients consisted of individuals who participated in the ISAC. Between September 2005 and December 2009, patients diagnosed with moderate-to-severe OSA (AHI ≥15 events/hour) and referred for PAP treatment to the Landspitali University Hospital in Reykjavik were invited to join the ISAC. Over 90% of eligible patients agreed to participate, resulting in the involvement of 822 individuals (81% male). Two years after the diagnosis, a follow-up evaluation was conducted, with 741 participants completing the same assessments as at baseline, and their PAP adherence was evaluated. More information regarding the methods and subjects can be found in Bjornsdottir et al. (2013) and Ye et al. (2014). Every participant provided written informed consent, and the study received ethical approval from the local ethical committee (National Bioethics Committee of Iceland; 02-078). Paper II utilized data from questionnaires, body measurements, and type 3 sleep studies (HSAT).

3.1.3 Sleep Apnea Global Interdisciplinary Consortium (SAGIC)

In papers III and IV, data were used from the SAGIC cohort, a multicenter, international clinical sample of OSA patients (https://www.med.upenn.edu/sleepctr/sagic.html). SAGIC consists of participants recruited from 10 sleep centers, including Chang Gung Memorial Hospital in Taipei, Taiwan; Charité University Hospital in Berlin, Germany; Universidade Federal de São Paulo in São Paulo, Brazil; Landspitali University Hospital in Reykjavik, Iceland; Ohio State University in Columbus, USA; the University of Pennsylvania in Philadelphia, USA; Royal North Shore Hospital in Sydney (University of Sydney), Australia; Sir Charles Gairdner Hospital in Perth, Australia; Ruijin Hospital in Shanghai, China; and Peking University in Beijing, China. Participants were men and women, aged > 18 years referred to a sleep center because of a suspicion of OSA or AHI ≥ 5 based on a prior sleep study. Subjects underwent in-laboratory PSG or HSAT at the SAGIC centers according to standard procedures. For further details on methods and subjects see (Keenan et al., 2018). The study protocol was approved by the National Bioethics Committee of Iceland; 13-087) and additional IRB approval was required and obtained at each site. Informed consent was obtained from all participants.

3.2 Measurements

3.2.1 Characteristics and lifestyle

In the three study cohorts, participants answered questionnaires on demographics, their height and weight were measured and BMI calculated as kg/m2. Smoking history was evaluated through self-report, where individuals who reported smoking regularly during the month preceding the exam were categorized as "current smokers." Those who reported prior smoking but denied having smoked regularly for a month before the exam were categorized as "former smokers," while those who reported no regular smoking at or before the exam were categorized as "never smokers." Additionally, ISAC (paper II) subjects were questioned on alcohol use where "heavy alcohol use" was defined as drinking 8 or more alcoholic drinks per week for the past month for women or 15 or more drinks per week for men (Bouchery et al., 2011). Subjects in ISAC were also asked if they exercised regularly and if so, how many times per week. Those answering three times or more often per week were considered as exercising regularly. In BOLD (paper I) information was gathered on years of education completed and in SAGIC (paper III and IV) subjects were asked about their ethnicity and if they worked shifts.

3.2.1.1 Chronotype

In ISAC (paper II), the Horne-Ostberg Morningness-Eveningness questionnaire was used to assess chronotype preferences (Horne and Ostberg, 1976). The questionnaire

comprises 19 items and has a total score ranging from 16 to 86, with a higher score indicating morningness and a lower score indicating eveningness. Apart from the total score, participants were grouped as morning types (score of 59–86), neither (42–58), or evening types (16–41). Chronotype was also accessed in the SAGIC cohort used in paper III where individuals were asked to identify which one of the following "types" they considered themselves to be; (1) Definitely a "morning" type, (2) More a "morning" than an "evening" type, (3) More an "evening" than a "morning" type, (4) Definitely an "evening" type.

3.2.1.2 Quality of life

QOL measurements were performed in both BOLD (paper I) and ISAC participants (paper II) using the 12-item Short-Form Health Survey (SF-12) for physical and mental quality of life (Ware et al., 1996).

3.2.1.3 Medical disorders and medication use

Participants were defined as having hypertension and diabetes if they reported a doctor-diagnosis of those previously mentioned diseases and were using medication for their treatment. Having cardiovascular disease was defined if subjects reported doctor-diagnosed myocardial infarction, stroke and/or heart failure and, similarly, hypothyroidism was defined by self-report of doctor diagnosis. In ISAC (paper II) metabolic syndrome was defined if subjects fulfilled three or more criteria as defined by the National Cholesterol Education Program Adult Treatment Panel III (P. L. Huang, 2009). In the general population sample (paper I) Chronic Obstructive Pulmonary Disease (COPD) was defined by spirometry as having post-bronchodilatory Forced Expiratory Volume in 1 second (FEV1)/Forced Vital Capacity (FVC) ratio <0.7 (Buist et al., 2007). Asthma was defined as current self-reported doctor's diagnosis of asthma, asthmatic bronchitis or allergic bronchitis. In ISAC (paper II), COPD and asthma were diagnosed by self-report of a doctor's diagnosis and only presented in combination as having "obstructive lung disease". ISAC participants answered questions about the name and doses of medication for hypertension, diabetes, and insomnia (paper II) and in SAGIC participants were asked about the names of medications they used, the dose and length of treatment (paper III).

In the general population cohort (paper I) the multivariable apnea prediction (MAP) index was used to categorize individuals as either high or low risk for OSA (Maislin et al., 1995). The MAP index takes into account self-reported occurrence of OSA symptoms (snoring or gasping, apneas, choking or struggling for breath during the night) as well as BMI, age and gender. The index ranges from 0 to 1, with those scoring 0 being the least likely to have OSA. A cut-off of 0.5 has been used to identify subjects at high risk of OSA, and using this cut-off has an estimated sensitivity and specificity of 0.88 and 0.55 respectively (Maislin et al., 1995).

3.2.1.4 Sleep-related symptoms

The symptom of nGER was defined as the report of experiencing heartburn after going to bed ≥1 times per week. Insomnia symptoms were defined as difficulties initiating sleep (DIS), maintaining sleep (DMS) or early morning awakenings (EMA) ≥3 times/week (Bjornsdottir et al., 2013). Subjects were asked how often they felt rested when they woke up and those answering three or more times during the week were defined as feeling rested. Habitual snoring was defined as snoring ≥3 nights/week (Emilsson et al., 2016). Similarly, those indicating that they had been told they stopped breathing ≥3 nights/week were defined as having witnessed apneas. Frequent night-time sweating was defined as subjects reporting heavy perspiration during the night ≥3 times/week (Arnardottir et al., 2013). Participants answered questions on symptoms of RLS and characterized as having RLS based on recommendations from the International Restless Legs Syndrome Study Group (Allen et al., 2003).

3.2.1.5 EDS and persistent sleepiness

The EDS components were assessed using two different measures, the ESS and one question assessing frequency of feeling sleepy during the day. Participants were defined as having "risk of dozing" if they scored >10 points on the ESS. In the general population (paper I) and ISAC (paper II) cohorts, the one question from the BNSQ "Do you feel sleepy during the day?" was used to assess general sleepiness. Participants rated their answers on a 5-point scale: never/almost never (1); less than once a week (2); one or twice a week (3); three to five times a week (4); every day or almost every day of the week (5) and those answering three times or more often per week (scores 4 and 5) were considered as "feeling sleepy". In the SAGIC cohort (papers III and IV) a similar method was used where subjects were asked to take a position on the statement "I feel sleepy during the day" with three times or more often per week (scores 4 and 5 on a 5-point scale) considered as "feeling sleepy". In SAGIC, the additional option "don't know" was given and subjects answering the sleepiness question in this way were excluded from the analysis (n=29 in paper II and n=24 in paper IV). Using these two components of sleepiness, 4 clinical sleepiness phenotypes were identified:

1. "Non-sleepy"; ESS score ≤10 and reporting feeling sleepy <3 times per week
2. "Risk of dozing"; ESS score >10 but reporting feeling sleepy <3 times per week
3. "Feeling sleepy"; ESS score ≤10 but reporting feeling sleepy ≥3 times per week
4. "Both at risk of dozing and feeling sleepy"; ESS score >10 and reporting feeling sleepy ≥3 times per week

For examination of persistent sleepiness in the ISAC (paper II), participants who were compliant with PAP treatment (see details below) and exhibited EDS (e.g. "risk of dozing" and/or "feeling sleepy") were reassigned to one of the four sleepiness phenotypes based on their responses to the questionnaires at the 2-year follow-up. Participants that were still reporting"risk of dozing" and/or "feeling sleepy" at follow-up were characterized as having "persistent sleepiness" whereas those who were no longer sleepy were characterized as having "improved sleepiness". Additionally, the prevalence of persistent sleepiness was compared to that determined using the conventional definition of residual sleepiness, which is based solely on the ESS (e.g. having "risk of dozing" at baseline and follow-up despite complying with PAP treatment) (Gasa et al., 2013; Koutsourelakis et al., 2009; Pepin et al., 2009).

3.2.2 Sleep studies

ISAC participants (paper II) were diagnosed with OSA by a HSAT performed in one of the five clinical sites in Iceland performing sleep studies. Subjects with an AHI ≥15 on the diagnostic study were included in the study. To ensure homogenous scoring, all sleep studies were re-evaluated by a centralized scoring laboratory in the University of Pennsylvania using the Somnilogical Studio (Embla™) software. A classification of a hypopnea required ≥ 30% decrease in flow with ≥ 4% oxygen desaturation or a ≥ 50% decrease in flow for ≥ 10 sec with a sudden increase in flow at the end of the event. Apnea was defined as ≥ 80% decrease in flow for ≥ 10 sec. The AHI was calculated as number of apneas and hypopneas per hour and the oxygen desaturation index (ODI) was defined as the number of oxygen desaturations ≥ 4% per hour. The minimum SpO2 was defined as the lowest oxygen saturation reached during the study and time spent at SpO2 <90% (TST90) was evaluated. For further details on sleep studies and scoring in the ISAC cohort, see (Arnardottir et al., 2012)

In the SAGIC (paper IV), 1,513 (72%) participants were diagnosed using an in-laboratory full-night PSG, 102 (5%) had split-night PSG and 482 (23%) had HSAT. Uniform data collection was ensured by implementing standard operating procedures at each site. The reliability of scoring between the centers has been tested both for in-laboratory PSG and HSAT and has shown a strong inter-rater agreement for common metrics of OSA severity (Magalang et al., 2016; Magalang et al., 2013). As both clinically obtained data and measures derived directly from the in-laboratory PSG using

specialized software were evaluated, the total sample size varied for specific traits. Standards from the AASM (2014) were used to score sleep stages, arousals, and respiratory events. Similarly, as in ISAC, AHI, ODI, minimum and average SpO2 and TST90 were evaluated. In addition, for participants undergoing a PSG, sleep stages, arousal index, arousal intensity, periodic limb movement index (PLMI) were assessed. Absolute (minutes) and relative (percent) time of wake, NREM sleep stages N1, N2, N3 and REM were evaluated. Two markers of arousal intensity were investigated; arousal intensity using a validated automated wavelet transformation producing an index from 1 to 9 according to increasing intensity (Amatoury et al., 2016; Azarbarzin et al., 2015) and heart rate response to arousal, which has been directly correlated with arousal intensity (Azarbarzin et al., 2014). Sleep latency was assessed as minutes awake from "lights out" until falling asleep and wake after sleep onset (WASO) as minutes spent awake after initially falling asleep.

The odds ratio product (ORP) was calculated for a subset of participants in the SAGIC (paper IV). The ORP is a continuous marker of sleep depth and is calculated for every 3 seconds from the power spectrum of the EEG (in contrast to the 30 second epochs used for traditional sleep stages) (Younes and Giannouli, 2020; Younes et al., 2015; Younes et al., 2020). The method for calculating the ORP has been described in detail (Younes et al., 2015). The ORP ranges from 0 (deep sleep) to 2.5 (full wakefulness). In this present study ORP was expressed as average ORP during the analysis, during wake and in each sleep stage (NREM, REM), ORP distribution or proportion of epochs with ORP values in different categories of size 0.25 across the night and ORP-9 and the ORP in the immediate 9 seconds after arousal reflecting the speed of which a person returns to sleep after arousal. The intra-class correlation coefficient for the relationship between the average ORP in 30 second epochs of the right to left EEG signals was assessed for the entire PSG (right/left ORP correlation) as it has been associated with driving safety in individuals in OSA and is considered a marker of accumulated sleep loss (Azarbarzin et al., 2021). Additionally, each participant was assigned a 2-digit type number based on a rank of the distribution of ORP values in deep sleep (ORP<0.05) and in full wakefulness (ORP>2.25). The first and second digit in the type number was assigned as "1" if % of epochs in decile 1 and 10 was in the first quartile of its distribution respectively, "2" if in the second or third quartile range and "3" if in the fourth interquartile range. Using these 3 numbers, 9 different ORP types were identified where e.g. type 1.1 had both deep sleep and full wakefulness in their respective lowest quartiles. For further detail on the ORP types see (Younes et al., 2022).

3.2.3 PAP treatment

In the ISAC (paper II), PAP use (ResMed Corp., San Diego, California, USA) was assessed two years after its initiation. The patients received care at the outpatient clinic at Landspitali University Hospital in Iceland, where they were provided with guidance

from trained staff in selecting the appropriate device and settings. When available, adherence was estimated by objective data from memory cards over the last 28 days (available for 72% of subjects). Alternatively, for those who did not have objective adherence data, PAP adherence was estimated by self-report from questionnaires (28% of subjects). PAP adherence was defined as using PAP for ≥20 nights and ≥4 hours/night on average for the previous four weeks based on objective data or ≥5 nights/week for ≥60% of the night by subjective data (see prior study for validation of this definition (Keenan et al., 2014)). Subjects who were using PAP but did not meet these criteria were classified as partial users and were excluded from further analysis when assessing treatment effects. Non-users reported no PAP use or returned the PAP machine within 1 year of initiation. For further details on PAP treatment in the ISAC cohort, see (Arnardottir et al., 2015). At the 2-year follow-up, the participants were also questioned about their use of alternative treatments for OSA. Among them, 49 (6.8%) reported using a mandibular advancement device, while 107 (14.8%) underwent OSA surgery. Additionally, 21 subjects (2.9%) reported a weight loss exceeding 10% based on measurements taken between the baseline and 2-year follow-up.

3.3 Statistical analysis

In paper I, categorical variables were summarized as percentages and compared between groups with Pearson's chi-square test. Continuous variables were summarized as means ± standard deviation (SD) and compared between sleepiness phenotypes using analysis of variance (ANOVA). Multiple linear regression controlling for age, sex, BMI, smoking history and study center was used to explore the independent association of health status (e.g. HTN), quality of life measures, sleep-related symptoms (e.g. reporting apneas) and MAP index between the sleepiness phenotypes using the "non-sleepy" phenotype as reference. To investigate if different cut-off values for the ESS score had impact on our results, we performed a sensitivity analysis using >8, >9, >11 and >12 as cut-off points for the ESS score. All calculations were done using STATA software, version 13.0 (Stata Corporation, College Station, Texas).

In paper II, categorical variables were summarized as percentages and compared between sleepiness phenotypes with Pearson's chi-square test. Continuous variables were summarized as means ± SD and compared between sleepiness phenotypes using ANOVA. A Bonferroni-corrected threshold was used to adjust for multiple comparisons and the threshold adjusted for the total number of measures evaluated within each measurement domain. A $p < 0.05$ was considered nominally significant in all analyses. A pairwise comparison was performed if differences between groups were significant or nominal. At follow-up, categorical and continuous variables were summarized using percentages and means ± SD and compared between those with and without persistent sleepiness using a Pearson's chi-square test and Student's t-test respectively. Subject-specific change scores were calculated as the difference in values from baseline to follow-up in symptoms of sleepiness, insomnia and QoL. Change scores were

compared between PAP and non-PAP users overall and within sleepiness phenotypes. To determine whether the changes with PAP adherence differed based on sleepiness phenotype, we evaluated the significance of the interaction term between sleepiness phenotypes and PAP adherence (PAP users versus non-PAP users) in the context of a linear regression model fit in the full sample (including main effect terms). Analysis was controlled for age, sex, BMI and AHI at baseline. We also calculated standardized mean differences (SMDs) based on normalized outcomes (i.e. z-scores) to facilitate comparisons across measurements. All calculations were done using STATA software, version 16.0 (Stata Corporation, College Station, Texas).

In paper III, categorical variables were summarized using percentages and compared among sleepiness phenotypes using Pearson's chi-square test. Continuous variables were summarized using means ± SD and compared between sleepiness phenotypes with ANOVA. Medians were also assessed and compared between groups using a Kruskal-Wallis test for all continuous variables and showed similar results. As in paper II, significant p-values were adjusted for the total number of measures using a Bonferroni correction within each domain. A $p < 0.05$ was considered nominally significant. To understand the relative magnitude of difference in variables among the sleepiness phenotypes, standardized effect sizes were calculated as eta-squared for continuous variables ($\eta 2$; 0.01 = small, 0.06 = medium, 0.14 = large) and Cramer's V for categorical variables (0.1 df = small, 0.3 df = medium, 0.5 df = large, where df for a given contingency table equals [rows – 1] * [columns – 1]) (Cohen, 1988). All calculations were done using STATA software, version 16.0 (Stata Corporation, College Station, Texas).

In paper IV, categorical variables were summarized using percentages and compared among sleepiness phenotypes using Pearson's chi-square test. Continuous variables were summarized using means ± SD or 95% confidence interval and compared between sleepiness phenotypes with ANOVA. Variables that were not normally distributed were log or square root transformed prior to parametric analysis. In addition, for all continuous variables, medians and interquartile ranges (IQR) were assessed and compared using a Kruskal-Wallist test. Results were similar when using a non-parametric Kruskal Wallis test and therefore only results from parametric tests are presented in this thesis. A $p<0.05$ was considered nominally significant. A Hochberg "step up" approach was used to adjust for a family-wise error rate at 5% within three physiological domains of interest – measures of OSA severity/hypoxemia, sleep stages/arousals and ORP metrics (Hochberg, 1988; Y. F. Huang and Hsu, 2007). A pairwise comparison was performed if differences among sleepiness phenotypes achieved nominal significance. As in paper III, eta-squared was calculated to measure the proportion of variance in the PSG variables that can be explained by the sleepiness phenotypes (($\eta 2$; 0.01 = small, 0.06 = medium, 0.14 = large effect) (Cohen, 1988). In addition, Cohen's d was calculated between each pair of sleepiness phenotypes (0.2 = small, 0.5 = medium, 0.8 = large) (Cohen, 1988). A sensitivity analysis was performed

for all calculations with subjects with at least moderate disease (AHI ≥ 15, n=1372). All calculations were done using STATA software, version 16.0 (Stata Corporation, College Station, Texas).

4 Results

The results of this thesis are presented as follows:

First the baseline characteristics of the study populations are presented. Secondly, the two EDS components in the general population are explored and the four different sleepiness phenotypes identified. Thirdly, the characteristics and prevalence of the sleepiness phenotypes are investigated among untreated OSA patients. Fourthly, response to PAP treatment is compared between the sleepiness phenotypes in OSA and, finally, PSG characteristics of OSA patients within the four sleepiness phenotypes are explored.

4.1 General characteristics of the study cohorts

In the general population cohort (paper I), 81.8% and 62.2% of eligible and approach subjects agreed to participate in the study in Reykjavik and Uppsala respectively. Altogether, 1,366 participated but, of those, 28 subjects were excluded as information on risk of dozing (ESS score) or feeling sleepy (from BNSQ) were missing, resulting in a final sample of 1,338 participants (53% males) with a mean age of 57.4±11.5 years (**Table 4**).

In the ISAC (paper II), the participation rate was over 90% with a total of 822 subjects participating at baseline. Of those, 12 individuals did not answer the ESS or sleepiness question and were excluded from the analysis, resulting in a final baseline study cohort of 810 participants (81% males) with a mean age of 54.5±9.1 years (**Table 4**). Altogether, 722 subjects (89%) completed all relevant assessments at the 2-years follow-up (for further details see **Figure 9**).

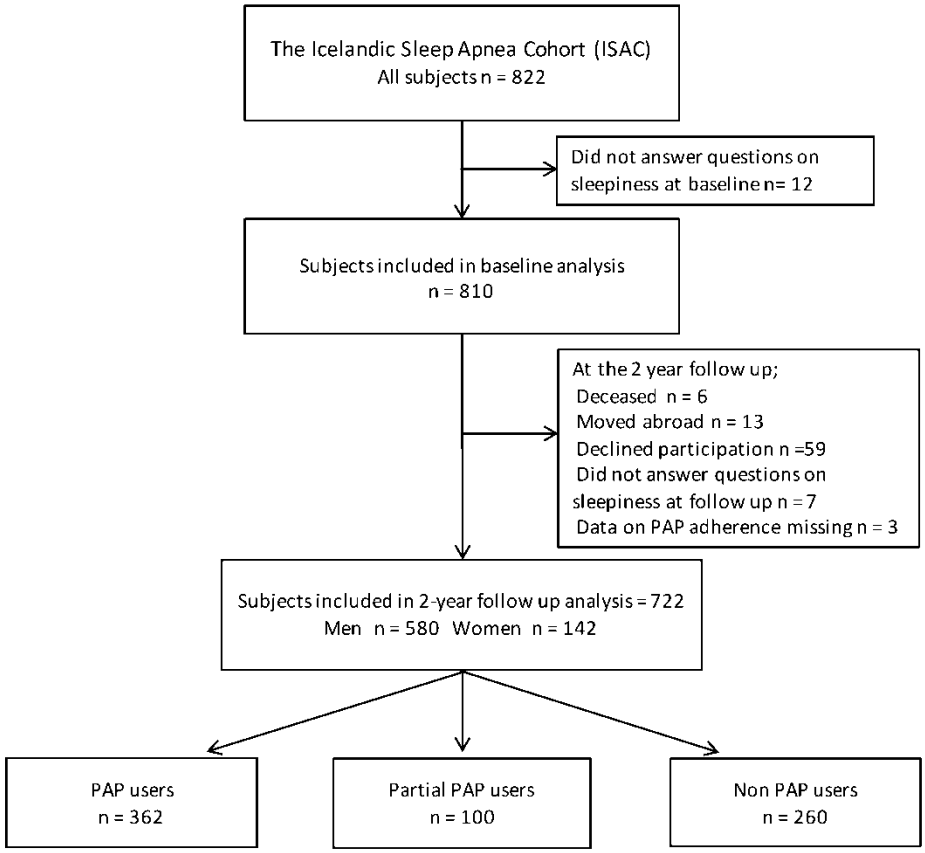

Figure 9. Flow chart of the study population in the Icelandic Sleep Apnea Cohort. Abbreviations: ISAC = Icelandic Sleep Apnea Cohort, PAP = Positive airway pressure

The SAGIC cohort was composed of 5,470 subjects that were referred to the SAGIC sites for a sleep study. Of those, 1,952 did not have OSA (AHI<5) and 61 subjects did not have information on sleepiness or answered "don't know" and were excluded, resulting in 3,457 subjects with mild-to-severe OSA that had relevant data on sleepiness. Paper III included only patients with moderate-to-severe disease (AHI ≥15) resulting in 2,352 subjects (77% males) and a mean age of 50.0±13.3 (**Table 4**). In paper IV, PSG characteristics among patients with mild-to-severe disease were explored. Of the ten clinical sites, Beijing had not yet finished processing PSG data and was excluded in the calculations resulting in n=2097 subjects (68% males, mean age 51.5±13.4) being included in paper IV (**Figure 10** and **Table 4**).

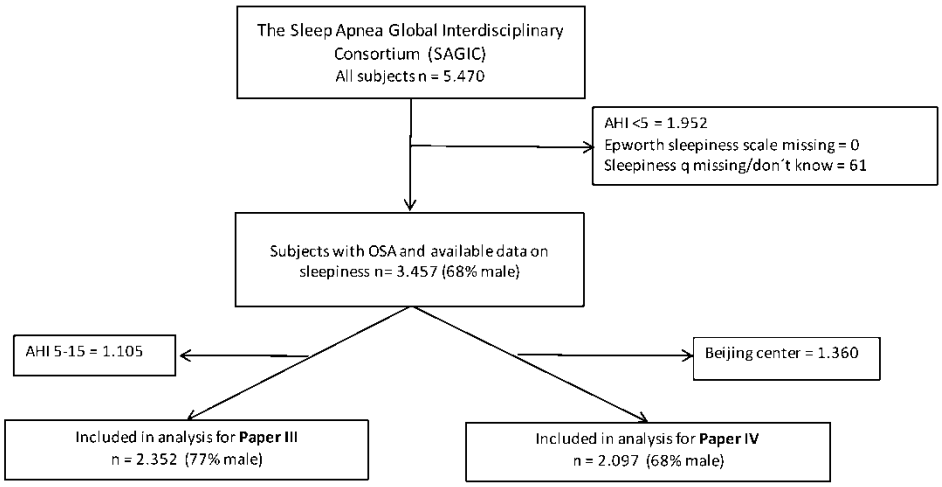

Figure 10. Flow chart of the study populations in SAGIC used for paper III and IV. Abbreviations: SAGIC: Sleep Apnea Global Interdisciplinary Consortium, q = question, OSA: obstructive sleep apnea, AHI = Apnea hypopnea index

The characteristics of the study cohorts are shown in **Table 4.** Subjects in the general population sample (paper I) were less often men, had lower BMI and were less likely to report hypertension and diabetes than the OSA subjects in the ISAC (paper II) and SAGIC cohorts (paper III and IV). The OSA patients with moderate-to-severe disease in the ISAC (paper II) were somewhat younger and more obese than those with the same OSA severity in SAGIC (paper III).

Table 4. General characteristics and reported sleepiness in the study populations

	General population cohort (Paper I) n=1338	ISAC cohort (Paper II) n=810	SAGIC cohort subset (Paper III) n=2352	SAGIC cohort subset (Paper IV) n=2097
General characteristics				
Age, years	57.4 ± 11.5	54.5 ± 10.6	59.9 ± 13.3	51.5 ± 13.4
Male gender	52.7	81.0	76.7	68.1
Body Mass Index, kg/m2	27.5 ± 4.7	33.5 ± 5.7	31.0 ± 6.9	32.1 ± 7.8
Large waist*	N/A	85.4	70.9	78.1
Neck circumference, cm	N/A	42.7 ± 3.7	41.1 ± 4.3	41.0 ± 4.4
Medical disorders				
Hypertension	30.5	54.3	50.9	49.3
Cardiovascular disease	12.5	18.7	9.9	10.3
Diabetes	4.3	8.8	13.4	14.9
Obstructive lung disease	16.8**	17.0***	N/A	N/A
OSA severity and ESS score				
Apnea-Hypopnea Index, h^{-1}	N/A	45.0 ± 20.7	43.6 ± 24.5	31.9 ± 26.4
Oxygen Desaturation Index, h^{-1}	N/A	35.6 ± 20.2	40.0 ± 27.9	30.2 ± 29.1
Minimum SpO_2, %	N/A	76.7 ± 8.0	75.6 ± 9.5	79.0 ± 8.9
TST90, %	N/A	14.0 ± 18.3	15.6 ± 20.0	11.7 ± 18.8
ESS score	6.1 ± 3.9	11.7 ± 5.1	10.9 ± 5.5	9.8 ± 5.6
Sleepiness components				
Risk of dozing off (ESS score >10)	13.1	57.5	52.0	43.2
Feeling sleepy (≥ 3 times per week)	23.2	74.7	31.3	32.2
Sleepiness phenotypes				
Non-sleepy	70.2	17.7	41.5	47.7
Risk of dozing only	6.7	7.7	27.1	20.1
Feeling sleepy only	16.7	24.7	6.5	9.1
Both at risk of dozing and feeling sleepy	6.4	49.9	24.8	23.1

Data are presented as mean ± standard deviation (continuous variables) or percentages (categorical variables), *Waist circumference ≥102 cm in males, ≥88 cm in females, **Chronic obstructive pulmonary disease (COPD) as assessed by spirometry, ***Self-report of asthma and/or COPD, Abbreviations: SD = Standard deviation, SpO2 = Oxygen Saturation, TST90 = Percentage of sleep time spent <90% SpO2, ESS = Epworth Sleepiness Scale, ISAC = Icelandic Sleep Apnea Cohort, SAGIC = Sleep Apnea Global Interdisciplinary Consortium.

4.2 Sleepiness in the general population sample

4.2.1 Prevalence of sleepiness as defined by the two definitions and distribution of the four sleepiness phenotypes

In the general population, feeling sleepy ≥ 3 times per week was more common than having an ESS score >10 (23.2% vs. 13.1% respectively) (**Table 4** and **Figure 11**). Interestingly, as shown in **Figure 11, t**here was only a small overlap of the two sleepiness components. Of those with an ESS score >10, 49.1% (86 out of 175 subjects) also reported feeling sleepy ≥ 3 times per week. Among those who reported feeling sleepy ≥ 3 times per week, only 27.7% (86 out of 310 subjects) also had an ESS score >10. When comparing reported sleepiness between the two clinical sites, a greater percentage of participants from Uppsala reported feeling sleepy ≥ 3 times per week compared to those from Reykjavik (26.3% vs. 20.7% respectively, p=0.02) but no significant difference was found in having an ESS score >10 (13.6% for Uppsala, 12.7% for Reykjavik, p=0.634) or mean ESS scores (6.1±3.9 for both centers, p=0.884) between the two clinical sites.

Four different sleepiness phenotypes were identified: "non-sleepy", at "risk of dozing only", "feeling sleepy only" and "both at risk of dozing and feeling sleepy". The majority of subjects were "non-sleepy" (n=939, 70.2%), followed by 16.7% (n= 224) that were "feeling sleepy only", 6.7% (n=89) were at "risk of dozing only" and 6.4% (n=86) were "both at risk of dozing and feeling sleepy" (**Table 4** and **Figure 11**).

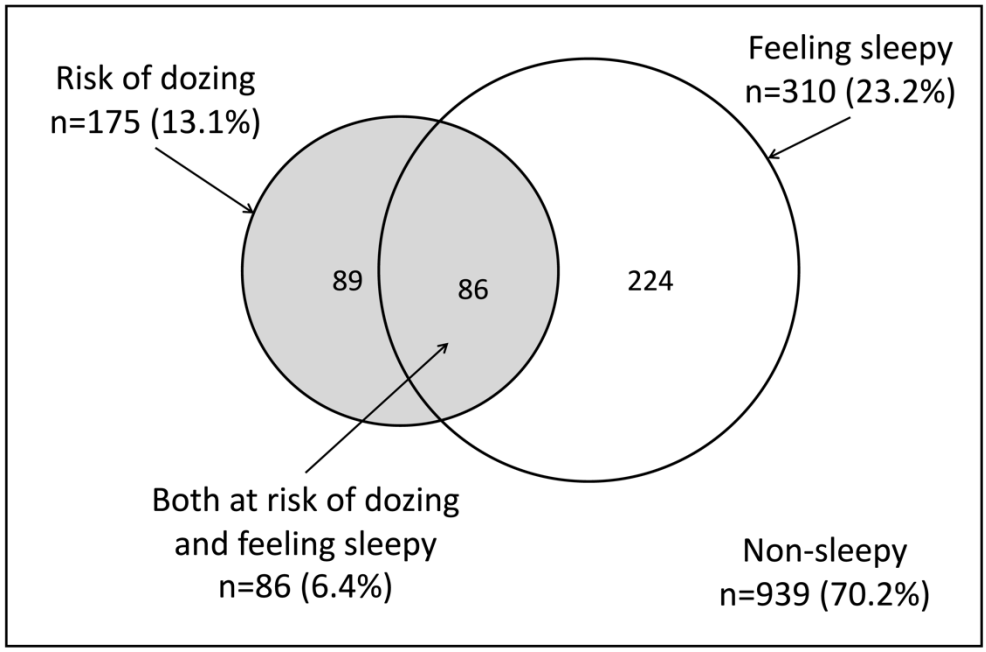

Figure 11. Prevalence and overlap of the sleepiness components in the general population sample (n=1338). Grey circle: subjects at risk of dozing (Epworth sleepiness scale score >10), White circle: subjects feeling sleepy during the day ≥3 times per week.

4.2.2 General characteristics, health and quality of life among the sleepiness phenotypes

The phenotype at "risk of dozing only" was on average younger but there was no significant difference in gender distribution, BMI or smoking history between the sleepiness phenotypes (**Table 5**).

Table 5. General characteristics, health and quality of life of the sleepiness phenotypes in the general population cohort

	Non-sleepy (n=939)	**Risk of dozing only** (n=89)	**Feeling sleepy only** (n=224)	**Both at risk of dozing and feeling sleepy** (n=86)	p-value*
General characteristics					
Age, years	57.4 ± 11.6	54.56± 8.2	59.0 ± 12.4	56.1 ± 10.1	**0.015**
Male gender	52.8	58.0	48.2	57.0	0.333
Body Mass Index, kg/m^2	27.4 ± 4.6	26.7 ± 3.7	27.9 ± 5.0	28.2 ± 5.3	0.094
Education, years	13,0 ± 4.0	14.0 ± 4.0	12.0 ± 4.0	14.0 ± 4.0	**0.020**
Smoking history					0.633
Never	41.1	47.7	38.6	36.1	
Past	43.0	34.1	43.6	45.4	
Current	15.9	18.2	17.7	18.6	
Medical disorders					
COPD	16.8	9.1	19.9	17.1	0.159
Asthma	7.6	5.7	10.5	18.6	**0.003**
Hypertension	28.5	21.6	41.8	32.6	**<0.001**
Cardiovascular disease	11.5	5.7	19.6	12.8	**0.002**
Diabetes	3.4	4.6	7.3	7.0	**0.041**
Quality of life (SF-12)					
Mental component score, total score	50.3 ± 9.4	49.3 ± 8.4	45.8 ± 10.2	45.2 ± 10.0	**<0.001**
Physical component score, total score	49.6 ± 9.0	51.2 ± 6.5	44.7 ± 11.4	45.6 ± 9.7	**<0.001**

Data are presented as mean ± standard deviation (continuous variables) or percentages (categorical variables). *p-value from Pearson's chi-square test (categorical variables) and one-way analysis of variance (continuous variables). Significant differences are in **bold** ($p<0.05$). Abbreviations: COPD = chronic obstructive pulmonary disease, SF-12 = Short Form (12) Health Survey.

In unadjusted analysis there was significant difference in reporting asthma, hypertension, cardiovascular disease, diabetes and QoL measures between the sleepiness phenotypes (**Table 5**). After adjusting for age, gender, BMI, smoking status, education and study center, those reporting "feeling sleepy only" were significantly more likely to have a history of hypertension (OR 1.70, CI 1.22-2.36), cardiovascular disease (OR 1.86, CI1.20-2.89) and diabetes (OR 1.96, CI 1.03-3.73) compared to "non-sleepy" subjects (Those "both at risk of dozing and feeling sleepy" more often reported having asthma (OR 2.94, CI 1.60-5.40) compared to the "non-sleepy" phenotype. QoL measurements (both mental and physical components of the SF-12) showed significantly worse QoL among the two phenotypes reporting "feeling sleepy" (with or without risk of dozing) compared to "non-sleepy" subjects (**Table 6**). The phenotype "at risk of dozing only" was similar to the "non sleepy" phenotype in reporting medical disorders and QoL (**Table 6**).

Table 6. Independent associations between medical disorders and quality of life in relation to the sleepiness phenotypes in the general population sample

	Risk of dozing only (n=89)	**Feeling sleepy only** (n=224)	**Both at risk of dozing and feeling sleepy** (n=86)
Medical disorders			
COPD	0.68 (0.31, 1.48)	1.12 (0.73, 1.73)	1.36 (0.71, 2.60)
Asthma	0.83 (0.32, 2.14)	1.28 (0.77, 2.13)	**2.94 (1.60, 5.40)**
Hypertension	0.90 (0.52, 1.56)	**1.70 (1.22, 2.36)**	1.32 (0.80, 2.18)
Cardiovascular disease	0.74 (0.28, 1.93)	**1.86 (1.20, 2.89)**	1.50 (0.72, 3.12)
Diabetes	1.92 (0.65, 5.70)	**1.96 (1.03, 3.73)**	2.03 (0.80, 5.18)
Quality of life (SF-12)			
Mental component score, total score	-0.49 (-2.22, 1.24)	**-3.74 (-4.19, -2.58)**	**-4.14 (-5.89, -2.40)**
Physical component score, total score	0.71 (-1.17, 2.60)	**-3.84 (-5.11, -2.58)**	**-3.95 (-5.85, -2.05)**

Data are presented as adjusted odds ratios (for medical disorders) or beta-coefficients (for quality of life measures) and 95% confidence interval with the "non-sleepy" phenotype as reference. Adjustments are made for age, gender, body mass index, education, smoking history and study-center. Significant differences are in **bold**. Abbreviations: COPD = chronic obstructive pulmonary disease, SF-12 = Short Form (12) Health Survey

4.2.3 Sleep-related symptoms among the sleepiness phenotypes

In unadjusted analysis there was a significant difference in all reported sleep-related symptoms between the sleepiness phenotypes (**Table 7**). In general, those "both at risk of dozing and feeling sleepy" had the highest prevalence of OSA-related symptoms

(reported snoring, nocturnal sweating, nGER and apneas) and higher proportion of a MAP index >0.5 compared to the other sleepiness phenotypes.

Table 7. Prevalence of reported sleep-related symptoms and MAP index >0.5 among the sleepiness phenotypes in the general population cohort.

	Non-sleepy (n=939)	**Risk of dozing only** (n=89)	**Feeling sleepy only** (n=224)	**Both at risk of dozing and feeling sleepy** (n=86)	p-value*
Restless legs syndrome	12.3	14.5	25.0	23.3	**<0.001**
Snoring, ≥3 nights/week	41.6	57.1	51.8	66.2	**<0.001**
Apneas, ≥1 night/week	5.4	13.0	14.3	31.3	**<0.001**
Sweating, ≥3 nights/week	10.5	9.0	18.1	26.8	**<0.001**
nGER, ≥1 night/week	5.6	6.7	13.6	16.3	**<0.001**
Not feeling rested ≥1 day/week	9.5	13.5	28.8	27.9	**<0.001**
Difficulties initiating sleep, ≥3 nights/week	10.8	5.6	30.9	19.1	**<0.001**
Difficulties maintaining sleep, ≥3 nights/week	25.4	28.4	47.8	48.8	**<0.001**
MAP index >0.5	15.8	20.3	25.4	41.7	**<0.001**

Data are presented as percentages. *p-value from Pearson's chi-square test. Significant differences are in **bold** (p<0.05). Abbreviations: nGER = nocturnal gastroesophageal reflux, MAP = multivariable apnea prediction index

In adjusted analysis these associations remained significant (**Table 8**). Interestingly those "both at risk of dozing and feeling sleepy" had the far highest odds of reported apneas with an odds ratio of 7.79 (95% CI 3.71 to 16.4) and having a MAP index >0.5 (OR 13.52, 95% CI 4.30 to 42.55) compared to "non-sleepy" subjects after adjusting for age, gender, BMI, smoking status, education and study center (**Table 8**).

Table 8. Independent association between sleep-related symptoms and MAP index in relation to the sleepiness phenotypes in the general population

	Risk of dozing only (n=89)	**Feeling sleepy only** (n=224)	**Both at risk of dozing and feeling sleepy** (n=86)
Restless legs syndrome	1.23 (0.64-2.37)	**2.37 (1.62-3.46)**	**2.39 (1.37-4.19)**
Snoring, ≥3 nights/week	**1.96 (1.19-3.24)**	**1.55 (1.08-2.21)**	**2.42 (1.39-4.22)**
Apneas, ≥1 night/week	**2.55 (1.14-5.71)**	**3.20(1.77-5.79)**	**7.79 (3.71-16.4)**
Sweating, ≥3 nights/week	0.91 (0.42-1.95)	**1.78 (1.18-2.68)**	**2.97 (1.73-5.12)**
nGER, ≥1 night/week	1.28 (0.53-3.09)	**2.63 (1.62-4.28)**	**3.19 (1.67-6.10)**
Not feeling rested ≥1 day/week	1.50 (0.78-2.88)	**3.82 (2.63-5.53)**	**3.57 (2.11-6.04)**
Difficulties initiating sleep, ≥3 night/week	0.57 (0.22-1.44)	**3.49 (2.42-5.01)**	**2.11 (1.16-3.83)**
Difficulties maintaining sleep, ≥3 night/week	1.52 (0.90-2.58)	**2.62 (1.87-3.68)**	**3.31 (2.03-5.42)**
MAP index >0.5	**5.49 (2.03-14.86)**	**3.44 (1.65-7.18)**	**13.52 (4.30-42.55)**

Data are presented as adjusted odds ratios and 95% confidence interval with the "non-sleepy" phenotype as reference. Adjustments are made for age, gender, body mass index, education, smoking history and study-center. Significant differences are in **bold.** Abbreviations: nGER = nocturnal gastroesophageal reflux, MAP = multivariable apnea prediction index

In contrast, the two phenotypes reporting "feeling sleepy" (with and without risk of dozing) had higher prevalence of RLS, reporting not feeling rested, and insomnia symptoms (difficulties initiating and maintaining sleep) compared to "non sleepy" (**Table 7**). These findings were still significant after adjusting for confounders (**Table 8**). However, when comparing those at "risk of dozing only" to "non-sleepy" subjects, they were more likely to report snoring (OR 1.96, 95% CI 1.19 to 3.24), apneas (OR 2.55, 95%CI 1.14 to 5.71) and having a MAP index >0.5 (OR 5.49, 95% CI 2.03 to 14.86) but were otherwise similar to the "non-sleepy subjects in reporting RLS, nocturnal sweating, nGER, not feeling rested and insomnia symptoms (**Table 8**).

4.2.4 Sensitivity analysis using alternative cut-off values for ESS scores

In paper I, a sensitivity analysis was performed to determine the robustness of the results of the study to changes in the cut-off values for ESS scores. All calculations were re-evaluated using alternative cut-off values of over 8, 9, 11 and 12 for the ESS scores. In general, using different cut-off values had no or only minimal impact on our results.

4.3 Sleepiness in untreated obstructive sleep apnea patients

In paper II, the characteristics and associated conditions and symptoms were explored among the sleepiness phenotypes in OSA patients with untreated moderate-to-severe disease. The aim of paper III was to further validate these findings in a large international population of OSA patients with the same disease severity. In this chapter of the thesis, findings from baseline analysis in paper II and results from paper III are described and compared.

4.3.1 Sleepiness symptoms and distribution of the four sleepiness phenotypes

As expected, reporting sleepiness was more common among subjects in the OSA cohorts (ISAC and SAGIC) than in the general population cohort, both having an ESS score >10 and feeling sleepy ≥3 times per week (**Table 4**). The mean ESS score was 6.1±3.9 among subjects in the general population and 11.7±5.1 and 10.9±5.5 among OSA patients in ISAC and SAGIC respectively. Prevalence and distribution of the two sleepiness components in ISAC (paper II) and SAGIC (paper III) are shown in **Table 4** and **Figure 12**.

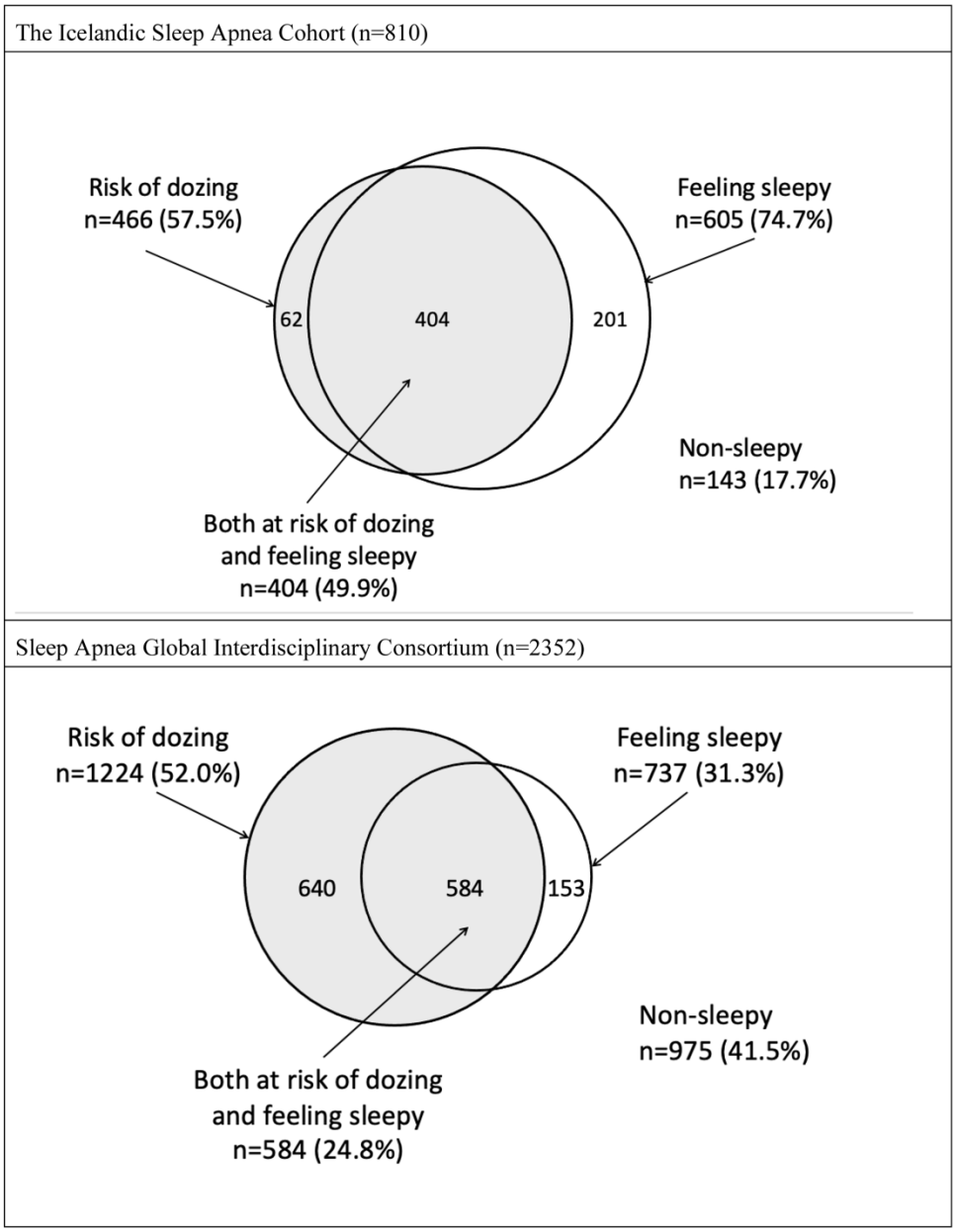

Figure 12. Prevalence and overlap of the sleepiness components in the Icelandic Sleep Apnea Cohort (upper) and the Sleep Apnea Global Interdisciplinary Consortium cohort (lower).Grey circle: subjects at risk of dozing (Epworth sleepiness Scale score >10), white circle: subjects feeling sleepy ≥3 times per week.

Overall, the prevalence of having an ESS score >10 was similar between the two cohorts (57.5% in ISAC and 52.0% in SAGIC). However, subjects in the ISAC reported more often feeling sleepy ≥3 times per week than subjects from the international

SAGIC cohort (74.7% and 31.3% respectively). Because of the difference in reporting feeling sleepy among the two cohorts, the distribution of the sleepiness phenotypes was somewhat different between the two cohorts. Among the Icelandic OSA patients in ISAC (paper II), almost half (49.9%) of the study population were "both at risk of dozing and feeling sleepy" compared to 24.8% in the SAGIC cohort (**Figure 13**). In the ISAC, only 17.7% were non-sleepy compared to 41.5% in the SAGIC cohort.

4.3.2 Ethnic differences in sleepiness phenotypes

The the SAGIC, ethnic differences in reporting sleepiness were explored. The majority of the subjects in the SAGIC cohort used in paper III were Asians (n=1336 (59%)) followed by White (n=657, 29.1%). **Figure 13** shows the association between the sleepiness phenotypes among the largest ethnic groups. White subjects had a higher prevalence of reporting "feeling sleepy" (35.7%) compared to Asian subjects (26.3%). "Risk of dozing" was, however, more common among Asians (53.8%) than White (42.6%).

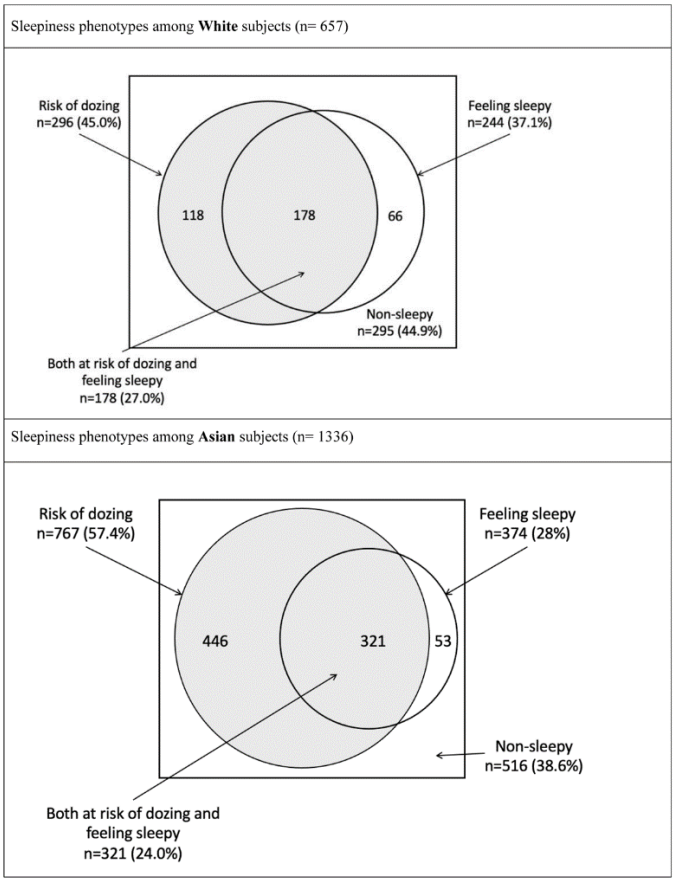

Figure 13. Prevalence and overlap of the sleepiness components among White subjects (upper) and Asian subjects (lower).

4.3.3 Reported symptoms of daytime impairment among the four sleepiness phenotypes

Figure 14 shows how reported symptoms of daytime impairment associate with the four sleepiness phenotypes. Measures of sleep propensity (e.g. falling asleep involuntarily and when relaxed) was more commonly reported among the two phenotypes with "risk of dozing (with or without feeling sleepy)". Feeling tired was however more often reported by the two phenotypes "feeling sleepy" (with or without risk of dozing). Reporting not feeling rested was most common in those "both at risk of dozing and feeling sleepy" and least common in those "non-sleepy". Nevertheless, altogether 50% of the "non-sleepy" subjects reported not feeling rested.

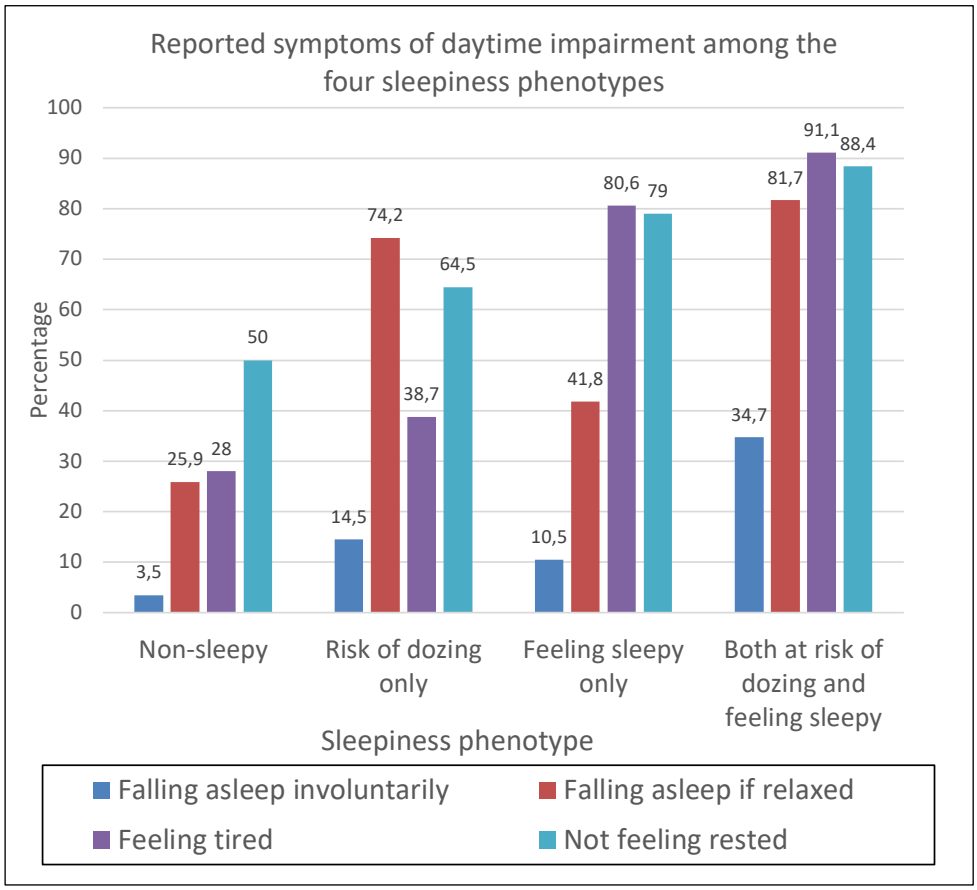

Figure 14. Prevalence of reporting symptoms of daytime impairment ≥3 times per week among the four sleepiness phenotypes in the Icelandic Sleep Apnea Cohort.

Figure 15 shows how the sleepiness phenotypes were distributed among those 146 subjects that reported dozing off at the steering wheel at least once per week. The majority (87%) was identified as having "risk of dozing" (79% were "both at risk of dozing and feeling sleepy" and 8% were at "risk of dozing only"). However, another 11% were "feeling sleepy only" and 2% were identified as "non-sleepy".

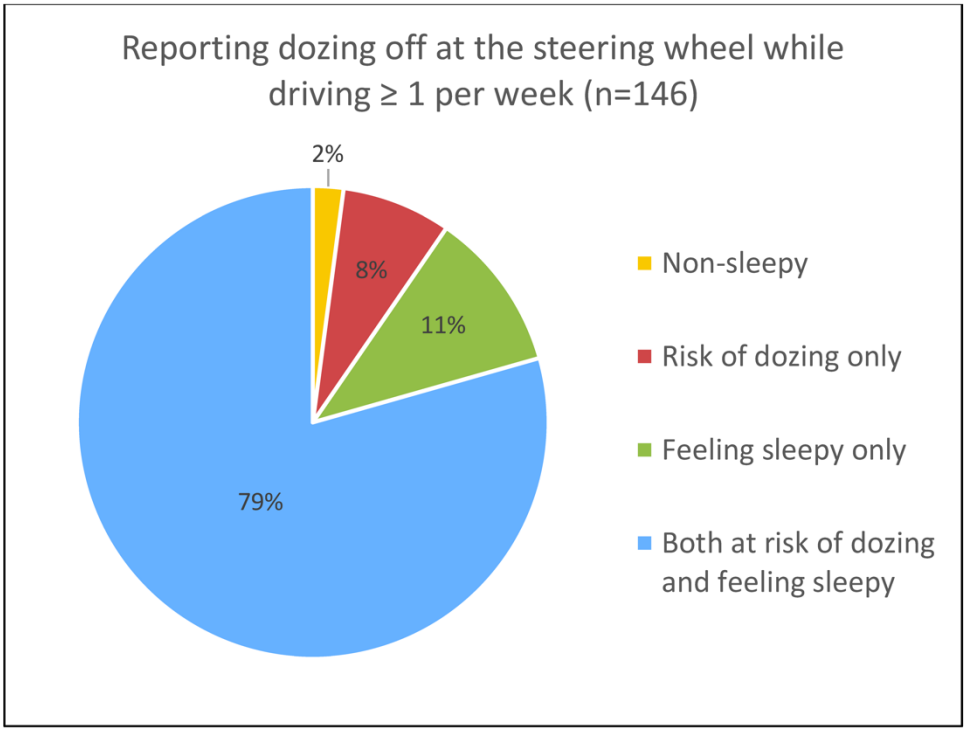

Figure 15. Distribution of the sleepiness phenotypes among those reporting dozing off at the steering wheel while driving more often than once per week. Results from OSA patients with moderate-to-severe disease in the Icelandic Sleep Apnea Cohort.

4.3.4 Sleep-related symptoms, chronotype, insomnia and quality of life among the sleepiness phenotypes

Table 9 shows the prevalence of sleep-related symptoms, chronotype, insomnia symptoms and QoL among the four sleepiness phenotypes in ISAC. RLS was more often reported by the two phenotypes with "risk of dozing" (with and without feeling sleepy) compared to "non-sleepy" and "feeling sleepy only" phenotypes. Symptoms of OSA (reporting snoring, apneas and nocturnal sweating) were most prevalent in those "both at risk of dozing and feeling sleepy" and least common among "non-sleepy" subjects. The two phenotypes "feeling sleepy" (with or without risk of dozing) had more eveningness as indicated by a lower mean Horne-Osteberg score and more often falling into the category of "evening type" and less often being identified as "morning

type". There was also a nominal or significant difference in reporting insomnia symptoms between the four sleepiness phenotypes. Those "feeling sleepy only" had DIS significantly more often and those having "both risk of dozing and feeling sleepy" more often reported having DMS and EMA than "non-sleepy" and "risk of dozing only" phenotypes (**Table 9**).

Table 9. Association of sleep-related symptoms, insomnia, chronotype and quality of life among the sleepiness phenotypes in the Icelandic Sleep Apnea Cohort before treatment (n=810)

Measurement	Non-sleepy (n=143)	Risk of dozing only (n=62)	Feeling sleepy only (n=201)	Both at risk of dozing and feeling sleepy (n=404)	p-value*
Sleep-related symptoms °					
Restless legs syndrome	25.9[b,d]	47.5[a,c]	28.9[b,d]	43.3[a,c]	**<0.001**
Snoring, ≥3 nights/week	90.9[d]	93.3	94.9	97.4[a]	0.016
Apneas, ≥1 night/week	65.7[d]	77.4	74.6[d]	82.0[a,c]	**0.001**
Sweating, ≥3 nights/week	20.3[c,d]	22.6[d]	30.4[a]	37.4[a,b]	**0.001**
nGER, ≥1 night/week	10.5	11.3	15.6	14.7	0.491
Chronotype §					
Horne-Ostberg, total score	58.1 ± 9.2[c,d]	57.9 ± 8.3[c,d]	53.3 ±10.0[a,b]	54.8 ±11.2[a,b]	**<0.001**
Morning type[e]	57.5	49.2	33.9	40.0	**<0.001**
Evening type[f]	5.2	3.3	11.1	14.0	
Neither[g]	37.3	47.5	55.0	46.0	
Insomnia symptoms ¢					
Difficulties initiating sleep, ≥3 nights/week	12.0[c]	9.7[c]	22.4[a,b,d]	14.4[c]	**0.014**
Difficulties maintaining sleep, ≥3 nights/week	46.9[d]	51.6[d]	54.7[d]	65.6[a,b,c]	**<0.001**
Early morning awakening, ≥3 nights/week	21.0[d]	19.4	29.5	31.2[a]	0.045
Quality of life (SF-12)§					
Mental component score, total score	52.5 ± 9.7[c,d]	49.4 ± 10.9	47.5 ± 11.5[a]	47.0 ± 10.7[a]	**<0.001**
Physical component score, total score	42.7 ±10.4[c,d]	42.3 ± 13.1	40.8 ± 10.4[a]	38.7 ± 10.7[a]	**<0.001**

Data are presented as mean ± standard deviation (continuous variables) or percentages (categorical variables).°Bonferroni corrected significance level: p<0.01; §Bonferroni corrected significance level: p<0.025; ¢Bonferroni corrected significance level: p<0.0167; *p-value from Pearson's chi-square test (categorical variables) and one-way analysis of variance (continuous variables). Significant p-values after Bonferroni correction are in **bold.** [a]p <0.05 (significantly different from "non-sleepy"); [b]p<0.05 (significantly different from "risk of dozing only"); [c]p<0.05 (significantly different from "feeling sleepy only"); [d]p<0.05 (significantly different from "both at risk of dozing and feeling sleepy"), [e]Horn-Ostberg score ≥59, [f]Horn-Ostberg score ≤ 41, [g]Horn-Ostberg score 41-59. Abbreviations: nGER = nocturnal gastroesophageal reflux, SF-12 = Short Form (12) Health Survey.

The two phenotypes "feeling sleepy" (with and without risk of dozing) reported significantly worse QoL as measured by the mental and physical component scores of the SF-12 questionnaire compared to the "non-sleepy" phenotype (**Table 9**).

The OSA patients in ISAC were overall more symptomatic than subjects in the international SAGIC cohort (**Figure 16**). Comparing ISAC and SAGIC, the overall prevalence of RLS was 37% vs. 7.1%, snoring 95.4% vs. 84.5%, DMS 58.5% vs. 26.3% and EMA 28.1% vs. 15.4% respectively.

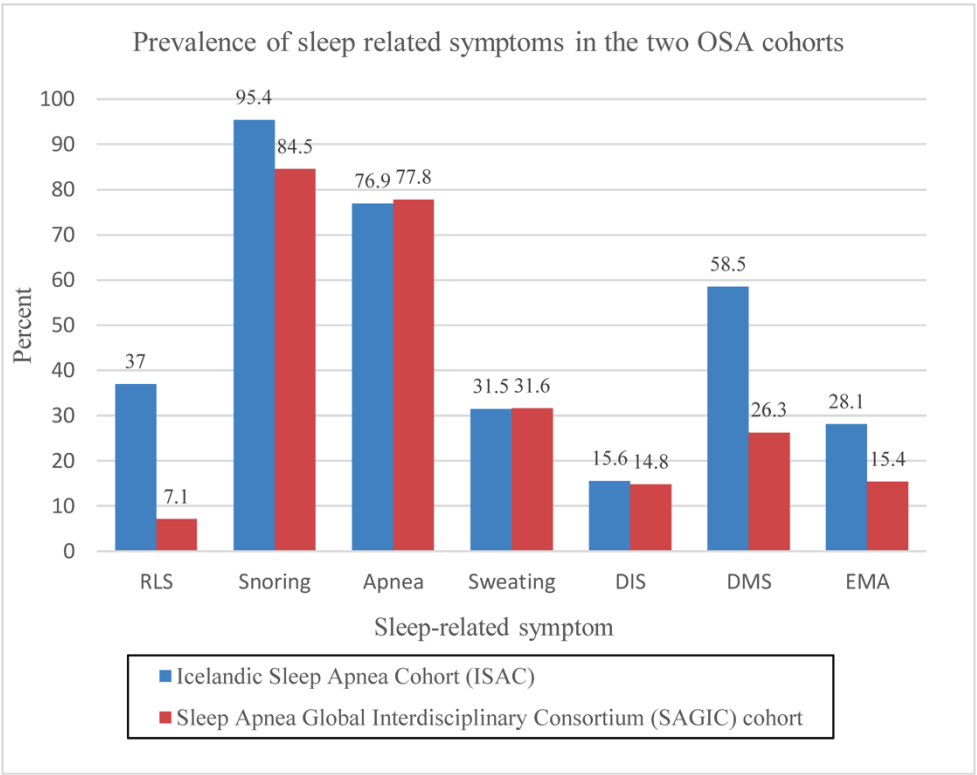

Figure 16. Prevalence of sleep-related symptoms among untreated sleep apnea patients in the Icelandic Sleep Apnea Cohort (ISAC) and the Sleep Apnea Global Interdisciplinary Consortium (SAGIC) cohort.

Table 10 shows the prevalence of sleep-related symptoms, self-reported sleep length, chronotype and insomnia symptoms among the four sleepiness phenotypes in the SAGIC cohort. Although there was a difference in symptom burden between the two OSA cohorts, similar trends were seen in how subjects within the four sleepiness phenotypes reported sleep-related symptoms, chronotype and insomnia symptoms (**Table 10**). Additionally, in the SAGIC cohort, self-reported sleep-length was assessed and nominal difference was observed between the sleepiness phenotypes (p=0.036). Those "feeling sleepy only" estimated that their sleep duration was on average half an

hour shorter (24 minutes) each night than reported by those who were "non-sleepy" (**Table 10**).

Table 10. Association of sleep-related symptoms, chronotype and insomnia symptoms among the sleepiness phenotypes in the Sleep Apnea Global Interdisciplinary Consortium cohort (n=2.352)

Measurement	Non-sleepy (n=975)	Risk of dozing only (n=640)	Feeling sleepy only (n=153)	Both at risk of dozing and feeling sleepy (n=584)	p-value*
Sleep-related symptoms °					
Restless legs syndrome	5.4[c,d]	4.9[c,d]	14.9[a,b]	10.8[a,b]	**<0.001**
Snoring, ≥3 nights/week	78.1[b,d]	89.8[a,c]	78.4[b,d]	90.4[a,c]	**<0.001**
Apneas, ≥1 night/week	72.0[b,d]	80.4[a]	75.4[d]	84.5[a,c]	**<0.001**
Sweating, ≥3 nights/week	22.7[b,c,d]	30.8[a,c,d]	39.5[a,b]	45.4[a,b]	**<0.001**
Self-reported sleep length, hours	6.8 ± 1.2[c,d]	6.7 ± 1.2[c]	6.2 ±1.5[a,b,d]	6.5 ± 1.3[a,c]	0.036
Chronotype					
Definitely a morning type	25.9	23.0	21.4	19.0	**<0.001**
More a morning type than an evening type	34.2	27.5	17.1	25.3	
More an evening than a morning type	29.9	40.0	39.3	38.9	
Definitely an evening type	10.1	9.6	22.1	16.9	
Insomnia symptoms ¢					
Difficulties initiating sleep, ≥3 nights/week	14.0[b,c,d]	9.5[a,c,d]	28.8[a,b,d]	18.7[a,b,c]	**<0.001**
Difficulties maintaining sleep, ≥3 nights/week	20.1[c,d]	20.5[c,d]	43.3[a,b]	39.3[a,b]	**<0.001**
Early morning awakening, ≥3 nights/week	12.6[c,d]	11.1[c,d]	31.1[a,b,d]	20.9[a,b,c]	**<0.001**

Data are presented as mean ± standard deviation (continuous variables) or percentages (categorical variables). °Bonferroni corrected significance level: p<0.01, ¢Bonferroni corrected significance level: p<0.0167; *p-value from Pearson's chi-square test (categorical variables) and one-way analysis of variance (continuous variables). Significant p-values after Bonferroni correction are in **bold**. [a]p <0.05 (significantly different from "non-sleepy"); [b]p<0.05 (significantly different from "risk of dozing only"); [c]p<0.05 (significantly different from "feeling sleepy only"); [d]p<0.05 (significantly different from "both at risk of dozing and feeling sleepy.

4.4 PAP adherence and treatment response in the four sleepiness phenotypes among OSA patients

In the ISAC cohort, subjects were assessed before and after 2 years of treatment. This chapter of the thesis describes results from follow-up in the ISAC cohort.

4.4.1 PAP adherence and alternative treatments at the 2-year follow-up

At the 2-year follow-up, 362 (50.1%) were adherent PAP users and 260 (36.0%) were non-PAP users (**Figure 9**). Another 100 (13.9%) were defined as partial PAP users and were excluded from analysis evaluating treatment effects. As shown in **Table 11**, there was no significant difference in PAP usage and adherence among the four sleepiness phenotypes. When comparing the prevalence of alternative treatments between the phenotypes at the 2-year follow-up, no significant difference was observed for using a mandibular advancement device, having undergone surgery for OSA or having lost >10% of bodyweight at the 2-year follow-up (p>0.117 for all, data not shown).

Table 11. Comparisons of positive airway pressure usage between the four sleepiness phenotypes in the Icelandic Sleep Apnea Cohort

Measurement	Non sleepy	Risk of dozing off	Feeling sleepy	Risk of dozing off and feeling sleepy	p-value*
N (%)	121 (16.8)	57 (7.9)	172 (23.8)	372 (51.5)	-
Any PAP usage, n (%)	70 (57.9)	38 (66.7)	102 (59.3)	252 (67.7)	0.108
PAP usage group, n (%)					
PAP user	55 (45.5)	29 (50.9)	84 (48.8)	194 (52.1)	0.289
Partial PAP user	15 (12.4)	9 (15.8)	18 (10.5)	58 (15.6)	
Non PAP user	51 (42.1)	19 (33.3)	70 (40.7)	120 (32.3)	
Hours of PAP usage					
Mean ± SD	5.9 ± 2.1	5.8 ± 2.0	6.3 ± 2.3	6.1 ± 2.0	0.670
Median (Range)	6.3 (0.0, 9.28)	6.4 (0.5, 9.4)	6.5 (0.0, 10.2)	6.5 (0.0, 10.2)	0.459
Nights PAP used last 28 days					
Mean ± SD	23.3 ± 6.8	23.0 ± 7.6	23.6 ± 7.4	24.4 ± 6.2	0.531
Median (Range)	26.0 (0.0, 28.0)	27.0 (1.0, 28.0)	27.0 (0.0, 28.0)	27.0 (0.0, 28.0)	0.501

*p-value from Pearson's chi-square test (categorical variables), one-way analysis of variance (comparing means) or Kruskal Wallis test (comparing medians). Abbreviations: PAP = positive airway pressure, SD = standard deviation

4.4.2 Impact of PAP adherence on change in symptoms of daytime impairment, insomnia and quality of life at 2-year follow-up

Table 12 shows the difference in the change in symptoms of daytime impairment, insomnia and QoL at the 2-year follow-up between PAP and non-PAP users within and between sleepiness phenotypes, adjusted for gender, baseline age, BMI and AHI. Interaction tests showed a significant or nominal difference between the four sleepiness phenotypes in the effect of PAP on the ESS score (p=0.002), feeling sleepy during the day (p=0.002), falling asleep involuntarily during the day (p<0.0001), falling asleep if relaxed (p=0.012), feeling physically tired (p=0.007) and feeling rested when waking up (p=0.001). Overall, larger benefits of PAP adherence were observed among the two phenotypes with "risk of dozing" (with or without feeling sleepy), compared to smaller or non-significant difference between PAP uses and non-PAP users in the "non-sleepy" and "feeling sleepy only" phenotypes. These differences between phenotypes were not observed on insomnia symptoms or QoL.

The phenotype "both at risk of dozing and feeling sleepy" showed more statistically significant differences between PAP and non-PAP users than other sleepiness phenotypes when examining within-group benefits of PAP adherence (**Table 12**). The phenotype "both at risk of dozing and feeling sleepy" showed improvement of all symptoms of daytime impairment except for dozing off when driving, with moderate to large absolute standardized mean differences (SMDs) ranging from 0.41 to 0.93. Additionally, this phenotype showed improvement of DMS (p=0.0003).

The phenotype at "risk of dozing only" also showed significant improvement of symptoms with PAP, including the largest PAP effect on improvement in the ESS score (adjusted difference in change of ESS score -4.00), falling asleep if relaxed (SMD -0.65, p=0.039), feeling physically tired (SMD -1.16, p<0.0001) and waking up rested (SMD 0.96, p=0.0001).

Subjects reporting "feeling sleepy only" showed less PAP-related improvements than phenotypes with "risk of dozing". Only a nominally significant PAP-related improvement was found in feeling rested when waking up in the morning (SMD 0.40, p=0.021). However, this phenotype reported an increase in reported frequency of EMA associated with PAP usage (SMD 0.38, p=0.027). No other significant PAP-related effects were found on other symptoms among those "feeling sleepy only".

Finally, among the "non-sleepy" phenotype, significant PAP-related improvement was found in the ESS score (adjusted difference in change of ESS score -1.80, p=0.001) and feeling physically tired during the day (SMD -0.47, p=0.023) but no other significant effects of PAP were observed for other measures.

Table 12. Adjusted differences in change in symptom variables between PAP and non PAP users overall and within individual sleepiness phenotype (table continues on next page)

Measurement	Group by PAP user interaction p-value*	Non-sleepy			Risk of dozing off		
		PAP vs. non-PAP user	SMD	p**	PAP vs. non-PAP user	SMD	p**
Sleepiness symptoms ‡							
Epworth sleepiness scale	**0.002**	-1.80 (-2.87, -0.73)	-0.64	**0.001**	-4.00 (-6.99, -1.01)	-0.76	0.010
I feel sleepy during the day	**0.002**	-0.45 (-1.00, 0.10)	-0.33	0.109	-0.68 (-1.59, 0.23)	-0.46	0.140
I fall asleep involuntarily during the day	**<0.001**	0.26 (-0.09, 0.61)	0.30	0.139	-0.66 (-1.43, 0.11)	-0.53	0.092
I fall asleep if I relax (Television)	0.012	-0.30 (-0.72, 0.11)	-0.30	0.154	-0.81 (-1.58, -0.04)	-0.65	**0.039**
I doze off at the steering wheel when driving	0.219	-0.07 (-0.20, 0.07)	-0.19	0.346	-0.33 (-1.05, 0.38)	-0.27	0.348
I take a nap during the day	0.247	-0.10 (-0.46, 0.26)	-0.11	0.595	-0.23 (-1.11, 0.66)	-0.17	0.608
I feel physically tired during the day	0.007	-0.63 (-1.17, -0.09)	-0.47	0.023	-1.77 (-2.62, -0.93)	-1.16	**<0.001**
I feel rested when I wake up	**0.001**	0.38 (-0.23, 0.99)	0.25	0.220	1.31 (0.55, 2.08)	0.96	**0.001**
Insomnia ¢							
Difficulties initiating sleep	0.700	-0.16 (-0.66, 0.34)	-0.13	0.516	0.27 (-0.39, 0.93)	0.28	0.410
Difficulties maintaining sleep	0.805	-0.52 (-1.13, 0.09)	-0.35	0.091	-0.71 (-1.91, 0.49)	-0.39	0.237
Early morning awakening	0.249	0.42 (-0.17, 1.02)	0.29	0.161	-0.28 (-1.08, 0.52)	-0.23	0.486
Quality of life §							
SF-12 mental component	0.915	0.96 (-3.22, 5.14)	0.10	0.649	2.74 (-3.96, 9.44)	0.28	0.412
SF-12 physical component	0.244	3.47 (-0.35, 7.29)	0.38	0.075	1.92 (-2.75, 6.58)	0.28	0.410

Models adjusted for gender, baseline age, body mass index, and apnea–hypopnea index. [a]Estimates presented as SMD in scores and 95% confidence intervals comparing PAP users and non-PAP users. *p value testing for a two-way interaction among sleepy groups, time, and PAP adherence within the linear mixed model, which tests whether differences in symptom response between PAP and non-PAP users differ among sleepiness phenotypes.; **p value comparing PAP users versus non-PAP users within each sleepiness phenotype. Significant p values after Bonferroni correction are in bold. ‡Bonferroni corrected significance level: $p < 0.0063$. ¢Bonferroni corrected significance level: $p < 0.0167$. §Bonferroni corrected significance level: $p < 0.025$. Abbreviations: PAP= positive airway pressure, SF-12 =Short Form (12) Health Survey, SMD= standardised mean difference.

Table 12. Continued

Feeling sleepy			Risk of dozing off and feeling sleepy			Overall		
PAP vs. non-PAP user	SMD	p**	PAP vs. non-PAP user	SMD	p**	PAP vs. non-PAP user	SMD	p**
-0.06 (-1.23, 1.11)	-0.02	0.921	-1.97 (-3.02, -0.91)	-0.41	**<0.001**	-1.89 (-2.65, -1.13)	-0.40	**<0.001**
-0.43 (-0.88, 0.01)	-0.33	0.054	-1.14 (-1.41, -0.87)	-0.87	**<0.001**	-0.84 (-1.08, -0.60)	-0.56	**<0.001**
0.16 (-0.25, 0.56)	0.13	0.444	-0.81 (-1.17, -0.45)	-0.50	**<0.001**	-0.43 (-0.67, -0.20)	-0.30	**0.003**
-0.22 (-0.64, 0.19)	-0.18	0.295	-0.80 (-1.10, -0.50)	-0.57	**<0.001**	-0.60 (-0.80, -0.39)	-0.45	**<0.001**
-0.06 (-0.29, 0.17)	-0.08	0.633	-0.24 (-0.50, 0.02)	-0.22	0.068	-0.21 (-0.37, -0.05)	-0.22	0.010
-0.17 (-0.60, 0.26)	-0.13	0.431	-0.58 (-0.92, -0.25)	-0.41	**<0.001**	-0.40 (-0.62, -0.18)	-0.30	**<0.001**
-0.20 (-0.68, 0.28)	-0.14	0.413	-0.93 (-1.23, -0.63)	-0.67	**<0.001**	-0.77 (-1.00, -0.54)	-0.53	**<0.001**
0.66 (0.10, 1.22)	0.40	0.021	1.41 (1.08, 1.73)	0.93	**<0.001**	1.05 (0.80, 1.30)	0.66	**<0.001**
-0.09 (-0.55, 0.36)	-0.07	0.684	0.06 (-0.21, 0.34)	0.05	0.651	0.01 (-0.19, 0.21)	0.01	0.940
-0.32 (-0.88, 0.23)	-0.20	0.250	-0.56 (-0.93, -0.20)	-0.36	**0.003**	-0.52 (-0.78, -0.26)	-0.32	**<0.001**
0.61 (0.07, 1.16)	0.38	0.027	-0.04 (-0.38, 0.31)	-0.03	0.833	0.21 (-0.03, 0.46)	0.15	0.090
0.85 (-3.04, 4.73)	0.08	0.667	0.19 (-2.65, 3.02)	0.02	0.878	0.81 (-1.09, 2.71)	0.07	0.402
-2.27 (-5.82, 1.28)	-0.23	0.209	0.93 (-1.47, 3.33)	0.10	0.486	0.97 (-0.68, 2.62)	0.10	0.250

4.4.3 Change in sleepiness phenotype among PAP and non-PAP users

At the 2-year follow-up, subjects were reclassified into the four sleepiness phenotypes based on repeated questionnaire answers. **Figure 17** shows the change in sleepiness phenotypes between PAP and non-PAP users from baseline to follow-up. The phenotype "both at risk of dozing and feeling sleepy" was the only phenotype that had significant difference in sleepiness phenotypes distribution between PAP and non-PAP users at the 2-year follow-up ($p<0.001$). Within this phenotype, 54.1% of PAP users became "non-sleepy" at follow-up compared to 19.2% of non-PAP users. Similar trends were seen among other phenotypes, with PAP users being more likely to become "non-sleepy" than non-PAP users at the 2-year follow-up. Among those at "risk of dozing only", 65.5% of PAP users became "non-sleepy" and among the "feeling sleepy only", 55.2% became "non-sleepy" at follow-up. Interestingly, the baseline sleepiness phenotypes were fairly persistent, with the majority of patients who did not become "non-sleepy" typically remaining within the same sleepiness phenotype at the 2-year follow-up.

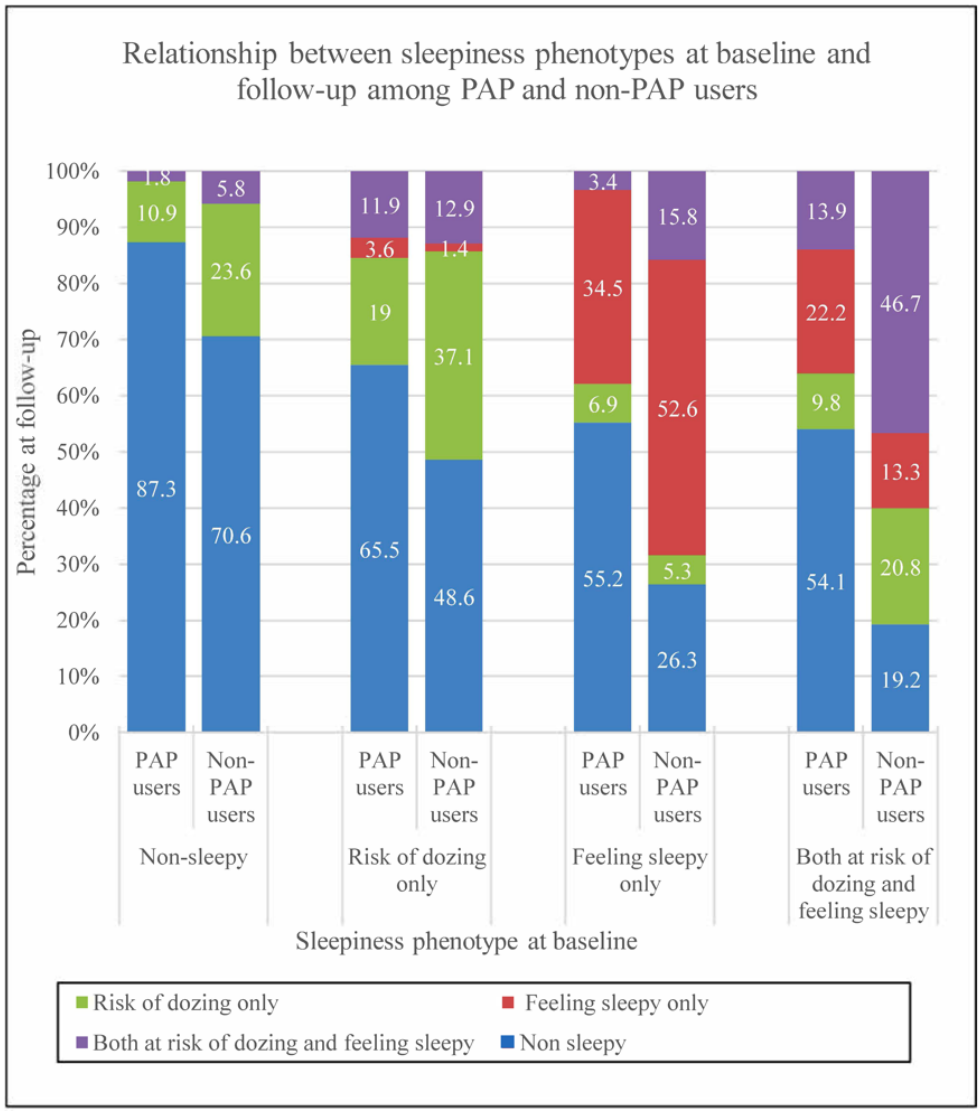

Figure 17. Relationship between baseline and follow-up sleepiness phenotypes among PAP and non-PAP users. *p-values from chi-square test comparing distribution of sleepiness phenotypes at follow-up between PAP and non-PAP users. Abbreviations: PAP = positive airway pressure

4.4.4 Persistent sleepiness with PAP treatment

Of the 362 PAP users, 305 subjects (84.3%) had sleepiness at baseline (i.e. risk of dozing and/or feeling sleepy). Relationships between the sleepiness phenotypes at baseline and follow-up are shown in **Figure 18**.

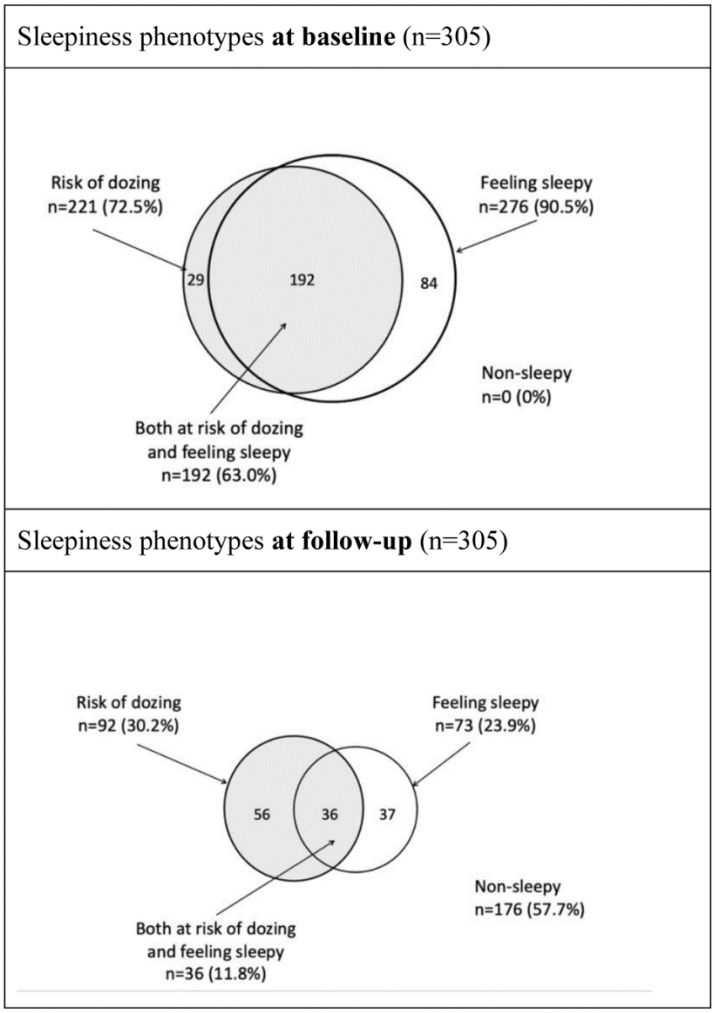

Figure 18. Venn diagrams showing the relationship between the sleepiness phenotypes at baseline (upper) and 2-year follow-up (lower) among PAP-users in the Icelandic Sleep Apnea Cohort

Of the 305 with EDS at baseline, 129 subjects (42.3%) had persistent sleepiness (i.e. were at risk of dozing and/or feeling sleepy at follow-up). In comparison, only 26% met the more traditional residual sleepiness definition of having an ESS score >10 at baseline and follow-up. Although the analysis was restricted to patients defined as being PAP users, those with persistent sleepiness used their PAP machine on average 30 min less per night than those whose sleepiness improved (mean 6.6 ±1.3 vs. 7.1 ±1.1 hours/night respectively; p = 0.0004; **Table 13**).

Table 13. Demographics and characteristics of subjects with persistent sleepiness compared to those whose sleepiness improved at the 2-year follow-up

Measurement	All	Improved sleepiness	Persistent sleepiness	p-value*
Characteristics and habits †				
N (%)	305 (100)	176 (57.7)	129 (42.3)	-
Male gender	81.4	79.0	84.7	0.200
Age, years	57.0 ± 10.7	57.5 ± 10.4	56.3 ± 11.0	0.342
Body mass index, kg/m^2	35.1 ± 5.6	35.7 ± 5.6	34.2 ± 5.6	0.020
Large waist[a]	92.5	92.6	92.2	0.905
Neck circumference, cm	43.5 ± 3.6	44.0 ± 4.2	42.9 ± 3.6	0.023
Smoking history				0.577
Never	25.6	26.9	23.9	
Past	54.7	55.4	53.8	
Current	19.7	17.7	22.3	
Heavy alcohol use	2.6	2.3	3.1	0.683
Current regular exercise	66.6	67.5	65.3	0.702
Medical disorders and medication use ‡				
Hypertension	49.0	51.7	45.4	0.274
Cardiovascular disease	16.9	14.8	19.8	0.241
Type 2 diabetes	12.5	9.8	16.2	0.096
Metabolic syndrome	74.7	75.4	73.6	0.724
Hypothyroidism	6.9	8.0	5.4	0.372
Obstructive lung disease	16.9	18.2	15.3	0.501
Use of antidepressant	19.6	18.8	20.8	0.660
Use of hypnotics	11.8	13.1	10.0	0.410
Use of anti-hypertensives	57.2	59.1	55.4	0.517
PAP use				
Hours of PAP use per night	6.9 ± 1.2	7.1 ± 1.1	6.6 ± 1.3	**0.004**
Sleep-related symptoms °				
Restless legs syndrome	21.8	18.2	26.7	0.073
Snoring, ≥3 nights/week	19.7	12.0	30.8	**<0.001**
Apneas, ≥1 night/week	19.7	12.7	29.0	**<0.001**
Sweating, ≥3 nights/week	12.7	8.0	19.2	**0.004**
nGER, ≥1 night/week	4.3	3.4	5.4	0.403
Chronotype §				
Horne-Ostberg, total score	58.1 ± 10.4	59.1 ± 9.4	56.8 ± 11.6	0.071
Morning type[b]	55.3	58.6	50.8	0.125
Evening type[c]	7.2	4.7	10.5	
Neither[d]	37.5	36.7	38.7	
Insomnia symptoms ¢				
Difficulties initiating sleep, ≥3 nights/week	7.8	8.0	7.6	0.917
Difficulties maintaining sleep, ≥3 nights/week	29.4	22.2	39.2	**0.001**
Early morning awakening, ≥3 nights/week	20.3	14.8	27.7	**0.005**
Quality of life (SF-12)§				
Mental component score, total score	51.2 ± 10.2	52.1 ± 9.7	50.0 ± 10.9	0.079
Physical component score, total score	43.3 ± 11.4	44.4 ± 11.5	41.7 ± 11.1	0.040

Data are presented as mean ± standard deviation (continuous variables) or percentages (categorical variables) unless otherwise stated. †Bonferroni corrected significance level: p<0.0063; ‡Bonferroni corrected significance level: p<0.0056; °Bonferroni corrected significance level: p<0.01; §Bonferroni corrected significance level: p<0.025; ¢Bonferroni corrected significance level: p<0.0167; *p-value from chi-square test (categorical variables) and T-test (continuous variables). [a]waist circumference ≥102cm in males, ≥88cm in females; [db]Horn-Ostberg score ≥59; [c]Horn-Ostberg score ≤ 41; [d]Horn-Ostberg score 41-59. Abbreviations: PAP = positive airway pressure, nGER = nocturnal gastro-esophageal reflux, SF-12 = Short Form (12) Health Survey.

Subjects with persistent sleepiness and whose sleepiness improved had similar characteristics and habits and did not differ in reporting medical disorders and medication use at the 2-year follow-up (**Table 13**). Although both groups had severe OSA on average, those with persistent sleepiness had significantly less severe OSA at baseline compared to those whose sleepiness improved, both AHI (mean 45.2 ±18.8 versus 53.5 ±22.6 respectively, p<0.001), ODI (mean 35.5 ±18.7 versus 45.3 ±23.0 respectively, p<0.001), minimum SpO_2 (mean 76.6 ±7.1 versus 73.2 ±9.0 respectively, p<0.001) and TST90 (mean 13.2 ±17.3 versus 21.8 ±22.5, p<0.001). At the 2-year follow-up, reporting snoring, apneas and nocturnal sweating was significantly more frequent among those with persistent sleepiness and they more often reported DMS (22.2% for improved sleepiness vs. 39.2% persistent sleepiness, p=0.001) and EMA (14.8% for improved sleepiness, 27.7% for those with persistent sleepiness, p=0.005) at the 2-year follow-up (**Table 13**). At baseline, physical (p=0.133) and mental (p=0.096) QoL was similar between those with and without persistent sleepiness but at follow-up there was a nominal difference in QoL, with a lower physical component score among those with persistent sleepiness compared to those whose sleepiness improved (41.7 ±11.1 vs. 44.4 ±11.5, p=0.040; **Table 13**).

4.5 PSG characteristics of the sleepiness phenotypes in obstructive sleep apnea

The PSG characteristics of the sleepiness phenotypes in the large, multicenter SAGIC cohort, including patients with mild-to-severe disease, were investigated in paper IV, and are described in this chapter of the thesis.

4.5.1 Measures of hypoxemia

The participants in SAGIC included in paper IV had moderate-to-severe OSA on average, with a mean AHI of 31.9±26.4 and a median AHI of 22.4 (IQR 12.0-44.1). As shown in **Table 14**, there were significant differences between the sleepiness phenotypes in OSA severity (AHI) and all assessed markers of hypoxemia, including ODI, average SpO2, minimum SpO2, TST90 and hypoxic burden.

Table 14. Unadjusted analysis comparing polysomnographic parameters between the sleepiness phenotypes.

Characteristic	Data (n)	Overall	Sleepiness phenotypes				p-value*
			Non sleepy	Risk of dozing only	Feeling sleepy only	Both risk of dozing and feeling sleepy	
Measures of hypoxia							
AHI, h^{-1}	2097	31.9 ± 26.4	30.2 ± 24.2	32.3 ± 25.9	29.0 ± 26.5	36.0 ± 30.4	**0.004**†
ODI, h^{-1}	2036	30.2 ± 29.1	28.3 ± 26.9	32.0 ± 31.9	26.0 ± 29.2	34.4 ± 30.4	**<0.001**†
Average SpO_2, %	1922	92.9 ± 3.2	93.2 ± 2.9	92.8 ± 3.1	93.1 ± 3.1	92.3 ± 3.8	**<0.001**
Minimum SpO2, %	1977	79.0 ± 8.9	79.9 ± 8.5	78.1 ± 8.9	80.1 ± 8.3	77.5 ± 9.8	**<0.001**
TST90, %	1936	11.7 ± 18.8	10.2 ± 16.9	13.1 ± 19.5	8.5 ± 15.5	14.9 ± 22.2	**<0.001**†
Hypoxic Burden, %min/h	933	110.3 ± 137.0	112.3 ± 137.0	103.5 ± 124.7	66.7 ± 81.2	126.1 ± 157.0	**0.007**†
Sleep stages, %							
Wake	802	22.8 ± 14.7	24.8 ± 15.2	20.7 ± 13.6	23.8 ± 15.5	19.5 ± 13.6	**<0.001**†
NREM Stage N1	802	17.1 ± 9.9	17.1 ± 9.8	17.8 ± 9.5	16.3 ± 9.2	16.6 ± 10.7	0.516†
NREM Stage N2	802	42.2 ± 12.2	41.5 ± 11.9	43.0 ± 12.4	41.1 ± 11.1	43.4 ± 12.8	0.215
NREM Stage N3	802	6.1 ± 7.2	5.5 ± 6.3	6.0 ± 6.8	7.2 ± 8.7	7.4 ± 8.9	0.276†
REM	802	8.8 ± 6.9	8.3 ± 6.8	9.0 ± 6.3	7.9 ± 8.2	10.2 ± 7.1	**0.012**†
Arousals and limb movements							
Sleep latency, min	1593	20.7 ± 31.3	22.9 ± 36.0	18.7 ± 28.3	20.5 ± 23.7	17.5 ± 23.3	**0.003**†
WASO, min	1480	82.4 ± 59.3	86.0 ± 59.6	86.0 ± 63.0	85.9 ± 58.7	69.9 ± 53.7	**<0.001**†
Arousal Index, h^{-1}	1554	34.4 ± 24.8	33.5 ± 22.5	34.8 ± 27.6	33.7 ± 24.7	36.5 ± 27.2	0.554†
Arousal intensity, 1-9	796	3.2 ± 0.6	3.2 ± 0.5	3.2 ± 0.6	3.1 ± 0.6	3.3 ± 0.7	**0.030**†
HR response to arousals, beats/min	693	2.8 ± 1.3	2.7 ± 1.3	2.7 ± 1.2	2.6 ± 1.4	2.9 ± 1.3	0.106
PLMI, h^{-1}	802	15.8 ± 22.0	15.3 ± 21.5	17.6 ± 20.5	20.2 ± 29.3	14.0 ± 21.7	0.063†
Odds ratio product							
Avg. ORP	802	1.27 ± 0.31	1.31 ± 0.31	1.25 ± 0.29	1.28 ± 0.35	1.22 ± 0.31	**0.017**
Avg. Wake ORP	801	2.11 ± 0.14	2.13 ± 0.14	2.11 ± 0.15	2.10 ± 0.14	2.10 ± 0.15	0.092
Avg. NREM ORP	802	0.98 ± 0.26	0.99 ± 0.26	0.97 ± 0.24	0.99 ± 0.31	0.97 ± 0.27	0.778
Avg. REM ORP	688	1.30 ± 0.31	1.33 ± 0.32	1.30 ± 0.26	1.21 ± 0.34	1.28 ± 0.30	0.088
Avg. ORP-9	794	1.19 ± 0.29	1.22 ± 0.29	1.17 ± 0.26	1.21 ± 0.32	1.16 ± 0.29	0.066
Right/Left ORP Correlation	695	0.83 ± 0.10	0.84 ± 0.09	0.82 ± 0.10	0.83 ± 0.08	0.80 ± 0.11	**<0.001**

Data are presented as mean ± standard deviation; *p-values from one-way analysis of variance (ANOVA) comparing mean values between sleepiness phenotypes, †p values from ANOVA comparing log or square root transformed values between sleepiness phenotypes. Abbreviations: OSA = Obstructive Sleep Apnea, AHI = Apnea Hypopnea Index, ODI = Oxygen Desaturation Index, SpO2 = Oxygen Saturation, TST90 = Total Sleep Time Spend Under 90% SpO_2., NREM = Non-Rapid Eye Movement; REM = Rapid Eye Movement, WASO = Wake After Sleep Onset; HR = Heart Rate, PLMI = Periodic Limb Movement Index, ORP = Odds Ratio Product, ORP-9 = ORP in the immediate 9 seconds after arousal, min = Minute, h = Hour.

After adjusting for age, gender, BMI and ethnicity, these differences were still significant (**Table 15**).

Table 15. Adjusted* analysis comparing parameters related to hypoxemia between sleepiness phenotypes.

Sleep Study Metric	Non sleepy (n=1001)	Risk of dozing only (n=422)	Feeling sleepy only (n=190)	Both at risk of dozing and feeling sleepy (n=484)	P†
AHI, h^{-1}	30.2 (28.7, 31.7)[d]	31.8 (29.5, 34.1)[d]	30.7 (27.3, 34.2)[d]	35.8 (33.6, 37.9)[a,b,c]	**0.002**‡
ODI, h^{-1}	28.3 (26.6, 29.9)[b,d]	31.2 (28.7, 33.8)[a,c]	28.5 (24.6, 32.3)[b,d]	34.1 (31.8, 36.5)[a,c]	**<0.001** ‡
Average SpO_2, %	93.2 (93.0, 93.4)[b,d]	92.7 (92.4, 93.0)[a]	93.1 (92.6, 93.5)[d]	92.4 (92.1, 92.6)[a,c]	**<0.001**
Minimum SpO2, %	79.9 (79.4, 80.5)[b,d]	78.2 (77.4, 79.0)[a,c]	79.7 (78.5, 80.9)[b,d]	77.5 (76.8, 78.3)[a,c]	**<0.001**
TST90, %	10.2 (9.1, 11.4)[b,d]	12.9 (11.2, 14.7)[a,c]	9.3 (6.6, 12.0)[b,d]	14.7 (13.1, 16.4)[a,c]	**<0.001**
Hypoxic Burden, %min/h	106.5 (95.3, 117.7)[c]	107.0 (88.7, 125.3)[c]	77.0 (49.6, 104.4)[a,b,d]	129.2 (113.1, 145.3)[c]	**0.014**‡

*Adjusted for age, gender, body mass index and ethnicity; Data presented as means (95% confidence intervals), with p-values statistically significant after Hochberg step-up correction shown in **bold**; †Adjusted p-value from ANOVA comparing mean values between the sleepiness phenotypes, controlling for age, gender, body mass index and ethnicity, ‡p values using log or square root transformed values; [a]p <0.05 (significantly different from "non-sleepy"); [b]p<0.05 (significantly different from "risk of dozing only"); [c]p<0.05 (significantly different from "feeling sleepy only");[d]p<0.05 (significantly different from "both at risk of dozing and feeling sleepy"); Abbreviations: AHI = Apnea Hypopnea Index, ODI = Oxygen Desaturation Index, SpO2 = Oxygen Saturation, TST90 = Total Sleep Time Spend Under 90% SpO_2, min = Minute, h = Hour.

Figure 19 shows the distribution of OSA severity as defined by traditional AHI cut-offs among the sleepiness phenotypes. The phenotype "both at risk of dozing and feeling sleepy" had the highest proportion of subjects with severe OSA (AHI≥30 events/h) and those "feeling sleepy only" had the lowest.

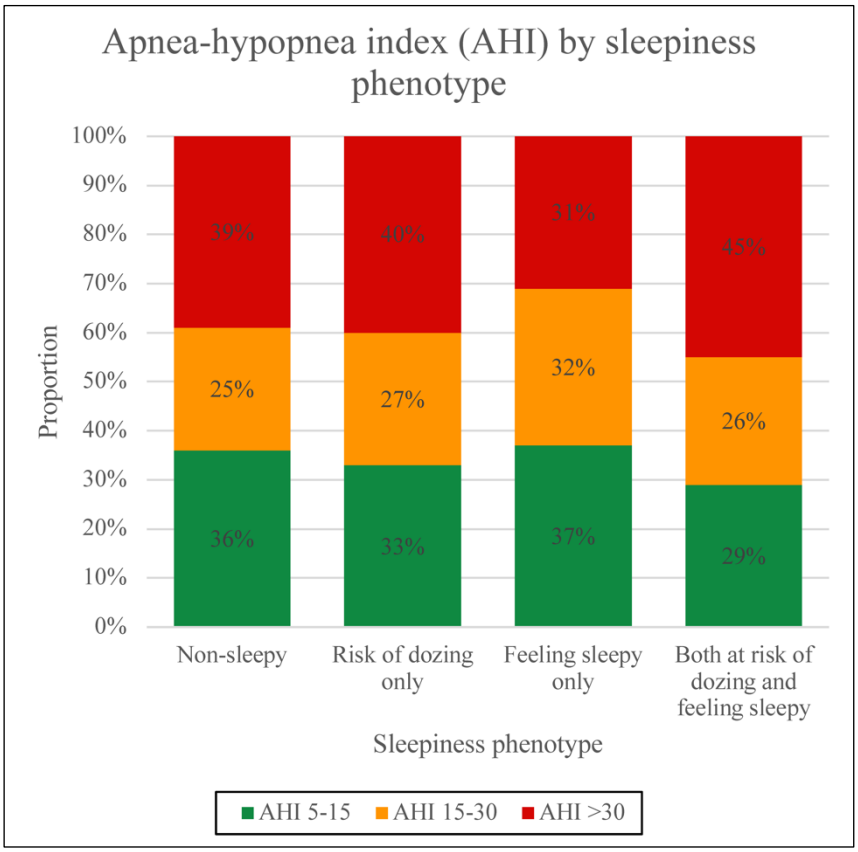

Figure 19. Association between Apnea-Hypopnea Index (AHI) categories and sleepiness phenotypes.

The two phenotypes with "risk of dozing" had more severe ODI, average and minimum SpO2 and TST90 than those who were "non-sleepy" and "feeling sleepy only" (**Table 15**). Hypoxic burden was significantly lower in those "feeling sleepy only" compared to other phenotypes (**Table 15**). While statistically significant, eta-squared values were all near 0.01 (ranged from 0.0009 to 0.015) for the hypoxic variables indicating that the sleepiness phenotypes had overall a small effect on the variance of these variables (**Table 16**). Cohen's d estimates showed that the largest differences were seen between the phenotypes "feeling sleepy only" and "both at risk of dozing and feeling sleepy" with estimates ranging from 0.21 to 0.42 suggesting small-to-medium effects (**Table 16**).

Table 16. Calculated effect sizes of the relationship between the polysomnographic variables and sleepiness phenotypes overall (eta-squared) and between each pair of sleepiness phenotypes (Cohen's d)

	Cohen's d‡						Eta-squared §
	Non vs. RD	**Non vs. FS**	**Non vs. FD**	**RD vs. FS**	**RD vs. FD**	**FS vs. FD**	
Measures of hypoxia							
AHI, h^{-1}	-0.083	0.050	-0.221	0.126	-0.133	-0.240	0.009
ODI, h^{-1}	-0.133	0.084	-0.219	0.195	-0.076	-0.281	0.009
Average SpO_2, %	0.138	0.034	0.268	-0.100	0.130	0.212	0.013
Minimum SpO2, %	0.217	-0.022	0.274	-0.235	0.062	0.281	0.015
TST90, %	-0.160	0.103	-0.248	0.248	-0.087	-0.311	0.013
Hypoxic Burden, %min/h	0.066	0.349	-0.096	0.325	-0.157	-0.419	0.013
Sleep stages							
Wake, min	0.305	0.089	0.360	-0.231	0.060	0.289	0.016
Wake, %	0.281	0.067	0.363	-0.221	0.089	0.307	0.015
ORP metric							
2.25 - 2.50	0.193	0.103	0.316	-0.091	0.130	0.226	0.010

‡Effect size calculated as Cohen's d quantifying standardized mean difference between each pair of sleepiness phenotypes (0.2=small effect, 0.5=medium effect, 0.8=large effect), §Effect size among sleepiness phenotypes calculated as eta-squared (0.01=small effect, 0.06=medium effect, 0.14=large effect). Abbreviations: Non = "Non-sleepy" phenotype, RD = "Risk of dozing only" phenotype, FS = "Feeling sleepy only" phenotype, FD = "Both at risk of dozing and feeling sleepy" phenotype, OSA = Obstructive Sleep Apnea, AHI = Apnea Hypopnea Index, ODI = Oxygen Desaturation Index, SpO2 = Oxygen Saturation, TST90 = Total Sleep Time Spend Under 90% SpO_2., ORP = Odds Ratio Product, min = Minute, h = Hour.

4.5.2 Sleep stages, sleep latency, WASO, arousals, and periodic limb movement index

The "non-sleepy" phenotype spent on average more time awake and had a longer sleep latency compared to the two phenotypes with "risk of dozing" (**Table 14**). This difference was still significant for total wake (in minutes and percentage of total recording time) after adjusting for age, gender, BMI and ethnicity (**Table 17**).

Table 17. Adjusted* analysis comparing sleep stages, sleep latency, arousals and limb movements between sleepiness phenotypes

Sleep Study Metric	Non sleepy	Risk of dozing only	Feeling sleepy only	Both at risk of dozing and feeling sleepy	p†
Sleep stage, min					
Wake	107.0 (101.1, 112.9)[b,d]	91.5 (8179, 101.2)[a]	100.4 (84.3, 116.5)	89.9 (80.9, 98.9)[a]	**0.002**‡
NREM Stage N1	71.7 (67.8, 75.6)	76.5 (70.0, 83.0)	73.9 (63.2, 84.5)	72.4 (66.5, 78.3)	0.308‡
NREM Stage N2	180.4 (175.1, 185.6)	182.0 (173.3, 190.8)	180.4 (166.0, 194.8)	184.1 (176.1, 192.1)	0.895
NREM Stage N3	25.4 (22.6, 28.1)	25.4 (20.9, 29.9)	28.9 (21.4, 36.3)	28.9 (24.7, 33.1)	0.812‡
REM	36.6 (33.7, 39.4)	37.7 (32.9, 42.4)	35.4 (27.6, 43.2)	42.5 (38.1, 46.8)	0.174‡
Sleep stage, %					
Wake	24.2 (22.9, 25.5)[b,d]	21.0 (18.8, 23.1)[a]	23.4 (19.9, 27.0)	20.7 (18.8, 22.7)[a]	**0.003**‡
NREM Stage N1	16.7 (15.8, 17.6)	17.9 (16.5, 19.4)	17.2 (14.8, 19.6)	16.9 (15.6, 18.3)	0.399‡
NREM Stage N2	41.9 (40.8, 43.0)	42.4 (40.5, 44.3)	41.5 (38.4, 44.5)	42.9 (41.2, 44.6)	0.737
NREM Stage N3	5.9 (5.3, 6.5)	6.1 (5.0, 7.1)	6.5 (4.8, 8.2)	6.6 (5.6, 7.6)	0.872‡
REM	8.5 (7.8, 9.1)	8.7 (7.7, 9.8)	8.2 (6.4, 9.9)	9.9 (8.9, 10.9)	0.107‡
Sleep latency, arousals and limb movements					
Sleep latency, minutes	22.8 (20.7, 25.0)[b,d]	19.8 (16.4, 23.3)[a]	19.2 (13.8, 24.6)	16.8 (13.5, 20.0)[a]	0.006‡
WASO, minutes	83.6 (79.6, 87.5)[d]	83.4 (77.0, 89.8)[c]	94.7 (84.7, 104.8)[b,d]	75.7 (69.7, 81.7)[a,c]	0.017‡
Arousal Index, h^{-1}	33.2 (31.6, 34.9)	34.7 (32.0, 37.4)	34.1 (29.9, 38.3)	36.6 (34.1, 39.2)	0.768‡
Arousal intensity, 1-9	3.21 (3.15, 3.26)	3.25 (3.16, 3.34)	3.08 (2.94, 3.23)	3.28 (3.20, 3.36)	0.134‡
HR response to arousals, beats/min	2.74 (2.62, 2.87)	2.67 (2.46, 3.11)	2.76 (2.41, 3.11)	2.91 (2.72, 3.10)	0.195‡
PLMI, h^{-1}	14.8 (12.8, 16.8)	17.2 (13.8, 20.6)	21.5 (16.0, 27.1)	14.9 (11.8, 18.0)	0.095‡

*Adjusted for age, sex, body mass index and ethnicity; Data presented as means (95% confidence intervals), with p-values statistically significant after Hochberg step-up correction shown in **bold**; †Adjusted p-value from ANOVA comparing mean values between the sleepiness phenotypes, controlling for age, sex, BMI and ethnicity, ‡p values using log-or square root transformed values, [a]p <0.05 (significantly different from non-sleepy); [b]p<0.05 (significantly different from risk of dozing); [c]p<0.05 (significantly different from feeling sleepy);[d]p<0.05 (significantly different from the group both at risk of dozing and feeling sleepy). Abbreviations: NREM = Non-Rapid Eye Movement, REM = Rapid Eye Movement, WASO = Wake After Sleep Onset, HR = Heart Rate, PLMI = Periodic Limb Movement Index.

Eta-squared values indicated that the sleepiness phenotypes had overall a small effect on the variance of wake time (both minutes and percentages) with values ranging from 0.008-0.016 (**Table 16**). Calculated Cohen's d comparing "non-sleepy" to those "both at risk of dozing and feeling sleepy" was 0.36 for both min and percentage of wake indicating small-to-medium effects. In unadjusted analysis (**Table 14**) the phenotype "both at risk of dozing and feeling sleepy" had the longest average time in REM and highest arousal intensity of the four sleepiness phenotypes but these differences were not significant after adjusting for confounders (**Table 16**). No significant differences were found in NREM sleep stages, arousal index, HR response to arousals or PLMI between the sleepiness phenotypes (**Table 14** and **Table 16**).

4.5.3 ORP characteristics

There was a significant difference between the sleepiness phenotypes in average ORP, where "non-sleepy" had the highest average ORP and Right/Left ORP correlation and those "both at risk of dozing and feeling sleepy" had the lowest (**Table 14**). **Table 18** shows average adjusted ORP characteristics of the sleepiness phenotypes. Overall, no significant differences were found between ORP metrics after adjusting for confounders except that the "non-sleepy" phenotype spent more time fully awake than the two phenotypes with "risk of dozing" as indicated by a higher proportion of epochs within the ORP in the ranges 2.25 to 2.50. As for other PSG measures, calculated eta-squared indicated that the effect of the sleepiness phenotypes on the proportion of ORP values in the range of 2.25-2.50 was small (eta-squared = 0.010). The largest difference were seen between "non-sleepy" and "both at risk of dozing and feeling sleepy" with a Cohen's d of 0.316 indicating small-to-medium effects (**Table 16**).

Table 18. Adjusted* analysis comparing odds ratio product parameters between sleepiness phenotypes.

ORP Metric	Non sleepy	Risk of dozing only	Feeling sleepy only	Both risk of dozing and feeling sleepy	p†
Avg. ORP	1.30 (1.27, 1.33)	1.25 (1.21, 1.30)	1.27 (1.19, 1.34)	1.24 (1.20, 1.28)	0.113
Avg. Wake ORP	2.13 (2.11, 2.14)	2.11 (2.09, 2.14)	2.09 (2.06, 2.12)	2.10 (2.08, 2.12)	0.068
Avg. NREM ORP	0.99 (0.96, 1.01)	0.97 (0.93, 1.01)	0.98 (0.92, 1.05)	0.97 (0.93, 1.01)	0.902
Avg. REM ORP	1.32 (1.29, 1.35)	1.28 (1.23, 1.33)	1.22 (1.13, 1.32)	1.30 (1.25, 1.34)	0.220
Avg. ORP-9	1.22 (1.19, 1.25)	1.17 (1.12, 1.21)	1.20 (1.13, 1.27)	1.16 (1.12, 1.21)	0.094
Right/Left ORP Correlation	0.84 (0.83, 0.85)[h]	0.82 (0.81, 0.84)	0.83 (0.81, 0.86)	0.81 (0.80, 0.83)[e]	0.017
ORP type, n (%)					
Type 1,1	42 (10.1)	23 (15.2)	6 (10.9)	21 (11.7)	0.147¥
Type 1,2	81 (19.4)	30 (20.0)	11 (20.0)	36 (20.1)	
Type 1,3	103 (24.7)	32 (21.2)	11 (20.0)	31 (17.3)	
Type 2,1	37 (8.9)	13 (8.6)	8 (14.6)	24 (13.4)	
Type 2,2	55 (13.2)	26 (17.2)	6 (10.9)	33 (18.4)	
Type 2,3	51 (12.2)	10 (6.6)	5 (9.1)	13 (7.3)	
Type 3,1	25 (6.0)	12 (8.0)	5 (9.1)	18 (10.1)	
Type 3,2	20 (4.8)	4 (2.7)	3 (5.5)	3 (1.7)	
Type 3,3	3 (0.7)	1 (0.7)	0 (0.0)	0 (0.0)	
ORP Distribution (% epochs)					
0.00 - 0.25	1.59 (1.35, 1.84)	1.31 (0.99, 1.64)	1.77 (1.09, 2.46)	1.58 (1.23, 1.92)	0.917
0.25 - 0.50	7.50 (6.94, 8.06)	6.58 (5.84, 7.33)	8.01 (6.44, 9.57)	7.49 (6.70, 8.28)	0.695
0.50 - 0.75	11.21 (10.69, 11.72)	10.85 (10.17, 11.53)	11.25 (9.82, 12.68)	11.09 (10.37, 11.82)	0.403
0.75 - 1.00	12.51 (12.08, 12.94)[f]	13.07 (12.50, 13.64)[e]	12.13 (10.93, 13.33)	12.77 (12.17, 13.37)	0.037
1.00 - 1.25	12.82 (12.45, 13.19)	13.66 (13.18, 14.15)	12.09 (11.07, 13.11)	13.55 (13.03, 14.06)	0.149‡
1.25 - 1.50	12.44 (12.08, 12.81)	13.41 (12.92, 13.90)	11.79 (10.76, 12.81)	13.12 (12.61, 13.64)	0.366‡
1.50 - 1.75	11.07 (10.68, 11.45)	11.98 (11.47, 12.49)	10.96 (9.89, 12.03)	11.56 (11.02, 12.10)	0.802‡
1.75 - 2.00	9.56 (9.18, 9.95)	9.97 (9.46, 10.49)	10.05 (8.97, 11.13)	9.88 (9.33, 10.42)	0.087‡
2.00 - 2.25	9.25 (8.83, 9.66)[f]	8.95 (8.40, 9.50)[e]	9.95 (8.79, 11.10)	8.93 (8.34, 9.51)	0.044‡
2.25 - 2.50	12.05 (11.34, 12.75)[f,h]	10.21 (9.26, 11.15)[e]	12.00 (10.03, 13.98)	10.03 (9.04, 11.03)[e]	**0.002**‡

*Adjusted for age, sex, body mass index and ethnicity; Data presented as means (95% confidence intervals) or number and percentages (for ORP types), with p-values statistically significant after Hochberg step-up correction shown in **bold**, †Adjusted p-value from ANOVA comparing mean values between the sleepiness phenotypes, controlling for age, sex, body mass index and ethnicity, ‡p values using log or square root transformed values, ¥p-value from Person's chi-square test, [a]p <0.05 (significantly different from "non-sleepy"); [b]p<0.05 (significantly different from "risk of dozing"); [c]p<0.05 (significantly different from "feeling sleepy");[d]p<0.05 (significantly different from the group "both at risk of dozing and feeling sleepy"). Type 1,1 = Little deep sleep (DS)-Little full wakefulness (FW), Type 1,2 = Little DS-Average FW, Type 1,3 = Little DS-Much FW, Type 2,1 = Average DS-Little FW, Type 2,2 = Average DS-Average FW, Type 2,3 = Average DS-much FW, Type 3,1 = Much DS-Little FW, Type 3,2 = Much DS-Average FW, Type 3,3 = Much DS-Much FW. Abbreviations: ORP = Odds Ratio Product; NREM = Non Rapid Eye Movement; REM = Rapid Eye Movement.

4.5.4 Sensitivity analysis

A sensitivity analysis was performed for all PSG characteristics in a restricted sample of patients with at least moderate OSA (AHI ≥15 events/h, n=1372). Overall, results for hypoxic variables were unchanged, with the two phenotypes with "risk of dozing"

having significantly worse hypoxemia than "non-sleepy" and "feeling sleepy only", except results did not reach significance for AHI (p=0.089) (data not shown). Among those with an AHI≥15 events/h, there was a significant difference in WASO between sleepiness phenotypes where those "feeling sleepy only" had the highest WASO (mean 100.7 minutes (95% CI 77.3, 114.0)) and those "both at risk of dozing and feeling sleepy" had the lowest (mean 78.0 minutes (95% CI 70.7, 85.2)). Similar results were seen in those with an AHI ≥5 but did not reach significance after Hochberg step up correction (p=0.017). No significant differences were observed in ORP characteristics in those with an AHI≥15 (data not shown).

5 Discussion

We aimed to test the hypothesis that EDS is not a uniform condition but a complex symptom consisting of more than one component. Our results show that there are at least two components of EDS; the "risk of dozing" and the general "feeling of sleepiness" that relate differently to sleep-related symptoms, general health aspects, OSA and quality of life both among the general population and in OSA patients. We found that many subjects with a general feeling of sleepiness will go undiagnosed if relying only on the ESS that only measures one component of sleepiness ("risk of dozing"). Furthermore, we found that measuring the general feeling of sleepiness among those with an ESS score >10 identifies individuals who are more likely to report sleep-related symptoms, have a lower quality of life and OSA patients that have more severe OSA. These OSA patients "both at risk of dozing and feeling sleepy" were also more likely to respond to PAP treatment. Therefore, our results indicate, that measuring both "risk of dozing" and a general feeling of sleepiness is an important contribution to clinical valuation when assessing subjects for EDS.

5.1 Prevalence and distribution of the sleepiness phenotypes in the general population

We found that among the general middle-aged population, altogether 13.1% reported EDS based on "risk of dozing" when using ESS>10. These findings are like previous studies on general population samples (Adams et al., 2016; Stradling et al., 2000). We also found that reporting "feeling sleepy" three or more times per week identified 23.2% of the total sample with EDS. As hypothesized, there was a substantial difference in how the two different measures identified individuals with EDS. Of those at "risk of dozing", 49.1% were also "feeling sleepy" but only 27.7% of those "feeling sleepy" had significant "risk of dozing". In total, 6.4% fulfilled both definitions. Our results therefore suggest that the two measures of EDS capture different components of sleepiness. This finding is important to acknowledge in future research on EDS. Choosing between the two different measures of sleepiness could substantially influence research findings by identifying different individuals with EDS. Furthermore, this is important knowledge for clinicians who use self-reported sleepiness measures to make important decisions, such as whether to refer individuals for OSA screening, initiate PAP treatment and reinstate driving licenses. Asking a patient how sleepy he or she feels or how likely the person is to fall asleep is not measuring the same thing, but both are important when evaluating a person's level of sleepiness.

5.2 Prevalence and distribution of the sleepiness phenotypes among OSA patients

Not surprisingly, OSA patients were substantially more likely to have EDS than subjects from the general population. Around half of the OSA patients with moderate-to-severe disease reported "risk of dozing" (57.5% among the Icelandic subjects, 52.0% among the international OSA cohort), which is similar to some previous studies on EDS in clinical OSA cohorts (REF). However, we did find that reporting "feeling sleepy" differed substantially between the two OSA cohorts. In the ISAC, 74.7% were defined as "feeling sleepy". However, in the international SAGIC cohort "feeling sleepy" was only reported by 31.3%. The reason for this difference is not immediately clear. We did find that prevalence of the four sleepiness phenotypes was significantly different between ethnicity groups. Asians were less likely to report feeling sleepy than White individuals (28.0% for Asian vs. 37.1% for White subjects) and more likely to report "risk of dozing" (57.4% for Asian vs. 45.0% for White subjects). As all the participants in ISAC were White but the SAGIC group used in paper III were 59% Asian and only 29.1% White subjects, the difference in reporting "feeling sleepy" could, at least partly, be explained by differences in ethnicity between the cohorts. Furthermore, prevalence of cardiovascular disease, diabetes, insomnia, and restless leg syndrome might vary between ethnic groups. Our results indicate that "feeling sleepy" is more closely related to various medical disorders and insomnia but is less OSA specific. Reporting "feeling sleepy" might vary between ethnic groups because they have different underlying comorbidities. The significant difference in prevalence of the sleepiness phenotypes between the investigating centers could also reflect different referral patterns, cultural or language differences in the practice of sleep medicine and in expression of sleepiness in different languages. Even though the questionnaires used in SAGIC were professionally translated forward and backward for each site to ensure accuracy, some differences in wording might have taken place. Finally, it is worth mentioning that the two studies were conducted during different time frames. Participants in ISAC were recruited earlier (2005-2009) whereas the SAGIC was conducted later (2013-2022). In more recent years there has been increased awareness that OSA patients are not solely obese, middle aged and sleepy, but some can even have minimal symptoms but with significant comorbidities associated with OSA (like atrial fibrillation) making physicians more likely to refer non-sleepy OSA patients for evaluation and PAP treatment (Ye et al., 2014).

The overlap of the two sleepiness components was greater among OSA patients than in the general population. In ISAC, 86.7% of those having "risk of dozing" also reported "feeling sleepy" and of those "feeling sleepy", 66.8% were at "risk of dozing". Nevertheless, because of how many subjects reported "feeling sleepy", 24.7% (201 out of 810 subjects) were "feeling sleepy only" without significant "risk of dozing" that would normally not be identified as having significant EDS when only using the ESS.

Therefore, these results support previous findings in that the two components of sleepiness, the "risk of dozing" and "feeling sleepy" capture two different components of EDS.

The OSA patients in ISAC were categorized into the four sleepiness phenotypes at two timepoints: at baseline and again after 2 years of PAP treatment. Interestingly, the sleepiness phenotypes were persistent, e.g. those who were only at "risk of dozing" at baseline were most likely to belong to the same phenotype 2 years later, if their sleepiness had not resolved. Similar findings were seen in those "feeling sleepy only". If they were not non-sleepy at the 2-year follow-up they were most likely to still be "feeling sleepy only". The persistence in reporting either "risk of dozing" or "feeling sleepy" might indicate that these different expressions of sleepiness are trait-like (reflect the individual differences in expressing sleepiness) or that the underlying cause of sleepiness is different in these groups that have persisted over the 2 years.

5.3 Characteristics of the sleepiness phenotypes

5.3.1 The "non sleepy" phenotype

In general, we found that the "non-sleepy" phenotype had the lowest symptom burden: they reported fewer apneas and less snoring, nocturnal sweating, nGER, insomnia symptoms and RLS than other sleepiness phenotypes. In the general population, the "non-sleepy" phenotype had the lowest prevalence of a MAP index >0.5 indicating that subjects in this phenotype were less likely to have OSA than subjects in other phenotypes. In our OSA cohorts, subjects belonging to the "non-sleepy" phenotype had less severe OSA on average, although results were only significant in the large multicenter SAGIC study. Although individuals in this phenotype were defined as "non-sleepy" at baseline, they showed a significant difference in reported sleepiness following PAP treatment. At the 2-year follow-up, those compliant to PAP had an additional improvement in the ESS score of -1.89 points than non-PAP uses. An improvement of ESS scores of 2 points or more is generally considered to be of clinical significance to the patient (Crook et al., 2019). Therefore, our results indicate that even though OSA patients are categorized as "non sleepy" with the two methods that we used to measure sleepiness, they can still show a significant reduction of sleepiness with PAP.

Among the untreated OSA patients in ISAC, the difference in terms of daytime impairment were assessed between the sleepiness phenotypes. For every symptom related to daytime impairment, the "non-sleepy" phenotype had the lowest prevalence, including the lowest prevalence of falling asleep involuntarily during the day and feeling physically tired, and they were less likely to feel unrested in the morning. Despite having the lowest prevalence of complaints of daytime impairment, only half of subjects within the "non-sleepy" phenotype reported feeling rested when they woke up

in the morning and 28% felt physically tired during the day 3 or more times per week. This high prevalence of "tiredness" and "feeling unrested" among OSA patients defined as "non-sleepy" indicates that a substantial proportion of OSA patients has complaints of daytime impairment that are not captured by the combination of the two methods we used. Even though 82.3% of the Icelandic OSA cohort was defined as having "risk of dozing" and/or were "feeling sleepy", this method might still be underestimating the symptom burden of daytime impairment related to OSA. Chervin et al (2000) investigated sleepiness and related terms in a group of 190 untreated OSA patients and asked which term best represented their problem. They found that fatigue, tiredness, and lack of energy were more often reported a problem (57%, 61% and 62% respectively) than sleepiness (47%). Moreover, when the OSA patients were asked which of the four possible complaints was most significant for them, the patients most often reported lack of energy to be the major problem they faced. In another study by the same authors (Chotinaiwattarakul et al., 2009), complaints of fatigue, tiredness and lack of energy were found to improve substantially with adequate adherence to PAP, indicating that these symptoms are a consequence of OSA and might be components of daytime impairment that sleepiness is also part of (**Figure 8** in introduction). We found similar results in the ISAC cohort, where symptoms of feeling tired and unrested significantly improved in those compliant to PAP treatment compared to those who were non-PAP users. However, this change was restricted to those who were "both at risk of dozing and feeling sleepy" at baseline.

5.3.2 The "risk of dozing only" phenotype

Overall, the subjects reporting "risk of dozing only" were similar to the "non-sleepy" subjects in reporting insomnia, chronotype preferences and sleep duration. Importantly, their QoL measures were not significantly different from those seen in "non-sleepy" subjects. In the general population, those at "risk of dozing only" more often reported snoring and apneas, the classical OSA symptoms than "non-sleepy" subjects and they were more likely to have a MAP index >0.5 indicating that these subjects were at increased risk of having OSA compared to "non-sleepy" subjects. Otherwise, the "risk of dozing only" phenotype was similar to the "non-sleepy" phenotype in the general population sample. Among OSA patients, having "risk of dozing only" was more closely related to more severe OSA measures on the PSG than "feeling sleepy only" and "non-sleepy". They had higher ODI and TST90 and lower average and minimum SpO2 than "non-sleepy" subjects. The "risk of dozing only" phenotype also showed significant benefits of PAP for multiple symptoms of daytime impairment, and they had the largest improvement in ESS score (-4.00 points) with PAP treatment. Overall, our results therefore suggest that having "risk of dozing only" is more closely related to OSA than the other factors we investigated, such as insomnia, evening chronotype and short sleep. A possible explanation could be that because OSA patients most often suffer from chronic sleepiness, they might not be aware that

they are "feeling sleepy" as this has become their accepted norm. It has been reported anecdotally by clinicians that treat OSA patients with successful PAP treatment that they often express alertness that they have not realized that they were missing. This is supported by studies that have shown that the disparities between subjective and objective assessments of sleepiness are typically greatest in the sleepiest individuals (Chervin et al., 1997; Olson et al., 1998). This suggests that chronically sleepy patients might experience gradual habituation to the sensation associated with increased sleep pressure, but without a corresponding diminution of the actual pressure to sleep. Therefore, asking chronically sleepy patients, such as OSA patients, if they have a general feeling of sleepiness might not accurately reflect their impairment as asking them about examples of sleepy behavior, such as risk of dozing.

5.3.3 The "feeling sleepy only" phenotype

Among the general population sample, the phenotype "feeling sleepy only" more often reported insomnia symptoms and worse QoL than the "non sleepy" and "risk of dozing only" phenotypes. They were older and reported a higher prevalence of RLS and some common chronic disorders (hypertension, cardiovascular disease, and diabetes) than those "non-sleepy" and at "risk of dozing only". In the OSA cohorts, this phenotype more often classified as being an evening chronotype and they reported using medications to help them sleep more often than other phenotypes. They also had the shortest self-reported sleep duration and less severe hypoxemia on the PSG, including the lower hypoxic burden than other sleepiness phenotypes. Thus, our results indicate that "feeling sleepy only" is more closely related to poor health, short sleep, insomnia, hypnotic use and poor QoL than to OSA.

Insomnia is a complex disorder that is characterized by having DIS, DMS or EMA. Insomnia has been associated with psychiatric conditions such as depression and anxiety and a higher prevalence of insomnia is found in many chronic medical disorders (M. Ohayon, 1996; Sutton et al., 2001). Studies have found that subjects suffering from insomnia are more likely to be long-term users of hypnotics (Quera-Salva et al., 1991). Individuals with insomnia frequently report daytime impairment, which is the main reason why they seek treatment (Aikens and Rouse, 2005). However, typically their complaints are described as fatigue, irritability, not feeling rested upon wakening and having work or school related issues rather than having increased propensity to fall asleep (American Academy of Sleep Medicine, 2014). One explanation for the high prevalence of insomnia symptoms among those "feeling sleepy only" is that the symptoms of daytime impairment seen in insomnia are more closely related to "feeling sleepy" than having "risk of dozing". In the ISAC cohort we found evidence that supports that theory. Among those "feeling sleepy only", 80.6% reported also being physically tired during the day and 79% reported not feeling rested in the morning. Reporting these symptoms was less common among those at "risk of dozing only" where 38.7% reported feeling physically tired and 64.5% felt unrested. Therefore, it is

likely that measuring general feeling of sleepiness rather than "risk of dozing" better reflects the daytime impairment seen in insomnia. However, specific scales have also been developed to measure insomnia-related fatigue, such as The Flinders Fatigue Scale, which is more specific in capturing the daytime impairment seen in insomnia (Krupp et al., 1989). Furthermore, "feeling sleepy only" might not only be a result of insomnia in this phenotype but also a side effect of poor overall health and use of hypnotics. In ISAC, subjects were asked if they took medication to help them sleep. Altogether, 11.9% reported hypnotic use and among the "feeling sleepy only" phenotype, 16.4% reported taking hypnotics. In the SAGIC cohort, we found even higher reports of hypnotic use where 19.7% of those "feeling sleepy only" reported taking medication to help them sleep. In a study on the Icelandic primary care population conducted at a similar time as the ISAC study, the prevalence of hypnotic/anxiolytic prescriptions was 13.9% among the total cohort, with 83% of the patients prescribed these medications twice or more per year having multimorbidity (Linnet et al., 2016). This could reflect the tendency of physicians to prescribe hypnotics to individuals with poor health and insomnia. The relationship between insomnia, health and the use of hypnotic medication is however complex. While hypnotics can provide a short-term relief for those suffering from sleep disturbances, they can also have potential side effects and risks, such as sleepiness and dependence (Van Gastel, 2022). Therefore, the use of hypnotics for insomnia should be approached with caution and used in combination with other strategies to promote good sleep hygiene and overall health.

5.3.4 The "both at risk of dozing and feeling sleepy" phenotype

In general, the phenotype "both at risk of dozing and feeling sleepy" had the highest prevalence of reporting sleep-related symptoms, such as reporting apneas, snoring, nocturnal sweating and RLS. They also reported worse QoL than "non-sleepy" and "risk of dozing only" phenotypes. Among patients with mild-to-moderate OSA in the SAGIC, this phenotype had the most severe OSA as measured by the AHI. Furthermore, when comparing treatment response in the four sleepiness phenotypes in the ISAC, those "both at risk of dozing and feeling sleepy" showed the most improvement of symptoms, including improvement of all measured symptoms of daytime impairment, except for "dozing off at the steering wheel", which did not reach significance ($p=0.068$). Furthermore, we found that this phenotype showed significant improvement in reporting DMS with PAP. This is in line with previous studies that have shown that PAP can be effective in reducing complaints of insomnia, especially DMS (Bjornsdottir et al., 2013). Given the increased benefit of PAP among those "both at risk of dozing and feeling sleepy", one might expect that this phenotype would be more likely to be adherent to treatment. We did not find however that PAP adherence significantly differed between sleepiness phenotypes.

In SAGIC, the two phenotypes with "risk of dozing" had, compared to "non-sleepy" and "feeling sleepy only" subjects, significantly higher AHI and more severe hypoxemia, including higher ODI, TST90 and lower minimum and average SpO2. This is in line with many previous studies that have found OSA patients with EDS (based on ESS) to have more severe OSA and hypoxemia than those without EDS (Basta et al., 2008; Chen et al., 2011; Gottlieb et al., 1999; Jacobsen et al., 2013; Ulander et al., 2022). Although we found a significant association between the sleepiness phenotypes and markers of OSA severity and hypoxemia, effects sizes indicated that the association was overall weak. This indicates that other mechanisms than PSG variables might be more important to explain EDS among OSA patients. As some experts have pointed out, EDS often has multiple causes and as OSA patients are often obese, have higher risk of RLS, insomnia, and depression, the cause of their EDS is likely to be multifactorial, obscuring the association between PSG markers and EDS (Balthazar et al., 2022; Stroe et al., 2010). Also, it has been found that genetic factors contribute to variation in sleepiness in general, which might also contribute to the variation in sleepiness among OSA patients. The heritability of daytime sleepiness has been estimated to be between 0.37 and 0.48 in twin studies (Carmelli et al., 2001; Watson et al., 2006), 0.17 in family studies (Wing et al., 2012) and between 0.084 and 0.17 in Genome Wide Association Studies (Gottlieb et al., 2007; Lane et al., 2017).

We also investigated two markers of sleep depth in relation to the sleepiness phenotypes, the relative amount of different sleep stages and ORP. We found that the "non-sleepy" subjects spent more time awake during the PSG and they had a greater proportion of ORP in the 2.20-2.25 range, indicating more wakefulness than the two phenotypes with "risk of dozing". This might simply reflect that the "non-sleepy" subjects have a lower propensity for sleep than those with "risk of dozing". Otherwise we did not find that markers of sleep depth differed between the sleepiness phenotypes and therefore our results support previous studies that have not found EDS among OSA patients to be associated with disruption in sleep architecture (Jacobsen et al., 2013; Kapur et al., 2005; Rey de Castro and Rosales-Mayor, 2013). Also, we did not find that arousal index, arousal intensity or PLMI differed significantly between our sleepiness phenotypes.

Among the OSA patients in ISAC, 146 subjects (18% of the total cohort) reported they dozed off at the steering wheel at least once per week while driving. We explored how the different measures of sleepiness captured these individuals at high risk of falling asleep at the steering wheel, causing significant risk to the individual itself and others on the road. When using only the ESS score >10 (as is a common praxis when assessing sleepy drivers), the majority (87%) of these drivers are identified as having EDS. However, when adding a measure of the more general feeling of sleepiness, as done in this present study, an additional 11% were identified with EDS. Therefore, if a combination of these two methods is used, 98% of these sleepy drivers falling asleep

are identified. This further underlines the importance of not solely relying on the ESS when assessing individuals with potential EDS.

5.4 Persistent sleepiness with PAP treatment

When using our expanded method of measuring sleepiness, we found that nearly 43% of OSA patients adherent to PAP had persistent sleepiness (e.g. were at "risk of dozing" and/or "feeling sleepy" both at baseline and at the 2-year follow-up). Using only the ESS, 26% had persistent sleepiness, which is similar to the results reported in a previous multicenter study on 4852 PAP-treated OSA patients (Bonsignore, Pepin, et al., 2021). Gasa et al. (2013) and Pepin et al. (2009) however found that persistent sleepiness was less common, with only 12-13% having an ESS score >10. In their study, however, all individuals with other contributing factors to sleepiness, such as depression, chronic sleep deprivation and a residual AHI of ≥15 events/hour were excluded. As previously reported (Gasa et al., 2013; Koutsourelakis et al., 2009), our results showed that persistent sleepiness was associated with less severe OSA at the time of diagnosis. The reason for this finding might be that individuals with OSA and additional causes of sleepiness, might experience more severe sleepiness despite less severe OSA. As PAP only resolves their sleep disordered breathing but does not affect other causes of sleepiness, they have persistent symptoms. In our study, we did find that those with persistent sleepiness more often reported insomnia symptoms (e.g. DMS and EMA). This could indicate that insomnia is one of those factors that co-exists with OSA and causes sleepiness but is not necessarily affected by PAP treatment and therefore it causes persistent sleepiness in those subjects. We also found that even though we only investigated those who were defined as full-PAP users for persistent sleepiness, those with persistent sleepiness used their PAP machine on average 30 minutes less than those whose sleepiness improved. Those with persistent sleepiness were also more likely to report persistent OSA symptoms at the 2-year follow-up, such as snoring, apneas and nocturnal sweating. In our study, we defined adequate PAP adherence as using PAP ≥20 nights and ≥4 hours/night on average for the previous four weeks based on objective data or ≥5 nights/week for ≥60% of the night by subjective data. Our results suggest that OSA subjects might benefit from using their PAP machine even more. This is in line with a previous study by Weaver et al. that found a dose-response relationship between PAP use and sleepiness, and increasing the mean duration of PAP per night from 5 to 6 hours resulted in an even further decrease in persistent sleepiness (Weaver et al., 2007). Therefore, in the ISAC cohort, persistent sleepiness might at least partly be caused by inadequate OSA treatment.

5.5 Strengths and limitations

The strengths of this study include the large number of subjects included and the high participation rates in the general population of individuals recruited from two countries

with the same well-defined methods. Because of the high participation rate (81.8% in Reykjavik and 62.2% in Uppsala) and minimal differences between responders and non-responders (Buist et al., 2007), we believe the participants accurately reflect the general population in these two countries. In ISAC, the participation rate was >90% in a typical clinical population and therefore the ISAC cohort represents most patients diagnosed with moderate-to-severe OSA in Iceland that were referred for PAP treatment between September 2005 to December 2009. In SAGIC, the large-scale design of the study, standardized methods, as well as the detailed investigations of participants with an overnight PSG, make this cohort of OSA patients highly representative. Using the two different cohorts of OSA patients also made it possible to verify our findings between cohorts and further strengthen our results.

Overall, one of the main limitations of this study is that we did not have an objective measure of sleepiness which could have given a more complete understanding of the individual's sleepiness level. However, objective measures, such as the MSLT, are time consuming, costly, and not practical in epidemiological studies. Also, we did not have information about depression, which is one important factor when evaluating possible causes of sleepiness. We did however have quality of life measures, including an individual's evaluation of mental QoL, which in part may reflect their psychological state.

The general population cohort was restricted to individuals aged 40 years and older. Therefore, our results cannot be generalized to younger individuals in the general population. In our general population cohort, another limitation is that we did not have information on OSA diagnosis, an important risk factor for sleepiness. Therefore, we did not have information on how many subjects had untreated OSA and to what extent OSA has influenced the prevalence of EDS. We used the MAP index, a widely used and validated tool to assess the risk of OSA, but we were only able to calculate the MAP index for 760 out of 1338 subjects because many answered the OSA symptom questions (snoring, apnea, snorting) with "I don´t know". Also, we did not have information on sleep duration in the general population sample and were therefore not able to estimate the role of sleep length for the association with sleepiness in this cohort.

Although the 2-year follow-up of the ISAC patients is a strength of the study, it can also be considered a limitation as we did not have a short-term follow-up. During the 2 years of the study, many factors other than PAP treatment can have influenced the subject's sleepiness levels and therefore biased our results. However, we did perform a sensitivity analysis excluding subjects that reported having had other treatment for OSA (using MAD and having surgery because of OSA) and also those who had lost a significant amount of their body weight. These factors did not influence our results. Also, this was an observational study but not a randomized controlled trial (RCT), which may be considered a limitation. However, performing a RCT with such a long-term

follow-up of severely affected OSA patients would be hard to perform for many practical and ethical reasons.

5.6 Future perspectives

Currently, many scales and tests are available to measure sleepiness, but as they evaluate sleepiness from different clinical perspectives, they yield significantly different results regarding which individuals should be defined as sleepy and which should not. Consequently, the question: "which test is most suitable for measuring sleepiness" remains unanswered. The high number of tools used to measure sleepiness poses a significant challenge in the research of EDS. A well-defined, highly sensitive and specific tool to measure sleepiness could increase our understanding of the importance of sleep and sleep disturbances for health and well-being. Such a tool would also have important implications for clinical practice and public health.

One limitation of the current methods used to measure sleepiness subjectively is that they do not reflect the level of sleepiness over an extended period of time. The objective measures most often used today, such as the MSLT, are dependent on sleepiness at the time the test is performed. This may not reflect the individual's usual level of sleepiness or their sleepiness in specific situations, such as when driving. Results from subjective tests are also dependent on the individual experience and mood at the time the test is taken. Therefore, using a method that measures sleepiness continuously for a longer time might better reflect the individual's level of sleepiness. There are a few devices on the market that use pupillography to measure sleepiness continuously (Aidman et al., 2015). Pupillography is a non-invasive method that is based on the fact that when sleepiness increases, sympathetic tone is lost, which is reflected and measured in the diameter and response of the pupil to light. These systems can be integrated into a vehicle or in a wearable device that tracks changes of the pupil and alerts drivers and operators if signs of sleepiness are detected. Furthermore, with advancements in technology, various smartphone apps and wearable devices have been developed to track sleep and measure subjective sleepiness at regular intervals throughout the day. While these apps have not been fully validated yet, they can still provide some helpful insight into an individual's sleep patterns and level of sleepiness. Further research and validation could provide valuable insight into an individual's sleepiness in real-world situations.

Another potential way of improving sleepiness measures is by gaining a better understanding of the underlying mechanisms of sleepiness, which might open new ways to assess sleepiness. One promising area of research in this regard is to investigate the different traits of individuals in terms of being either vulnerable or tolerant to sleep deprivation. Several studies have found large, highly reliable individual differences in the magnitude of sleepiness one experiences in response to sleep deprivation (Van Dongen et al., 2003). Importantly, these traits are consistent

over time; if an individual has high levels of sleepiness (e.g. is vulnerable) or low levels of sleepiness (e.g. is tolerant) following an extended duration of wakefulness, similar findings are observed again on a repeated test, days, weeks or even years later, implying that the tolerance to sleep deprivation is a subject-specific trait (Dennis et al., 2017; Rupp et al., 2012; Veasey et al., 2004). The underlying mechanisms of these differences are not clear and have not yet been accounted for by differences in demographic factors, BMI or sleep need (Yamazaki and Goel, 2020). Some researchers have suggested that this difference is genetically determined. In this regard, the trait-like vulnerability and tolerance to sleep deprivation has been associated with polymorphism in adenosinergic genes (ADA and ADORA2A) (Reichert et al., 2014; Rupp et al., 2013), core circadian clock genes (BHLHE41/DEC2 and PER3) (Pellegrino et al., 2014; Viola et al., 2007), genes related to cognitive development and functioning (BDNF and COMT) (Grant et al., 2018; Valomon et al., 2018), dopaminergic genes (DRD2 and DAT) and immune and clearance genes (AQP4, DQB1*0602, and TNFa). Therefore, understanding the genomics of the different neurobehavioral responses to sleep loss could help in predicting individual risk for sleepiness.

Furthermore, in more recent years there has been significant advances in the field of metabolomics. While genomics provides information on the genetic blueprint, metabolomics provides information on the downstream metabolic product of the genetic material that is influenced by a complex interaction of environmental factors. Importantly, oral fluid has proven its massive potential in metabolomic studies, making it an easily accessible and non-invasive biological fluid suitable for testing (Hyvarinen et al., 2021). Further investigations in this field of research might therefore produce reliable methods of assessing and quantifying sleepiness objectively with a simple procedure, such as with an analysis of buccal smear to identify individuals at risk of accidents or errors in high-risk, high-concentrating jobs, such as in transportation, healthcare and the military.

6 Conclusions

EDS is not a uniform condition but a complex symptom consisting of more than one component. Defining EDS based on both "risk of dozing" and the more "general feeling of sleepiness" identifies two different components of EDS that relate differently to sleep-related symptoms, health and lifestyle factors, OSA severity and quality of life among individuals in the general population, among Icelandic sleep apnea patients and in a large international group of OSA patients.

Defining EDS based on feeling sleepy ≥ 3 times per week does identify a group of individuals with EDS who are not captured by using the ESS score, which only measures one component of EDS ("risk of dozing"). The subjects "feeling sleepy only" have impaired general health characteristics, more sleep-related symptoms, are more often identified as evening chronotypes, have shorter sleep duration, frequent symptoms of insomnia and poorer QoL than "non-sleepy" individuals. Therefore, these individuals should not be defined as "non-sleepy". Furthermore, measuring the general feeling of sleepiness among those with an ESS score >10 identifies subjects that are more likely to report more frequent sleep-related symptoms and have a lower quality of life. Also, OSA patients "both at risk of dozing and feeling sleepy" have more severe OSA and are more likely to respond to PAP treatment. Therefore, our findings highlight the importance of a comprehensive approach to assessing EDS. Both among individuals in the general population and also patients with OSA, considering at least the "risk of dozing" and the "general feeling of sleepiness".

Our results also suggest that there are other components, yet-to-be identified and determined, that are closely related to EDS, such as "feeling tired" and "not feeling rested", that must be taken into consideration when assessing the magnitude and burden of daytime impairment, at least in subjects with OSA. By better understanding how the different symptoms of sleepiness and daytime impairment relate to causes and consequences of EDS, healthcare professionals can potentially develop more effective treatment plans and improve overall patient outcomes. Leveraging machine learning and data mining techniques could help uncover hidden patterns and associations to variables that may not be immediately apparent, such as certain lifestyle factors, physical activity, and diet. Furthermore, we did not find, in a large group of OSA patients, testing multiple traditional and novel PSG measures, that these variables were strongly related to EDS in OSA. This may be due to the complex and multifactorial nature of EDS in these patients, or the limitations of the PSG measurements in capturing the underlying mechanisms. Therefore, future research should incorporate biomarkers, such as genetic and metabolic markers, which could provide valuable insight into the mechanisms that contribute to EDS. This could potentially lead to more targeted diagnosis, as well as individual preventive and treatment options.

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Original Publications

Paper I

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REGULAR RESEARCH PAPER

Journal of Sleep Research

Definition of excessive daytime sleepiness in the general population: Feeling sleepy relates better to sleep-related symptoms and quality of life than the Epworth Sleepiness Scale score. Results from an epidemiological study

Elin H. Thorarinsdottir[1,2] | Erla Bjornsdottir[2,3,4] | Bryndis Benediktsdottir[2,3] | Christer Janson[5] | Thorarinn Gislason[2,3] | Thor Aspelund[2,6] | Samuel T. Kuna[7,8] | Allan I. Pack[7] | Erna S. Arnardottir[4,9]

[1]Department of Medicine, Landspitali - The National University Hospital of Iceland, Reykjavik, Iceland

[2]Faculty of Medicine, University of Iceland, Reykjavik, Iceland

[3]Sleep Department, Landspitali - The National University Hospital of Iceland, Reykjavik, Iceland

[4]School of Science and Engineering, Reykjavik University, Reykjavik, Iceland

[5]Department of Medical Sciences: Respiratory, Allergy and Sleep Research, Uppsala University, Uppsala, Sweden

[6]Icelandic Heart Association, Kopavogur, Iceland

[7]Department of Medicine and Center for Sleep and Circadian Neurobiology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, USA

[8]Department of Medicine, Corporal Michael J. Crescenz VA Medical Center, Philadelphia, Pennsylvania, USA

[9]Internal Medicine Services, Landspitali - The National University Hospital of Iceland, Reykjavik, Iceland

Correspondence
Elin Helga Thorarinsdottir, Faculty of Medicine, University of Iceland, Department of Medicine, Landspitali – The National University Hospital of Iceland, Reykjavik, Iceland.
Email: elinhelga@gmail.com

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Abstract

Many different subjective tools are being used to measure excessive daytime sleepiness (EDS) but the most widely used is the Epworth Sleepiness Scale (ESS). However, it is unclear if using the ESS is adequate on its own when assessing EDS. The aim of this study was to estimate the characteristics and prevalence of EDS using the ESS and the Basic Nordic Sleep Questionnaire (BNSQ) in general population samples. Participants aged 40 years and older answered questions about sleepiness, health, sleep-related symptoms and quality of life. Two groups were defined as suffering from EDS: those who scored >10 on the ESS (with increased risk of dozing off) and those reporting feeling sleepy during the day ≥3 times per week on the BNSQ. In total, 1,338 subjects (53% male, 74.1% response rate) participated, 13.1% reported an increased risk of dozing off, 23.2% reported feeling sleepy and 6.4% reported both. The prevalence of restless leg syndrome, nocturnal gastroesophageal reflux, difficulties initiating and maintaining sleep and nocturnal sweating was higher among subjects reporting feeling sleepy compared to non-sleepy subjects. Also, subjects reporting feeling sleepy had poorer quality of life and reported more often feeling unrested during the day than non-sleepy subjects. However, subjects reporting increased risk of dozing off (ESS > 10) without feeling sleepy had a similar symptom profile as the non-sleepy subjects. Therefore, reporting only risk of dozing off

without feeling sleepy may not reflect problematic sleepiness and more instruments in addition to ESS are needed when evaluating daytime sleepiness.

KEYWORDS
Basic Nordic Sleep Questionnaire, subjective sleepiness

1 | INTRODUCTION

Excessive daytime sleepiness (EDS) is a significant public health problem as it affects tasks that require vigilance, memory and executive function (Jackson, Howard, & Barnes, 2011). It interferes with daily activities and impairs quality of life (Engleman & Douglas, 2004). EDS can be a sign of insufficient sleep and poor sleeping habits and diseases such as sleep-related breathing disorders, restless leg syndrome (RLS), circadian rhythm disorders and narcolepsy (Murray, 2016). EDS is also associated with obesity (Bixler et al., 2005; Panossian & Veasey, 2012), chronic obstructive pulmonary disease (COPD) (Ali Zohal, Yazdi, & Kazemifar, 2013), asthma (Kallin et al., 2016) and stroke (Ding, Whittemore, & Redeker, 2016). Of conditions causing EDS, obstructive sleep apnea (OSA) is the most frequently made diagnosis (Jackson et al., 2011).

Excessive daytime sleepiness includes both an inability to stay alert and awake during the day and a more general feeling of sleepiness. The varying definitions and usage of many different instruments, both subjective and objective, to measure EDS is a well-known problem in epidemiological studies on EDS. As a result, prevalence rates range from 4% to 21% depending on the definition and method of assessment (Ohayon, 2008). The most commonly used questionnaire to assess EDS is the Epworth Sleepiness Scale (ESS), where subjects are asked to rate their likelihood of dozing off or falling asleep in eight different situations most people encounter in their daily lives (Johns, 1991). The higher the score, the higher the person's risk of dozing off during the day and a score higher than 10 is usually used to define EDS (Johns, 2016). However, the ESS has some limitations. For example, an individual suffering from insomnia and having difficulties falling asleep will probably rate his or her chance of dozing off in the different situations low and therefore have a low ESS score despite possibly feeling excessively sleepy during the day. Also, the ESS measures the tendency to doze off during some soporific conditions, which does not necessarily reflect problematic EDS, for example lying down to rest in the afternoon when circumstances permit. Furthermore, activities of daily life mentioned in the ESS might differ in different groups of subjects and may therefore affect a subject's answer regardless of how sleepy they are, for example depending on gender and age (Baldwin, Kapur, Holberg, Rosen, & Nieto, 2004; Ulander, Arestedt, Svanborg, Johansson, & Broström, 2013). Consequently, the ESS may not be a meaningful measure of EDS in many patients. Other questionnaires assess the more general feeling of sleepiness rather than the risk of dozing off. The Basic Nordic Sleepiness Questionnaire (BNSQ) assesses EDS by asking how often per week subjects feel sleepy (Partinen & Gislason, 1995). This question is widely used and has been shown to correlate with variables that contribute to EDS, including snoring (Young et al., 1993), nasal congestion (Young, Finn, & Kim, 1997) and OSA severity categories (Young, Hutton, Finn, Badr, & Palta, 1996; Young et al., 1993). EDS is usually defined when subjects experience daytime sleepiness at least 3 days per week and the prevalence of EDS in the general population has been found to be 17%–28.5% using that definition (Hara, Lopes Rocha, & Lima-Costa, 2004; Janson et al., 1995; Kallin et al., 2016).

The association between the different subjective measurement tools used to measure EDS has not been the topic of many papers. In the few studies on this matter, only a weak correlation between feelings of sleepiness and self-estimated sleep behaviour has been reported (Adams et al., 2016; Baldwin et al., 2004; Kim & Young, 2005; Pilcher, Pury, & Muth, 2003; Pilcher, Schoeling, & Prosansky, 2000). Also, studies have shown that the ESS is more likely to detect EDS among men than women and women more often report feeling unrested (Baldwin et al., 2004; Kim & Young, 2005). The ESS may therefore not be an adequate measure of sleepiness in women. Thus, there is a need for a better screening tool for EDS in order to improve the evaluation of the magnitude and aetiological factors of this highly prevalent condition in the general population.

The aim of this study was to determine the prevalence and characteristics of EDS in the general population in Iceland and Sweden using two frequently used questionnaires. EDS was defined both as the risk of dozing off assessed by the ESS and the general feeling of sleepiness using the BNSQ sleepiness question. Subjects were divided into three sleepiness categories based on a standard cut-off level for sleepiness in both questionnaires. Sleepiness categories were compared with different outcome measures: sleep-related symptoms, comorbidities and quality of life. The hypothesis was that the risk of dozing off and the general feeling of sleepiness describe different components of sleepiness. Using the more expansive definition of sleepiness using the BNSQ question will identify subjects with EDS who do not have a risk of dozing off during the day but might nevertheless have increased risk of sleep-related symptoms, comorbidities and reduced quality of life. Reporting only dozing off during the day without feeling sleepy may not reflect problematic EDS.

2 | METHODS

2.1 | Participants

The study population for this research was primarily individuals in the general population invited to participate in The Burden of

Obstructive Lung Disease (BOLD, www.boldstudy.org) initiative in Reykjavik, Iceland, and Uppsala, Sweden, a multicentre international study aiming to estimate the burden of COPD worldwide (Buist et al., 2007). Using the national registries of inhabitants in both countries, a random sample of adults aged 40 years and older was contacted and invited to participate in this general population-based study. The design and rationale for the BOLD study have been reported elsewhere (Benediktsdottir et al., 2010). In total, 1,366 (52% male) participated, 765 in Reykjavik and 601 in Uppsala. Response rates were 81.8% and 62.2%, respectively. Of those, 28 participants were excluded as information on risk of dozing off (ESS scores) or feeling sleepy (BNSQ) was missing.

2.2 | Questionnaires and measurements

As a part of the BOLD study protocol, all participants came to the outpatient clinic of the respective hospitals in Reykjavik and Uppsala, where they answered the same questionnaires on respiratory symptoms, risk factors for COPD, health status, medication use, healthcare utilization, comorbidities, respiratory diagnoses, limitation of activity and quality of life. Lung function (including forced expiratory volume in 1 s [FEV_1] and forced vital capacity [FVC]) was measured using the ndd EasyOne Spirometer (ndd Medizintechnik AG, Zurich, Switzerland), before and 15 min after inhaling salbutamol (200 μg). In addition to the BOLD protocol, the participants were asked to answer questions about sleepiness (Johns, 1991; Partinen & Gislason, 1995), RLS (Allen et al., 2003) and sleep-related symptoms, such as snoring, nocturnal sweating, difficulties initiating and maintaining sleep and nocturnal gastroesophageal reflux (nGER) (Emilsson, Janson, Benediktsdóttir, Júlíusson, & Gíslason, 2012). Each site obtained ethical approval from the local ethical committee (National Bioethics Committee of Iceland: 04-080; Swedish Research Council: 2006/146) and written informed consent was obtained from every participant.

2.3 | Assessment of EDS

Two aspects of EDS were evaluated: the risk of dozing off and a more general feeling of sleepiness. The participants were defined as having a risk of dozing off if they scored >10 on the ESS (Johns, 2016). As part of the BNSQ they were also asked a specific question 'Do you feel sleepy during the day?' and rated their answers on a five-point scale: never/almost never (1); less than once a week (2); once or twice a week (3); three to five times a week (4); every day or almost every day of the week (5). Those who answered three times or more often per week (scores 4 and 5) were considered to have subjective daytime sleepiness (Hara et al., 2004; Janson et al., 1995; Kallin et al., 2016).

These two definitions of EDS were evaluated separately and subsequently merged, and four different groups were identified.

1. Non-sleepy; ESS score ≤10 and reporting feeling sleepy <3 times per week on the BNSQ.
2. Risk of dozing off; ESS score >10 but reporting feeling sleepy <3 times per week on the BNSQ.
3. Feeling sleepy; ESS score ≤10 but reporting feeling sleepy ≥3 times per week on the BNSQ.
4. Both risk of dozing off and feeling sleepy; ESS score >10 and reporting feeling sleepy ≥3 times per week on the BNSQ.

2.4 | Assessment of body mass index, smoking history and previous health

Standardized methods were used to measure height and weight. Body mass index (BMI) was calculated as kg/m^2. Current smokers were defined as those who smoked tobacco regularly during the month preceding the examination. Former smokers were defined as those smokers who had denied having smoked regularly for a month prior to the examination. Those who reported no regular smoking at or prior to the examination were defined as never smokers.

The participants were defined as having diabetes if they reported doctor-diagnosed diabetes and were using medication for diabetes. Similarly, participants were considered to have hypertension if they reported a doctor's diagnosis and were on antihypertensive medication. Cardiovascular disease was defined if subjects reported doctor-diagnosed myocardial infarction, stroke and/or heart failure. Those with post-bronchodilatory FEV1/FVC ratio <0.70 were defined as having COPD (GOLD, 2018). Asthma was defined as when subjects reported ever having a doctor tell them they had asthma, asthmatic bronchitis or allergic bronchitis and reported still having this condition.

2.5 | Sleep-related symptoms and quality of life

As in our previous papers, nGER was defined as reporting heartburn after going to bed ≥ 1 time per week (Emilsson et al., 2012). Insomnia symptoms were defined as difficulties initiating sleep or maintaining sleep ≥3 times per week (Björnsdóttir et al., 2013). Habitual snoring was defined as snoring ≥3 times per week (Janson et al., 1995). Frequent nocturnal sweating was defined as subjects reporting heavy perspiration during the night ≥3 times per week (Arnardottir et al., 2013). Additionally, we used the multivariable apnea prediction (MAP) index to define subjects at high or low risk of OSA (Maislin et al., 1995). The MAP index is based on a self-reported frequency of occurrence of sleep apnea symptoms (snoring or gasping, breathing stops, choking or struggling for breath during the night) as well as BMI, age and gender. The MAP score ranges from 0 to 1, where subjects scoring 0 are least likely to have OSA. A cut-off of 0.5 has been used to define those subjects at high risk of OSA. The estimated sensitivity and specificity of this cut-point are 0.88 and 0.55, respectively (Maislin et al., 1995). Participants also answered the 12-item Short-Form Health Survey (SF-12) for physical and mental quality of life (Ware, Kosinski, & Keller, 1996) and questions on symptoms of RLS based on recommendations from the International Restless Legs Syndrome Study Group (Allen et al., 2003).

2.6 | Statistical analyses

All statistics were calculated using STATA software, Version 13.0 (Stata Corporation, College Station, Texas). Differences in categorical and continuous variables between the four groups identified were first compared using the Pearsons′s chi-squared test and one-way analysis of variance, respectively. This was also used when comparing the characteristics of individuals in the two study centres. Independent association of health status (e.g. hypertension) and sleep-related symptoms (e.g. snoring) in relation to the three different groups of subjects with EDS was calculated using multiple linear regression controlling for age, sex, BMI, smoking history and study centre. A sensitivity analysis was subsequently performed with different cut-off values for ESS scores to determine whether lower or higher values could impact our results. Four different cut-off values for ESS score were tested (>8, >9, >11 and >12).

3 | RESULTS

3.1 | Participation and characteristics

The baseline characteristics of the study population are shown in Table 1. Participants in Reykjavik were on average 2 years younger, had a higher BMI and more years of education and a higher prevalence of RLS than participants in Uppsala. No significant difference was found between the centres in gender distribution, smoking history or in the prevalence of hypertension, cardiovascular disease, diabetes, asthma and COPD.

3.2 | Prevalence of sleepiness

Participants from Uppsala more often reported feeling sleepy ≥3 times a week using the BNSQ than those from Reykjavik (26.3% versus 20.7%, respectively, $p = 0.015$) but no significant difference was found in the risk of dozing off (ESS > 10) between the two centres (Table 1). Altogether, 175 subjects (13.1%) reported an increased risk of dozing off, 310 subjects (23.2%) reported feeling sleepy and 86 subjects (6.4%) reported both (Figure 1). Of those at risk of dozing off, 49.1% also reported feeling sleepy, but only 27.7% of those reporting feeling sleepy also had significant risk of dozing off.

3.3 | Characteristics of the different sleepiness groups

There was a significant difference in age between the four groups identified, with the youngest being those reporting increased risk of dozing off only (Table 2). However, no differences in gender distribution or BMI were found between the four groups. After adjusting for age, sex, BMI, education, smoking history and study centre, those reporting only feeling sleepy were more likely to have a history of hypertension, cardiovascular disease and diabetes compared to non-sleepy subjects (Table 3). This was not found for the other sleepiness groups. However, reporting both risk of dozing off and feeling sleepy

TABLE 1 Baseline characteristics of the study population in the two centres

	Total (n = 1,338)	Reykjavik (n = 741)	Uppsala (n = 597)	p value*
Male gender (%)	52.7	53.3	51.9	0.619
Age (years)	57.4 ± 11.5	56.4 ± 11.7	58.7 ± 11.2	**<0.001**
Body mass index (kg/m^2)	27.5 ± 4.7	27.9 ± 4.9	27.0 ± 4.3	**<0.001**
Education (years)	13.2 ± 4.2	13.4 ± 4.3	12.9 ± 4.0	**0.038**
Smoking history (%)				0.055
Never	40.8	38.5	43.8	
Past	42.7	43.2	42.0	
Current	16.5	18.3	14.2	
COPD (%)	16.8	17.4	15.8	0.449
Asthma (%)	8.6	8.2	9.3	0.482
Hypertension (%)	30.5	32.1	28.6	0.174
Cardiovascular disease (%)	12.5	13.7	11.0	0.132
Diabetes (%)	4.3	4.6	3.9	0.545
Restless legs syndrome (%)	15.2	18.4	11.2	**<0.001**
ESS, total score	6.1 ± 3.9	6.1 ± 3.9	6.1 ± 3.9	0.884
Risk of dozing off, ESS > 10 (%)	13.1	12.7	13.6	0.634
Feeling sleepy ≥ 3 × week, BNSQ (%)	23.2	20.7	26.3	**0.015**

Data are presented as $M \pm SD$ or % where indicated. Significant differences are in bold ($p < 0.05$). *p-value from Pearson's chi-squared test (numerical variables) and unpaired t test (continuous variables).
BNSQ: Basic Nordic Sleep Questionnaire; COPD: chronic obstructive pulmonary disease; ESS: Epworth Sleepiness Scale.

was associated with increased odds of asthma. Subjects reporting feeling sleepy, both those with and without dozing off, had on average worse mental and physical quality of life than non-sleepy subjects, whereas no association was found with isolated risk of dozing off (Table 3).

3.4 | Sleep-related symptoms in the four sleepiness categories

Firstly, comparisons of characteristics between the two definitions of EDS were made separately (Supporting Information, Tables S1 and S2). In general, differences in sleep-related symptoms (snoring, sweating, nGER, apneas, not feeling rested, difficulties initiating and maintaining sleep and MAP index >0.5) were more significant between feeling sleepy and not feeling sleepy on the BNSQ ($p < 0.001$ for every sleep-related symptom) than when comparing those at risk of dozing off versus those not at risk of dozing off in the ESS.

After merging the two definitions, subjects within all three groups with EDS had a higher prevalence of snoring and reported apneas than non-sleepy subjects (Table 4) and this association remained significant after adjusting for age, sex, smoking history, BMI, education and study centre (Table 5). Interestingly, those both at risk of dozing off and feeling sleepy had the far highest odds of apneas, with an odds ratio of 7.79 (95% confidence interval, 3.71–16.4) when compared with the non-sleepy population (Table 5). Similarly, the MAP index was highest among those who were both at risk of dozing off and feeling sleepy (Table 4). After adjusting for age, sex, BMI, education, smoking history and study centre, the odds of having a MAP index >0.5 was significantly higher in all three sleepiness groups compared to the non-sleepy population but by far highest in those both at risk of dozing and feeling sleepy, with an OR of 13.52 (95% confidence interval, 4.30–42.55). These results are, however, limited because the MAP index was only available for 760 of 1,338 subjects. The prevalence of RLS, nocturnal sweating, nGER and not feeling rested was higher among those reporting feeling sleepy (with or without risk of dozing off) but not related to isolated risk of dozing off (Tables 4 and 5). Also, difficulties in initiating and maintaining sleep were related to feeling sleepy (with and without the risk of dozing off) but not to isolated risk of dozing off during the day (Table 5).

3.5 | Using other cut-off values for ESS scores: Results from the sensitivity analysis

When using lower cut-off values (>8 and >9) for the ESS score, the change primarily impacted results for those defined only at risk of dozing off, but not other sleepiness groups. When using >9 those only at risk of dozing off had increased odds of reporting cardiovascular disease and when using >8 they also had increased odds of diabetes. When using a cut-off value of >11, we found that those only at risk of dozing off during the day more often reported cardiovascular disease and diabetes but did not report apneas. When using a cut-off value of >12, those feeling sleepy only and both dozing off and feeling sleepy more often reported asthma compared to the non-sleepy group. In general, using different cut-off values for ESS scores had minimal impact on our results.

4 | DISCUSSION

This present study shows that reporting feeling sleepy is better correlated with many variables that contribute to EDS, such as RLS, nGER and difficulties initiating and maintaining sleep, than the risk of dozing off as measured with the ESS. Also, sleepy subjects complain more often of not feeling rested during the day and have a significantly poorer quality of life. However, those with risk of dozing off during the day but no subjective sleepiness had a similar symptom profile

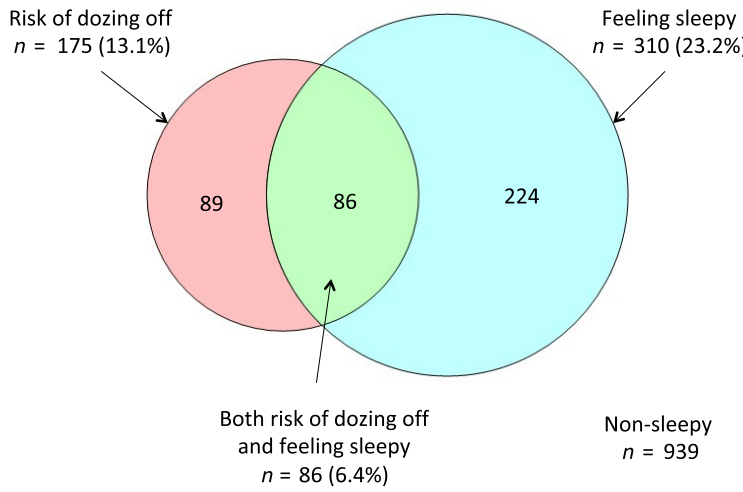

FIGURE 1 Prevalence and overlap of different categories of excessive daytime sleepiness in the general population sample. Pink: subjects at risk of dozing off (Epworth sleepiness scale score >10); blue: subjects reporting feeling sleepy during the day ≥3 times per week (Basic Nordic Sleep Questionnaire question); green: subjects reporting feeling sleepy ≥3 times per week and at risk of dozing off

TABLE 2 Characteristics of subjects in the four sleepiness categories

	Non-sleepy[a] (*n* = 939)	Dozing off only[b] (*n* = 89)	Feeling sleepy only[c] (*n* = 224)	Dozing off and feeling sleepy[d] (*n* = 86)	*p* value[e]
Male gender (%)	52.8	58.0	48.2	57.0	0.333
Age (years)	57.4 ± 11.6	54.56 ± 8.2	59.0 ± 12.4	56.1 ± 10.1	**0.015**
Body mass index (kg/m^2)	27.4 ± 4.6	26.7 ± 3.7	27.9 ± 5.0	28.2 ± 5.3	0.094
Education (years)	13.0 ± 4.0	14.0 ± 4.0	12.0 ± 4.0	14.0 ± 4.0	**0.020**
Smoking history (%)					0.633
Never	41.1	47.7	38.6	36.1	
Past	43.0	34.1	43.6	45.4	
Current	15.9	18.2	17.7	18.6	
COPD (%)	16.8	9.1	19.9	17.1	0.159
Asthma (%)	7.6	5.7	10.5	18.6	**0.003**
Hypertension (%)	28.5	21.6	41.8	32.6	**<0.001**
Cardiovascular disease (%)	11.5	5.7	19.6	12.8	**0.002**
Diabetes (%)	3.4	4.6	7.3	7.0	**0.041**
Quality of life (SF-12)					
MCS (total score)	50.3 ± 9.4	49.3 ± 8.4	45.8 ± 10.2	45.2 ± 10.0	**<0.001**
PCS (total score)	49.6 ± 9.0	51.2 ± 6.5	44.7 ± 11.4	45.6 ± 9.7	**<0.001**

Data are presented as *M* ± *SD* or % where indicated. Significant differences are in bold ($p < 0.05$). [a]ESS score ≤10 and reporting feeling sleepy <3 times per week on the BNSQ. [b]ESS score >10 but reporting feeling sleepy <3 times per week on the BNSQ. [c]ESS score ≤10 but reporting feeling sleepy ≥3 times per week on the BNSQ. [d]ESS score >10 and feeling sleepy ≥3 times per week on the BNSQ. [e]*p*-value from Pearson's chi-squared test (numerical variables) and one-way analysis of variance (continuous variables).
BNSQ: Basic Nordic Sleep Questionnaire; COPD: chronic obstructive pulmonary disease; MCS: mental health composite score; PCS: physical health composite score; SF-12: Short Form (12) Health Survey.

TABLE 3 Independent association between comorbidities and quality of life in relation to different categories of excessive daytime sleepiness expressed as adjusted (adjusted for age, sex, body mass index, education, smoking history and study centre) odds ratios or beta-coefficients (95% CI) with the non-sleepy[a] group as reference

	Dozing off only[b] (*n* = 89)	Feeling sleepy only[c] (*n* = 224)	Dozing off and feeling sleepy[d] (*n* = 86)
COPD (OR)	0.68 (0.31, 1.48)	1.12 (0.73, 1.73)	1.36 (0.71, 2.60)
Asthma (OR)	0.83 (0.32, 2.14)	1.28 (0.77, 2.13)	**2.94 (1.60, 5.40)**
Hypertension (OR)	0.90 (0.52, 1.56)	**1.70 (1.22, 2.36)**	1.32 (0.80, 2.18)
Cardiovascular disease (OR)	0.74 (0.28, 1.93)	**1.86 (1.20, 2.89)**	1.50 (0.72, 3.12)
Diabetes (OR)	1.92 (0.65, 5.70)	**1.96 (1.03, 3.73)**	2.03 (0.80, 5.18)
Quality of life (SF-12)			
MCS (β)	−0.49 (−2.22, 1.24)	**−3.74 (−4919, −2.58)**	**−4.14 (−5.89, −2.40)**
PCS (β)	0.71 (−1.17, 2.60)	**−3.84 (−5.11, −2.58)**	**−3.95 (−5.85, −2.05)**

Significant differences are in bold. [a]ESS score ≤10 and reporting feeling sleepy <3 times per week on the BNSQ. [b]ESS score >10 but reporting feeling sleepy <3 times per week on the BNSQ. [c]ESS score ≤10 but reporting feeling sleepy ≥3 times per week on the BNSQ. [d]ESS score >10 and feeling sleepy ≥3 times per week on the BNSQ.
B: beta-coefficient; BNSQ: Basic Nordic Sleep Questionnaire; CI: confidence interval; COPD: chronic obstructive pulmonary disease; MCS: mental health composite score; OR: odds ratio; PCS: physical health composite score; SF-12: Short Form (12) Health Survey.

as the non-sleepy population, except for snoring and self-reported apneas, where a higher prevalence was found in all three groups with EDS compared to non-sleepy subjects. This study therefore supports previous research that indicates that the ESS and self-reported EDS measure distinct aspects of sleepiness (Adams et al., 2016; Baldwin et al., 2004; Kim & Young, 2005; Pilcher et al., 2000, 2003).

Although there was some overlap, many subjects were characterized differently when using the two different methods to evaluate sleepiness. Similar to previous studies, 13.1% were at risk of dozing off during the day using the ESS (Adams et al., 2016; Stradling, Barbour, Glennon, Langford, & Crosby, 2000) and 23.2% reported feeling sleepy most days of the week (Hara et al., 2004; Kallin et al., 2016). As the ESS only measures the propensity to doze off during the day, our study shows that many subjects with EDS will go undiagnosed. This is in line with previous studies that have compared the ESS to questionnaires measuring the more general feeling of sleepiness rather than the propensity to doze off (Sangal, 2012). Also, the ESS measures the tendency to fall asleep in various situations, including some soporific circumstances that do not necessarily increase the risk of any adverse effect, for example when lying down to rest in the afternoon when circumstances permit. This may lead to overdiagnosing of subjects who do not have problematic EDS. This is supported by our results that show that subjects at risk of dozing off without feeling sleepy as measured by the BNSQ do not report poorer quality of life and have a similar symptoms profile as the non-sleepy population. Our study therefore supports previous studies that have found EDS to be a multidimensional symptom that needs more than one method of assessment when making a diagnosis (Kim & Young, 2005; Ohayon, Dauvilliers, & Reynolds, 2012). Designing

TABLE 4 Unadjusted analysis of sleep-related symptoms in the four sleepiness categories

	Non-sleepy[a] (*n* = 939)	Dozing off only[b] (*n* = 89)	Feeling sleepy only[c] (*n* = 224)	Dozing off and feeling sleepy[d] (*n* = 86)	*p*[e]
Restless legs syndrome (%)	12.3	14.5	25.0	23.3	**<0.001**
Snoring ≥ 3 n/w (%)	41.6	57.1	51.8	66.2	**<0.001**
Sweating ≥ 3 n/w (%)	10.5	9.0	18.1	26.8	**<0.001**
nGER ≥ 1 n/w (%)	5.6	6.7	13.6	16.3	**<0.001**
Apneas ≥ 1 n/w (%)	5.4	13.0	14.3	31.3	**<0.001**
Not feeling rested ≥ 1/w (%)	9.5	13.5	28.8	27.9	**<0.001**
Difficulties initiating sleep ≥ 3 n/w (%)	10.8	5.6	30.9	19.1	**<0.001**
Difficulties maintaining sleep ≥ 3 n/w (%)	25.4	28.4	47.8	48.8	**<0.001**
MAP index > 0.5 (%)	15.8	20.3	25.4	41.7	**<0.001**

Data are presented as %. Significant differences are in bold ($p < 0.05$). [a]ESS score ≤10 and reporting feeling sleepy <3 times per week on the BNSQ. [b]ESS score >10 but reporting feeling sleepy <3 times per week on the BNSQ. [c]ESS score ≤10 but reporting feeling sleepy ≥3 times per week on the BNSQ. [d]ESS score >10 and feeling sleepy ≥3 times per week on the BNSQ. [e]*p*-values from Pearson's chi-squared test.
BNSQ: Basic Nordic Sleep Questionnaire; MAP index: Multivariable Apnea Prediction index; nGER: nocturnal gastroesophageal reflux; n/w: nights per week.

TABLE 5 Independent association between sleep-related symptoms in relation to different categories of daytime sleepiness expressed as adjusted (adjusted for age, sex, body mass index, education, smoking history and study centre) odds ratios (95% CI) with the non-sleepy group[a] as reference

	Dozing off only[b] (*n* = 89)	Feeling sleepy only[c] (*n* = 224)	Dozing off and feeling sleepy[d] (*n* = 86)
Restless leg syndrome	1.23 (0.64–2.37)	**2.37 (1.62–3.46)**	**2.39 (1.37–4.19)**
Snoring ≥ 3 n/w	**1.96 (1.19–3.24)**	**1.55 (1.08–2.21)**	**2.42 (1.39–4.22)**
Sweating ≥ 3 n/w	0.91 (0.42–1.95)	**1.78 (1.18–2.68)**	**2.97 (1.73–5.12)**
nGERT ≥ 3 n/w	1.28 (0.53–3.09)	**2.63 (1.62–4.28)**	**3.19 (1.67–6.10)**
Apneas ≥ 1 n/w	**2.55 (1.14–5.71)**	**3.20(1.77–5.79)**	**7.79 (3.71–16.4)**
Not feeling rested ≥ 1/w	1.50 (0.78–2.88)	**3.82 (2.63–5.53)**	**3.57 (2.11–6.04)**
Difficulties initiating sleep ≥ 3 n/w	0.57 (0.22–1.44)	**3.49 (2.42–5.01)**	**2.11 (1.16–3.83)**
Difficulties maintaining sleep ≥ 3 n/w	1.52 (0.90–2.58)	**2.62 (1.87–3.68)**	**3.31 (2.03–5.42)**
MAP index > 0.5	**5.49 (2.03–14.86)**	**3.44 (1.65–7.18)**	**13.52 (4.30–42.55)**

Significant differences are in bold. [a]ESS score ≤10 and reporting feeling sleepy <3 times per week on the BNSQ. [b]ESS score >10 but reporting feeling sleepy <3 times per week on the BNSQ. [c]ESS score ≤10 but reporting feeling sleepy ≥3 times per week on the BNSQ. [d]ESS score >10 and feeling sleepy ≥3 times per week on the BNSQ.
BNSQ: Basic Nordic Sleep Questionnaire; CI: confidence interval; MAP index: Multivariable Apnea Prediction index; nGER: nocturnal gastroesophageal reflux; n/w: nights per week.

new questionnaires that capture different aspects of sleepiness will provide better diagnosis of the individual level of EDS (Guaita et al., 2015).

It is important to acknowledge that although a large portion of the population is defined as sleepy using the BNSQ question, these subjects have poorer quality of life and have increased frequency of sleep-related symptoms that could be worth diagnosing. Improvement in the diagnostic techniques can provide a more accurate picture of those really in need of specialized treatments that could potentially increase their quality of life.

In our study, we found that subjects with RLS expressed significantly more sleepiness than those without RLS. However, our RLS sufferers did not report significant risk of dozing off during the day compared with those without RLS. This is contradictory to some previous studies that have found that subjects with RLS have higher scores on the ESS (Benediktsdottir et al., 2010; Cuellar, Strumpf, & Ratcliffe, 2007). A possible explanation is that our RLS sufferers come from the general population and might be less symptomatic than those seeking help primarily for RLS complains. Also, in our data, we separated those with only risk of dozing off, those only reporting sleepiness and those reporting both, which could affect our results.

Our study showed that subjects reporting snoring and apneas during sleep also had an increased risk of dozing off during the day and reported sleepiness more often than subjects without snoring or apneas. Similarly, our study showed that subjects reporting nocturnal sweating and nGER, which are symptoms that have been associated with OSA (Arnardottir et al., 2013; Demeter, Visy, & Magyar, 2005) and insomnia (Hartz, Ross, Noyes, & Williams, 2013), also reported more often daytime sleepiness and a tendency to doze off during the day.

As in previous studies (Ford, Cunningham, Giles, & Croft, 2015; Janson et al., 1996; Kallin et al., 2016), we found that subjects reporting both risk of dozing off and feeling sleepy more often reported asthma. We also found that subjects with hypertension and cardiovascular disease more often reported feeling sleepy during the day, which is in line with previous studies (Gislason & Almqvist, 1987). However, having those previously mentioned diseases was only related to feeling sleepy and not to risk of dozing off. Subjects in all three sleepiness groups had almost twice as high odds of diabetes compared to the non-sleepy group. However, this was only statistically significant for the largest group (sleepy only). In our study, neither the risk of dozing off nor feeling sleepy was significantly related to BMI, in contrast to previous studies (Bixler et al., 2005; Panossian & Veasey, 2012; Resta et al., 2001).

The strengths of this study include the simultaneously analyzed various aspects of EDS in a well-defined target population recruited from the general population in two countries. Because of the high participation rate and the lack of differences between the responders and the non-responders (Buist et al., 2007), we believe the responders accurately reflected the general populations of the two countries. The study was based on a well-standardized protocol with excellent staff training, but the age distribution of the participants was a limitation as they were all over 40 years of age, as well as the fact that the diagnosis of cardiovascular disease, hypertension and diabetes was only based on self-report of a doctor's diagnosis and appropriate pharmacological treatment. We did not perform a sleep study on the participants to assess the prevalence of OSA and other sleep disorders. Therefore, we do not know how many subjects in the cohort had treated or untreated OSA and how much effect undiagnosed OSA had on the prevalence of EDS. We used the MAP index, a widely used and validated tool for OSA risk assessment, to minimize this effect on our results. However, because many subjects in our cohort answered questions on OSA symptoms (snoring, snorting and apneas during sleep) with 'I don't know', we were only able to calculate the MAP index for 760 out of 1,338 subjects (57%). Another limitation is the lack of information about sleep time as insufficient sleep is a common cause of EDS. Also, the current study was based entirely on subjective measures of sleepiness and no objective assessment was carried out, such as the multiple sleep latency test, which is considered today the 'reference standard' when measuring EDS (Littner et al., 2005); however, this is costly for large epidemiological studies. Also, no psychometric tests were performed, such as the psychomotor vigilance test, which is a limitation of the study. However, in a recent epidemiological study from our group (Arnardottir, Bjornsdottir, Olafsdottir, Benediktsdottir, & Gislason, 2016) we only found a significant relationship between OSA severity (measured by the apnea hypopnea index [AHI]) and psychomotor vigilance test in those with severe OSA (AHI ≥ 30) and not in those with less severe disease.

In conclusion, the current findings suggest that measuring both the feeling of sleepiness and the risk of dozing off is important when assessing patients with potential EDS. Also, our data suggest that the risk of dozing off without feeling sleepy does not necessarily have consequences on health and quality of life. As the ESS measures only one aspect of sleepiness it is not adequate, on its own, when assessing subjects with EDS. Future research on the definition and measurement of EDS is important so we can better evaluate the magnitude and aetiological factors of EDS.

AUTHOR CONTRIBUTIONS

All the authors have made substantial contributions to design, and acquisition and analysis of data for this article. Calculations were performed by the first author with help from Christer Janson and Thor Aspelund. The first author was mainly responsible for drafting the paper and the co-authors revised the article for important intellectual content. All the authors have approved this version to be published.

CONFLICT OF INTEREST

No conflicts of interest declared.

ORCID

Elin H. Thorarinsdottir https://orcid.org/0000-0001-6561-3746

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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RESEARCH ARTICLE

Different components of excessive daytime sleepiness and the change with positive airway pressure treatment in patients with obstructive sleep apnea: Results from the Icelandic Sleep Apnea Cohort (ISAC)

Elin H. Thorarinsdottir[1,2] | Christer Janson[3] | Thor Aspelund[2,4] | Bryndis Benediktsdottir[1,2] | Sigurður Júlíusson[5] | Thorarinn Gislason[2,6] | Samuel T. Kuna[7,8] | Allan I. Pack[7] | Brendan T. Keenan[7]

[1]Primary Health Care of the Capital Area, Reykjavik, Iceland

[2]Faculty of Medicine, University of Iceland, Reykjavik, Iceland

[3]Department of Medical Sciences: Respiratory, Allergy and Sleep Research, Uppsala University, Uppsala, Sweden

[4]Icelandic Heart Association, Kopavogur, Iceland

[5]Ear, Nose and Throat (ENT) Department, Landspitali – The National University Hospital of Iceland, Reykjavik, Iceland

[6]Sleep Department, Landspitali – The National University Hospital of Iceland, Reykjavik, Iceland

[7]Division of Sleep Medicine, Department of Medicine, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, USA

[8]Department of Medicine, Corporal Michael J. Crescenz VA Medical Center, Philadelphia, Pennsylvania, USA

Correspondence
Elin H. Thorarinsdottir, Faculty of Medicine, University of Iceland and Primary Health Care of the Capital Area, Efstaleiti 3, 103 Reykjavik, Reykjavik, Iceland.
Email: eth32@hi.is

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Summary

Excessive daytime sleepiness includes both an inability to stay awake during the day and a general feeling of sleepiness. We describe different dimensions of daytime sleepiness in adults with moderate–severe obstructive sleep apnea (OSA) before and after 2 years of positive airway pressure (PAP) treatment. Using the Epworth Sleepiness Scale (score >10 defined as "risk of dozing") and Basic Nordic Sleep Questionnaire (feeling sleepy ≥3 times/week defined as "feeling sleepy"), participants were categorised into sleepiness phenotypes labelled non-sleepy, risk of dozing only, feeling sleepy only, or both symptoms. Participants repeated baseline assessments and PAP adherence was evaluated after 2 years. PAP-adherent subjects with sleepiness symptoms at both baseline and follow-up were considered persistently sleepy. Of the 810 participants, 722 (89%) returned for follow-up. At baseline, 17.7% were non-sleepy, 7.7% were at risk of dozing only, 24.7% were feeling sleepy only, and 49.9% had both symptoms. PAP adherence did not differ by baseline sleepiness phenotype. Patients with risk of dozing demonstrated greater PAP benefits for sleepiness symptoms than non-sleepy and feeling sleepy only phenotypes. Using these phenotypes, 42.3% of PAP users had persistent sleepiness; they had less severe OSA ($p < 0.001$), more persistent OSA symptoms and more often had symptoms of insomnia than patients in whom sleepiness resolved. Our present results, therefore, suggest that measuring the risk of dozing and the feeling of sleepiness reflect different sleepiness components

and may respond differently to PAP. Patients feeling sleepy without risk of dozing may need more thorough evaluation for factors contributing to sleepiness before initiating treatment.

KEYWORDS
Basic Nordic Sleep Questionnaire, Epworth Sleepiness Scale, subjective sleepiness

1 | INTRODUCTION

Excessive daytime sleepiness (EDS) is a common symptom that interferes with daily activities and impairs quality of life (QoL; Engleman & Douglas, 2004). EDS has been associated with many medical and psychiatric disorders, e.g. obesity (Dixon et al., 2007; Dixon, Schachter, & O'Brien, 2001), neurodegenerative disease (Okamura et al., 2016), and depression (Plante, Finn, Hagen, Mignot, & Peppard, 2017), as well as insufficient or impaired sleep and sleep disorders (Murray, 2016). Of conditions causing EDS, obstructive sleep apnea (OSA) is the most frequent diagnosis (Jackson, Howard, & Barnes, 2011). OSA is a common disease characterised by upper airway obstruction during sleep that causes breathing cessations, oxygen desaturations, and frequent arousals (Heinzer et al., 2015; White, 1995). It is an established health concern affecting 9%–38% of the general population (Senaratna et al., 2017). Patients with OSA often have EDS and reduced QoL (Poceta et al., 1992; Valencia-Flores et al., 2016). The most effective treatment for moderate and severe OSA is the application of positive airway pressure (PAP) during sleep (Kushida et al., 2006). PAP has been shown to improve symptoms of sleepiness and increase QoL, both in the short and long terms (Giles et al., 2006; Kawahara, Akashiba, Akahoshi, & Horie, 2005; Lindberg, Berne, Elmasry, Hedner, & Janson, 2006). However, not all patients with OSA experience improvement of their symptoms with PAP. In some cases, other risk factors for EDS are present, such as short sleep, depression, or insomnia, which cause persistent sleepiness despite adequate PAP treatment. In a recent review (Chapman, Serinel, Marshall, & Grunstein, 2016), persistent sleepiness was considered to be caused by comorbid conditions of OSA, such as diabetes and obesity, not OSA itself.

The most commonly used measure of sleepiness in OSA patients is the Epworth Sleepiness Scale (ESS), a brief questionnaire that measures the tendency to doze (Johns, 1991). Subjects with an ESS score of >10 are considered to have EDS (Johns, 1992). Other questionnaires, such as the Basic Nordic Sleep Questionnaire (BNSQ), estimate the more general feeling of sleepiness and how frequently this occurs, rather than the tendency to fall asleep (Partinen & Gislason, 1995). In a recent study in the general population (Thorarinsdottir et al., 2019), we combined the ESS score (>10 points considered as having "risk of dozing") and the question "Do you feel sleepy during the day?" from the BNSQ (≥3 times/week considered as "feeling sleepy") to define four sleepiness phenotypes based on the presence or absence of these symptoms. Only 27.7% of those reporting "feeling sleepy" also had a "risk of dozing" (ESS score >10). Moreover, reporting "feeling sleepy" was better correlated with variables that contribute to EDS, such as restless legs syndrome (RLS), nocturnal gastro-oesophageal reflux (nGER) and insomnia symptoms, and these patients had poorer QoL than those at risk of dozing only. Our present results, therefore, indicated the ESS alone is insufficient to assess EDS in the general population.

The aim of the present study was to evaluate the prevalence and associations of these same sleepiness phenotypes in a clinical cohort of patients with moderate–severe OSA and to evaluate if sleepiness phenotype at baseline predicts PAP adherence and benefits. Differences in clinical characteristics, health outcomes, sleep-related symptoms, disease severity, and QoL were evaluated at baseline and after 2 years of PAP treatment. Using our multi-dimensional approach, we also investigated the prevalence and predictive factors of persistent sleepiness in PAP-treated patients. We hypothesised that adding the more general measure of feeling sleepy would identify more subjects with significant EDS who would otherwise not be recognised when using only the traditional ESS criterion.

2 | PATIENTS AND METHODS

2.1 | Participants and data collection

All patients diagnosed with moderate–severe OSA (apnea–hypopnea index [AHI] of ≥15 events/hr) from September 2005 to December 2009 who were referred for PAP treatment to the Landspitali University Hospital in Reykjavik were invited to join the Icelandic Sleep Apnea Cohort (ISAC; Björnsdóttir et al., 2013). After written informed consent was obtained, subjects completed standardised questionnaires, physical examination, and a home type III sleep study, and fasting morning blood samples were drawn. At 2 years after initiation of PAP treatment, subjects completed the same assessments as at baseline and their PAP adherence was evaluated (see details in Supporting Information). The study protocol was approved by the National Bioethics Committee, the Data Protection Authority of Iceland, and the University of Pennsylvania Institutional Review Board (Philadelphia, PA, USA).

2.2 | Measurements and questionnaires

Participants answered standardised questionnaires about health, habits, medication use and frequency of sleep-related symptoms, and their height and weight were measured. For further details, see Supporting Information.

2.3 | Assessment of QoL and chronotype

The QoL was measured using the 12-item Short-Form Health Survey (SF-12) for physical (PCS) and mental (MCS) QoL (Ware, Kosinski, & Keller, 1996). A lower score is indicative of worse QoL. Morningness–eveningness preference was assessed with the Horne–Ostberg Morningness–Eveningness Questionnaire (MEQ; Horne & Ostberg, 1976), a 19-item questionnaire with a total score ranging from 16 to 86. A higher score is indicative of morningness and a lower score of eveningness. In addition to the total score, individuals were categorised as morning types (MEQ score of 59–86), neither (42–58) or evening types (16–41; Horne & Ostberg, 1976).

2.4 | Assessment of OSA, PAP usage and adherence

Prior to PAP treatment, all patients with OSA had an overnight sleep study at home with a portable sleep monitor (Natus Medical Inc. or NoxMedical). The AHI, oxygen desaturation index (ODI ≥4%), minimum oxygen saturation (minSaO_2) and percentage of time spent at SaO_2 <90% were calculated (Supporting Information).

At 2 years after PAP initiation (ResMed Corp.), patients were invited to participate in the follow-up where PAP adherence was estimated either by objective usage data from memory cards or subjective data from self-report (Supporting Information). Subjects were subsequently defined as PAP users, non-PAP users or as partial users.

2.5 | Assessment of EDS and persistent sleepiness on PAP

As in our previous paper (Thorarinsdottir et al., 2019), EDS was evaluated using two different methods: the ESS (Johns, 1991) and one question from the BNSQ (Partinen & Gislason, 1995), "Do you feel sleepy during the day?". Those who scored >10 points on the ESS were considered at risk of dozing during the day (e.g. "risk of dozing"; Johns, 1992). For the question "do you feel sleepy during the day?", participants were asked to rate their answers on a 5-point scale: 1 = never/almost never; 2 = less than once a week; 3 = once or twice a week; 4 = three to five times a week; or 5 = every day or almost every day of the week. Those who answered three times or more often per week (scores 4 and 5) were considered as "feeling sleepy" (Janson et al., 1995). Participants at baseline (N = 810) and the 2-year follow-up were subsequently categorised into four different sleepiness phenotypes based on the presence or absence of these symptoms:

1. Non-sleepy: ESS score of ≤10 and reporting feeling sleepy <3 times/week (n = 143)
2. Risk of dozing only: ESS score of >10 and reporting feeling sleepy <3 times/week (n = 62)
3. Feeling sleepy only: ESS score of ≤10 and reporting feeling sleepy ≥3 times/week (n = 201)
4. Both risk of dozing and feeling sleepy: ESS score of >10 and reporting feeling sleepy ≥3 times/week (n = 404)

To examine the prevalence of persistent sleepiness using this multi-dimensional sleepiness definition, subjects that were adherent to PAP (see details below) and sleepy at baseline (e.g. "risk of dozing" and/or "feeling sleepy") were re-classified into the four sleepiness phenotypes according to their answers to the questionnaires at follow-up. Participants that were no longer sleepy at the 2-year follow-up were characterised as having "improved sleepiness". Those still reporting risk of dozing only (ESS score of >10), feeling sleepy only (≥3 times/week) or both were characterised as having "persistent sleepiness". Estimates of prevalence of persistent sleepiness were compared to those obtained using the traditional definition of residual sleepiness based solely on the ESS (Gasa et al., 2013; Koutsourelakis et al., 2009; Pépin et al., 2009).

2.6 | Statistical methods

At baseline, categorical variables were summarised using frequencies and percentages and compared among groups using chi-squared tests. Continuous variables were summarised using means and standard deviations (*SD*s) and compared among groups using analysis of variance (ANOVA). Statistical significance was based on a Bonferroni-corrected threshold adjusted for the total number of measures evaluated within each measurement domain, i.e. in Table 1: *characteristics and habits* (n = 8 measures, $p < 0.0063$), *medical disorders and medication use* (n = 9, $p < 0.0056$), *OSA severity* (n = 4, $p < 0.0125$), *sleep-related symptoms* (n = 5, $p < 0.01$), *chronotype* (n = 2, $p < 0.025$), *sleepiness symptoms* (n = 8, $p < 0.0063$), *insomnia symptoms* (n = 3, $p < 0.0167$), and *QoL* (n = 2, $p < 0.025$). A $p < 0.05$ was considered nominally significant in all analyses. If significant or nominal differences were observed among groups, pairwise comparisons were performed. At follow-up, comparisons between participants with and without persistent sleepiness were performed similarly, using t tests for continuous measures or chi-squared tests for categorical data. To compare sleepiness phenotypes at follow-up between PAP and non-PAP users within each sleepiness phenotype at baseline a chi-square test was used.

To examine changes in sleepiness, insomnia symptoms and QoL, subject-specific change scores were calculated as follow-up minus baseline values. For evaluating the response to PAP treatment, we

TABLE 1 Demographics and characteristics of the four sleepiness phenotypes at baseline

Measurement	Non-sleepy[a]	Risk of dozing only[b]	Feeling sleepy only[c]	Risk of dozing and feeling sleepy[d]	*p**
Characteristics and habits[†]					
N (%)	143 (17.7)	62 (7.7)	201 (24.7)	404 (49.9)	-
Male, %	81.1	82.3	80.1	81.2	0.981
Age, years, mean (*SD*)	56.9 (9.7)[k,l]	56.3 (9.3)[l]	54.5 (12.4)[i]	53.4 (10.0)[i,j]	**0.004**
Body mass index, kg/m^2, mean (*SD*)	33.5 (5.3)	32.2 (5.7)	33.5 (6.1)	33.8 (5.6)	0.261
Large waist[e], %	82.5	74.2[k,l]	86.1[j]	87.9[j]	0.026
Neck circumference, cm, mean (*SD*)	42.3 (3.7)	42.2 (4.2)	42.6 (3.8)	43.0 (3.7)	0.160
Smoking history, %					
Never	33.8	27.4	28.0	25.3	0.479
Past	50.0	54.9	50.0	52.1	
Current	16.2	17.7	22.0	22.6	
Heavy alcohol use, %	2.4	3.7	4.6	5.5	0.557
Current regular exercise, %	75.0[k,l]	63.3	64.1[i]	59.4[i]	0.012
Medical disorders and medication use[‡], %					
Hypertension	53.9	45.2	45.3	43.2	0.181
Cardiovascular disease	28.0[k,l]	17.7	19.0[i]	15.4[i]	0.011
Type 2 diabetes	7.0	12.9	11.0	7.7	0.296
Metabolic syndrome	78.3	69.4	73.6	75.3	0.551
Hypothyroidism	4.9	3.2	6.5	4.5	0.132
Obstructive lung disease	20.3	12.9	15.9	17.1	0.574
Use of antidepressant	16.8	11.3	22.4	17.8	0.206
Use of hypnotics	14.7	8.1	16.4[l]	9.2[k]	0.033
Use of anti-hypertensives	60.1	50.0	52.7	49.3	0.161
OSA severity at baseline[¤]					
AHI, events/hr, mean (*SD*)	43.6 (19.2)	44.8 (16.6)	45.7 (23.0)	45.3 (20.5)	0.812
ODI, events/hr, mean (*SD*)	33.1 (17.4)	36.4 (17.4)	35.7 (21.9)	36.3 (20.7)	0.426
minSaO_2, %, mean (*SD*)	76.2 (8.1)	76.2 (6.4)	77.0 (7.7)	75.7 (8.4)	0.336
Time spent at SaO_2 <90%, %, mean (*SD*)	12.8 (16.7)	13.9 (18.0)	13.0 (18.2)	14.9 (19.0)	0.513
Sleep-related symptoms[°], %					
Restless legs syndrome	25.9[i,l]	47.5[i,k]	28.9[i,l]	43.3[i,k]	**<0.001**
Snoring ≥ 3 nights/week	90.9[l]	93.3	94.9	97.4[i]	0.016
Witnessed apneas ≥1 night/week	65.7[l]	77.4	74.6[l]	82.0[i,k]	**0.001**
Sweating during sleep ≥3 nights/week	20.3[k,l]	22.6[l]	30.4[i]	37.4[i,j]	**0.001**
nGER ≥1 night/week	10.5	11.3	15.6	14.7	0.491
Chronotype[§]					
Horne–Ostberg total score, mean (*SD*)	58.1 (9.2)[k,l]	57.9 (8.3)[k,l]	53.3 (10.0)[i,j]	54.8 (11.2)[i,j]	**<0.001**
Morning type[f], %	57.5	49.2	33.9	40.0	**<0.001**
Evening type[g], %	5.2	3.3	11.1	14.0	
Neither[h], %	37.3	47.5	55.0	46.0	

TABLE 1 (Continued)

Measurement	Non-sleepy[a]	Risk of dozing only[b]	Feeling sleepy only[c]	Risk of dozing and feeling sleepy[d]	*p**
Sleepiness symptoms[†]					
Epworth Sleepiness Scale score, mean (*SD*)	6.0 (2.6)	14.4 (3.2)	7.4 (2.2)	15.4 (3.2)	**<0.001**
I feel sleepy during the day, ≥3 times/week, %	0.0	0.0	100.0	100.0	**<0.001**
I fall asleep involuntarily during the day, ≥3 times/week, %	3.5[l]	14.5[l]	10.5[l]	34.7[i,j,k]	**<0.001**
I fall asleep if I relax (Television), ≥3 times/week, %	25.9[j,k,l]	74.2[i,k]	41.8[i,j,l]	81.7[i,k]	**<0.001**
I doze off at the steering wheel when driving, ≥3 times/week, %	0.0[j,l]	8.1[i]	2.0[l]	12.9[i,k]	**<0.001**
I take a nap during the day, ≥3 times/week, %	7.7[k,l]	19.4[l]	25.4[i,l]	35.4[i,j,k]	**<0.001**
I feel physically tired during the day, ≥3 times/week, %	28.0[k,l]	38.7[k,l]	80.6[i,j,l]	91.1[i,j,k]	**<0.001**
I feel rested when I wake up, ≥3 times/week, %	50.0[j,k,l]	35.5[i,k,l]	21.0[i,j,l]	11.6[i,j,k]	**<0.001**
Insomnia symptoms[¢], %					
Difficulties initiating sleep, ≥3 nights/week	12.0[k]	9.7[k]	22.4[i,j,l]	14.4[k]	**0.014**
Difficulties maintaining sleep, ≥3 nights/week	46.9[l]	51.6[l]	54.7[l]	65.6[i,j,k]	**<0.001**
Early morning awakening, ≥3 nights/week	21.0[l]	19.4	29.5	31.2[i]	0.045
Quality of life[§], mean (*SD*)					
SF-12 mental component score	52.5 (9.7)[k,l]	49.4 (10.9)	47.5 (11.5)[i]	47.0 (10.7)[i]	**<0.001**
SF-12 physical component score	42.7 (10.4)[k,l]	42.3 (13.1)	40.8 (10.4)[i]	38.7 (10.7)[i]	**<0.001**

AHI, apnea–hypopnea index; minSaO_2, minimum oxygen saturation; nGER, nocturnal gastro-oesophageal reflux; ODI, Oxygen Desaturation Index; OSA, obstructive sleep apnea; *SD*, standard deviation; SF-12, Short Form (12) Health Survey.

[a]Epworth Sleepiness Scale (ESS) score ≤10 and reporting feeling sleepy <3 times/week.

[b]ESS score >10 but reporting feeling sleepy <3 times/week.

[c]ESS score ≤10 but reporting feeling sleepy ≥3 times/week.

[d]ESS score >10 and reporting feeling sleepy ≥3 times/week.

[e]waist circumference ≥102 cm in males, ≥88 cm in females.

[f]Horn–Ostberg score ≥59.

[g]Horn–Ostberg score ≤41.

[h]Horn–Ostberg score 41–59.

[i]$p < 0.05$, significantly different from non-sleepy.

[j]$p < 0.05$, significantly different from risk of dozing only.

[k]$p < 0.05$, significantly different from feeling sleepy only.

[l]$p < 0.05$, significantly different from the group both risk of dozing and feeling sleepy.

*p value from Pearson's chi-square test (categorical variables) and one-way analysis of variance (continuous variables). Significant p values after Bonferroni correction are in bold.

†Bonferroni corrected significance level: $p < 0.0063$.

‡Bonferroni corrected significance level: $p < 0.0056$.

¤Bonferroni corrected significance level: $p < 0.0125$.

°Bonferroni corrected significance level: $p < 0.01$.

§Bonferroni corrected significance level: $p < 0.025$.

¢Bonferroni corrected significance level: $p < 0.0167$.

compared change scores between PAP users and non-PAP users overall and within sleepiness phenotypes. To determine whether the changes with PAP adherence differed based on sleepiness phenotype, we evaluated the significance of the interaction term between sleepiness phenotypes and PAP adherence (PAP users versus non-PAP users) in the context of a linear regression model fit in the full sample (including main effect terms). All analyses were performed controlling for a priori baseline covariates of age, sex, body mass index (BMI), and AHI. To facilitate comparisons across measurements, differences in change scores were also presented as standardised mean differences (SMDs) calculated based on normalised outcomes (i.e. *Z* scores). All analyses were performed using Stata software, Version 16.0 (StataCorp).

3 | RESULTS

3.1 | Sample characteristics

Over 90% of eligible and approached subjects agreed to participate in the study. A total of 822 participants with untreated OSA were enrolled (Figure 1). In all, 12 (1.5%) individuals did not answer questions on sleepiness and were excluded from the analyses, resulting in a final baseline study cohort of 810 participants. Overall, participants were predominantly middle-aged (mean [*SD*] age of 54.5 [9.1] years), male (81%), obese (mean [*SD*] BMI of 33.5 [5.7] kg/m^2) and had severe OSA (mean [*SD*] AHI of 45.0 [20.7] events/hr, ODI of 35.6 [20.2] events/hr, minSaO_2 of 76.2 [8.0]% and percentage of time spent at SaO_2 <90% 14.0 [18.3]%). The 2-year follow-up assessment was completed by 722 (89.1%) participants.

3.2 | Sleepiness phenotypes at baseline

3.2.1 | Prevalence, characteristics, habits, and OSA severity

At baseline, approximately half (49.9%) of the participants reported both risk of dozing and feeling sleepy, 24.7% were feeling sleepy only, 7.7% were at risk of dozing only, and 17.7% were non-sleepy (Table 1). Significant or nominal differences among these sleepiness phenotypes were observed for age ($p = 0.004$), proportion with a large waist circumference ($p = 0.026$) and frequency of regular exercise ($p = 0.012$). Patients feeling sleepy (with or without the risk of dozing) were younger on average, more likely to have a large waist circumference, and less likely to report current regular exercise. Importantly, there was no significant difference in OSA severity among the four sleepiness groups (Table 1); all had severe OSA on average based on typical AHI thresholds.

3.2.2 | Medical disorders and medication use

There was a nominal difference across the sleepiness phenotypes at baseline in self-reported cardiovascular disease ($p = 0.011$) and use of hypnotics ($p = 0.033$) (Table 1). In pairwise comparisons, the

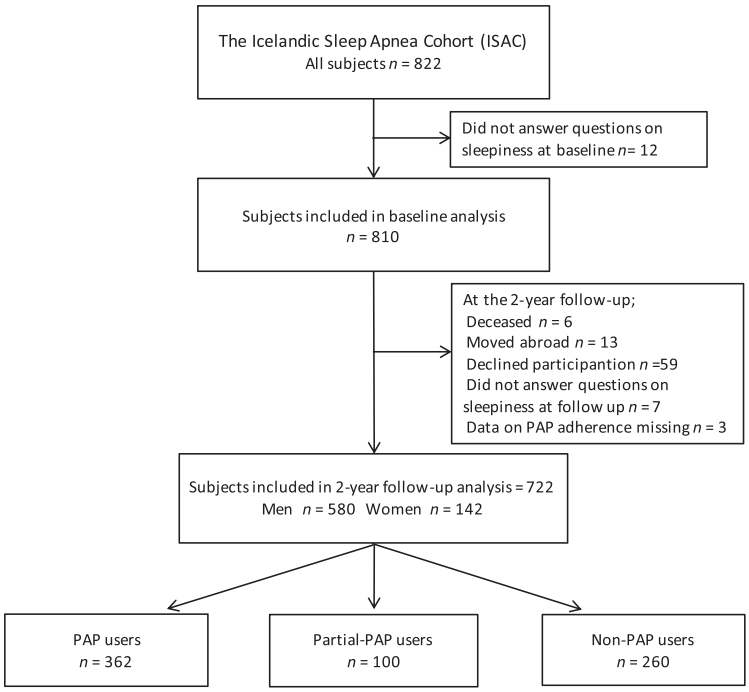

FIGURE 1 Flow chart of the study population

non-sleepy groups had the highest prevalence of cardiovascular disease (28%).

3.2.3 | Sleep-related symptoms and chronotype

Significant or nominal differences between the four sleepiness phenotypes were observed for all sleep-related symptoms, except nGER ($p = 0.49$; Table 1). Overall, the non-sleepy subjects were least likely to report sleep-related symptoms such as snoring, apneas, and nocturnal sweating. The difference was generally largest between the non-sleepy and those both at risk of dozing and feeling sleepy. The two phenotypes with risk of dozing were significantly more likely to report RLS compared to the non-sleepy and feeling sleepy only phenotypes. Reporting an evening chronotype was significantly more common among those feeling sleepy compared to those at risk of dozing and non-sleepy.

3.2.4 | Sleepiness symptoms

In general, the phenotype both at risk of dozing and feeling sleepy was more likely to report sleepiness symptoms than other phenotypes, such as falling asleep involuntarily, taking a nap, and feeling physically tired during the day (Table 1). These patients were also significantly less likely to feel rested in the morning than those in other phenotypes ($p < 0.001$). The difference in sleepiness symptoms was in general largest between the non-sleepy and the phenotype both at risk of dozing and feeling sleepy.

All those at risk of dozing, independent of feeling sleepy, were more likely than other phenotypes to report sleepiness symptoms involving risk of falling asleep, such as falling asleep when relaxing and dozing off at the steering wheel when driving (Table 1). Similarly, those feeling sleepy, independent of risk of dozing, significantly more often reported feeling physically tired during the day and not feeling rested in the morning. Furthermore, the phenotype only feeling sleepy more often reported falling asleep when relaxing, taking a nap during the day, feeling physically tired and not feeling rested in the morning than the non-sleepy phenotype (Table 1). However, the risk of dozing only phenotype was only significantly different in reporting sleepiness symptoms than non-sleepy phenotype for falling asleep if relaxing and dozing off at the steering wheel when driving (Table 1).

3.2.5 | Insomnia symptoms

There was a nominal or significant difference between the four phenotypes for all three insomnia symptoms (Table 1). The phenotype only feeling sleepy significantly more often reported difficulties initiating sleep ($p = 0.014$) than other phenotypes, whereas difficulties maintaining sleep were significantly more often reported among those both feeling sleepy and at risk of dozing ($p < 0.001$). Early morning awakenings was nominally more often reported by those both at risk of dozing and feeling sleepy compared to non-sleepy subjects.

3.2.6 | QoL

There were significant differences in both mental ($p < 0.001$) and physical ($p < 0.001$) QoL based on the SF-12 questionnaire among the four sleepiness phenotypes (Table 1). Patients reporting feeling sleepy (with or without the risk of dozing) had poorer mental and physical QoL than those who were non-sleepy.

3.3 | PAP adherence and response to treatment

3.3.1 | Adherence to PAP treatment and alternative treatment

At the 2-year follow-up, 362 (50.1%) subjects were adherent PAP users and 260 (36.0%) were non-PAP users (Figure 1). The remaining 100 (13.9%) subjects were classified as partial PAP users and excluded from analyses evaluating treatment effects. As shown in Table 2, there was no significant difference in PAP use and adherence between the sleepiness phenotypes. Furthermore, subjects were asked if they used an alternative treatment for OSA during the 2-year follow-up period. Among all participants that attended the 2-year follow-up, 49 subjects (6.8%) reported using a mandibular advancement device and 107 subjects (14.8%) had undergone a surgery for OSA. According to weight measurements, 21 subjects (2.9%) had lost >10% of their weight at the 2-year follow-up. However, there was no significant difference in reporting these alternative treatments and having weight loss between the sleepiness phenotypes at follow-up (all $p > 0.117$; data not shown).

3.3.2 | Impact of PAP adherence on change in sleepiness, insomnia symptoms and QoL

Table 3 shows the difference in the change in symptoms of sleepiness, insomnia, and QoL between PAP and non-PAP users within and between sleepiness phenotypes, adjusted for gender, baseline age, BMI, and AHI. Overall, interaction tests demonstrated significant or nominal evidence of differences between the four sleepiness phenotypes in the effect of PAP on ESS score ($p = 0.002$), feeling sleepy during the day ($p = 0.002$), falling asleep involuntarily during the day ($p < 0.001$), falling asleep if relaxed in front of the television ($p = 0.012$), feeling physically tired ($p = 0.007$), and feeling rested when waking up ($p = 0.001$). For each of these symptoms, larger benefits of PAP adherence were observed among the phenotypes with a risk of dozing off with or without feeling sleepy, compared with smaller or non-significant differences between PAP users and non-users in the non-sleepy and feeling sleepy only groups. There

TABLE 2 Comparisons of positive airway pressure (PAP) usage between the four sleepiness phenotypes

Measurement	Non sleepy[a]	Risk of dozing only[b]	Feeling sleepy only[c]	Risk of dozing and feeling sleepy[d]	*p**
N (%)	121 (16.8)	57 (7.9)	172 (23.8)	372 (51.5)	-
Any PAP usage, *n* (%)	70 (57.9)	38 (66.7)	102 (59.3)	252 (67.7)	0.108
PAP usage group, *n* (%)					
PAP user	55 (45.5)	29 (50.9)	84 (48.8)	194 (52.1)	0.289
Partial PAP user	15 (12.4)	9 (15.8)	18 (10.5)	58 (15.6)	
Non-PAP user	51 (42.1)	19 (33.3)	70 (40.7)	120 (32.3)	
PAP usage, hr					
Mean (*SD*)	5.9 (2.1)	5.8 (2.0)	6.3 (2.3)	6.1 (2.0)	0.670
Median (range)	6.3 (0.0–9.28)	6.4 (0.5–9.4)	6.5 (0.0–10.2)	6.5 (0.0–10.2)	0.459
Nights PAP used in last 28 days, *n*					
Mean (*SD*)	23.3 (6.8)	23.0 (7.6)	23.6 (7.4)	24.4 (6.2)	0.531
Median (range)	26.0 (0.0–28.0)	27.0 (1.0–28.0)	27.0 (0.0–28.0)	27.0 (0.0–28.0)	0.501

PAP, positive airway pressure; *SD*, standard deviation.

[a]Epworth Sleepiness Scale (ESS) score ≤10 and reporting feeling sleepy <3 times/week.

[b]ESS score >10 but reporting feeling sleepy <3 times/week.

[c]ESS score ≤10 but reporting feeling sleepy ≥3 times/week.

[d]ESS score >10 and reporting feeling sleepy ≥3 times/week.

**p* value from Pearson's chi-square test or Kruskal–Wallis test (categorical variables), one-way analysis of variance (continuous variables).

TABLE 3 Adjusted differences in change in symptom variables between positive airway pressure (PAP) and non-PAP users overall and within individual sleepiness phenotype

Measurement	Group by PAP user interaction *p* value*	Non-sleepy[a]			Risk of dozing only[b]	
		PAP versus non-PAP user[e]	SMD	*p***	PAP versus non-PAP user[e]	SMD
Sleepiness symptoms‡						
Epworth Sleepiness Scale	**0.002**	−1.80 (−2.87, −0.73)	−0.64	**0.001**	−4.00 (−6.99, −1.01)	−0.76
I feel sleepy during the day	**0.002**	−0.45 (−1.00, 0.10)	−0.33	0.109	−0.68 (−1.59, 0.23)	−0.46
I fall asleep involuntarily during the day	**<0.001**	0.26 (−0.09, 0.61)	0.30	0.139	−0.66 (−1.43, 0.11)	−0.53
I fall asleep if I relax (television)	0.012	−0.30 (−0.72, 0.11)	−0.30	0.154	−0.81 (−1.58, −0.04)	−0.65
I doze off at the steering wheel when driving	0.219	−0.07 (−0.20, 0.07)	−0.19	0.346	−0.33 (−1.05, 0.38)	−0.27
I take a nap during the day	0.247	−0.10 (−0.46, 0.26)	−0.11	0.595	−0.23 (−1.11, 0.66)	−0.17
I feel physically tired during the day	0.007	−0.63 (−1.17, −0.09)	−0.47	0.023	−1.77 (−2.62, −0.93)	−1.16
I feel rested when I wake up	**0.001**	0.38 (−0.23, 0.99)	0.25	0.220	1.31 (0.55, 2.08)	0.96
Insomnia¢						
Difficulties initiating sleep	0.700	−0.16 (−0.66, 0.34)	−0.13	0.516	0.27 (−0.39, 0.93)	0.28
Difficulties maintaining sleep	0.805	−0.52 (−1.13, 0.09)	−0.35	0.091	−0.71 (−1.91, 0.49)	−0.39
Early morning awakening	0.249	0.42 (−0.17, 1.02)	0.29	0.161	−0.28 (−1.08, 0.52)	−0.23
Quality of life§						
SF-12 mental component	0.915	0.96 (−3.22, 5.14)	0.10	0.649	2.74 (−3.96, 9.44)	0.28
SF-12 physical component	0.244	3.47 (−0.35, 7.29)	0.38	0.075	1.92 (−2.75, 6.58)	0.28

PAP, positive airway pressure; SF-12, Short Form (12) Health Survey; SMD, standardised mean difference.

Models adjusted for gender, baseline age, body mass index, and apnea–hypopnea index.

[a]Epworth Sleepiness Scale (ESS) score ≤10 and reporting feeling sleepy <3 times/week.

[b]ESS score >10 but reporting feeling sleepy <3 times/week.

[c]ESS score ≤10 but reporting feeling sleepy ≥3 times/week.

[d]ESS score >10 and reporting feeling sleepy ≥3 times/week.

[e]Estimates presented as SMD in scores and 95% confidence intervals comparing PAP users and non-PAP users.

**p* value testing for a two-way interaction among sleepy groups, time, and PAP adherence within the linear mixed model, which tests whether differences in symptom response between PAP and non-PAP users differ among sleepiness phenotypes.; ***p* value comparing PAP users versus non-PAP users within each sleepiness phenotype. Significant *p* values after Bonferroni correction are in bold.

‡Bonferroni corrected significance level: $p < 0.0063$.

¢Bonferroni corrected significance level: $p < 0.0167$.

§Bonferroni corrected significance level: $p < 0.025$.

was no significant difference in the effect of PAP on insomnia symptoms or QoL between the four phenotypes.

When examining within-group benefits of PAP adherence, the phenotype both at risk of dozing and feeling sleepy showed more statistically significant differences between PAP users and non-users than other groups (Table 3). This included improvement of all sleepiness symptoms except for dozing off when driving, with moderate to large absolute SMDs ranging from 0.41 to 0.93. This group also showed a significant improvement in reported frequency of difficulties maintaining sleep ($p = 0.003$). The group with risk of dozing only also showed significant benefits of PAP for multiple sleepiness-related symptoms, including the largest PAP effect on improvement in ESS score (adjusted difference in change of ESS score −4.00). This group also showed significant differences in change scores between PAP users and non-PAP users for falling asleep if relaxed in front of the television (SMD −0.65, $p = 0.039$), feeling physically tired (SMD −1.16, $p < 0.001$) and waking up rested (SMD 0.96, $p = 0.001$).

Patients reporting only feeling sleepy showed less PAP related improvements than groups with risk of dozing off. This phenotype showed only a nominally significant PAP-related improvement of feeling rested when waking up in the morning (SMD 0.40, $p = 0.021$). Also, the feeling sleepy only phenotype showed a nominal increase in reported frequency of early morning awakenings associated with PAP usage (SMD 0.38, $p = 0.027$). However, PAP use did not have a significant effect on other symptoms among the feeling sleepy phenotype. Finally, the non-sleepy phenotype showed some improvement in the ESS score with PAP use compared to non-PAP users (adjusted difference in change of ESS score −1.80, $p = 0.001$) and feeling physically tired during the day (SMD −0.47, $p = 0.023$), but did not show a significant effect of PAP on other measures.

3.3.3 | Change in sleepiness phenotype

Figure 2 shows the changes in the four sleepiness phenotypes between PAP adherent subjects and non-PAP users from baseline to follow-up. The phenotype both at risk of dozing and feeling sleepy at baseline was the only group that had a significant difference in sleepiness phenotypes at follow-up between PAP and non-PAP users ($p < 0.001$). In this group, 54.1% of PAP users became

	Feeling sleepy only[c]			Risk of dozing and feeling sleepy[d]			Overall		
*p***	PAP versus non-PAP user[e]	SMD	*p***	PAP versus non-PAP user[e]	SMD	*p***	PAP versus non-PAP user[e]	SMD	*p***
0.010	−0.06 (−1.23, 1.11)	−0.02	0.921	−1.97 (−3.02, −0.91)	−0.41	**<0.001**	−1.89 (−2.65, −1.13)	−0.40	**<0.001**
0.140	−0.43 (−0.88, 0.01)	−0.33	0.054	−1.14 (−1.41, −0.87)	−0.87	**<0.001**	−0.84 (−1.08, −0.60)	−0.56	**<0.001**
0.092	0.16 (−0.25, 0.56)	0.13	0.444	−0.81 (−1.17, −0.45)	−0.50	**<0.001**	−0.43 (−0.67, −0.20)	−0.30	**0.003**
0.039	−0.22 (−0.64, 0.19)	−0.18	0.295	−0.80 (−1.10, −0.50)	−0.57	**<0.001**	−0.60 (−0.80, −0.39)	−0.45	**<0.001**
0.348	−0.06 (−0.29, 0.17)	−0.08	0.633	−0.24 (−0.50, 0.02)	−0.22	0.068	−0.21 (−0.37, −0.05)	−0.22	0.010
0.608	−0.17 (−0.60, 0.26)	−0.13	0.431	−0.58 (−0.92, −0.25)	−0.41	**<0.001**	−0.40 (−0.62, −0.18)	−0.30	**<0.001**
<0.001	−0.20 (−0.68, 0.28)	−0.14	0.413	−0.93 (−1.23, −0.63)	−0.67	**<0.001**	−0.77 (−1.00, −0.54)	−0.53	**<0.001**
0.001	0.66 (0.10, 1.22)	0.40	0.021	1.41 (1.08, 1.73)	0.93	**<0.001**	1.05 (0.80, 1.30)	0.66	**<0.001**
0.410	−0.09 (−0.55, 0.36)	−0.07	0.684	0.06 (−0.21, 0.34)	0.05	0.651	0.01 (−0.19, 0.21)	0.01	0.940
0.237	−0.32 (−0.88, 0.23)	−0.20	0.250	−0.56 (−0.93, −0.20)	−0.36	**0.003**	−0.52 (−0.78, −0.26)	−0.32	**<0.001**
0.486	0.61 (0.07, 1.16)	0.38	0.027	−0.04 (−0.38, 0.31)	−0.03	0.833	0.21 (−0.03, 0.46)	0.15	0.090
0.412	0.85 (−3.04, 4.73)	0.08	0.667	0.19 (−2.65, 3.02)	0.02	0.878	0.81 (−1.09, 2.71)	0.07	0.402
0.410	−2.27 (−5.82, 1.28)	−0.23	0.209	0.93 (−1.47, 3.33)	0.10	0.486	0.97 (−0.68, 2.62)	0.10	0.250

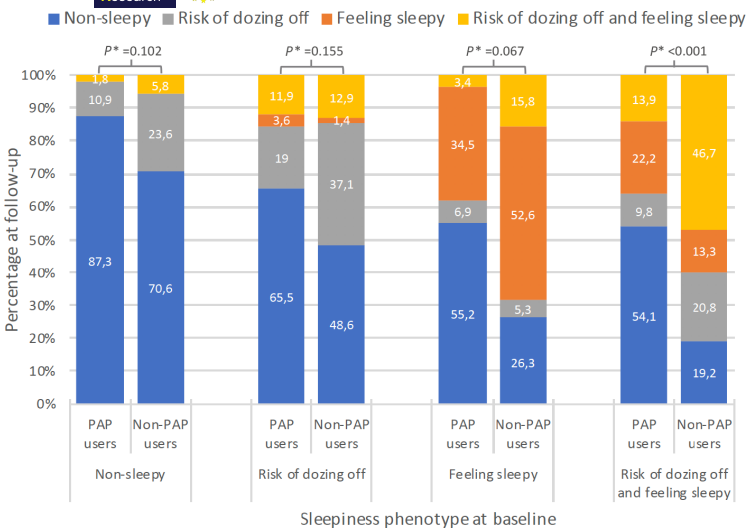

FIGURE 2 Relationship between baseline and follow-up sleepiness phenotypes among positive airway pressure (PAP) and non-PAP users. *p-values from chi-square test comparing distribution of sleepiness phenotypes at follow-up between PAP and non-PAP users

non-sleepy at follow-up, but only 19.2% became non-sleepy among non-PAP users. Similar trends were seen in other groups, with PAP users more likely to be non-sleepy at the 2-year follow-up. Among those at risk of dozing only, 65.5% of PAP users reported being non-sleepy at the 2-year follow-up. Similarly, among those feeling sleepy only, 55.2% of PAP users became non-sleepy at follow-up. Interestingly, the baseline sleepiness phenotypes were fairly persistent, with the majority of patients who did not become non-sleepy typically remaining within the same group at the 2-year follow-up.

3.3.4 | Persistent sleepiness

Of the 362 PAP users, 305 subjects (84.3%) had baseline sleepiness (i.e. risk of dozing, feeling sleepy, or both). When re-classifying these patients based on their self-reported sleepiness symptoms at follow-up, 42.3% met criteria for persistent sleepiness (Table 4). In comparison, only 26% of our cohort met the more traditional residual sleepiness definition of having an ESS score of >10 at baseline and follow-up. While this analysis was restricted to patients characterised as PAP users, those with persistent sleepiness had used their PAP machine ~30 min less per night on average than those whose sleepiness improved (mean [*SD*] 6.6 [1.3] versus.7.1 [1.1] hr/night; $p = 0.004$; Table 4).

Overall, PAP users with persistent sleepiness and those whose sleepiness improved had similar general characteristics, except that those with persistent sleepiness had evidence of lower BMI at both baseline (mean [*SD*] 33.2 [5.6] versus 35.1 [5.5] kg/m^2; $p = 0.004$; Table S1) and the 2-year follow-up (mean [*SD*] 34.2 [5.6] versus 35.7 [5.6] kg/m^2; $p = 0.020$; Table 4). Interestingly, those with persistent sleepiness had significantly less severe OSA, although both groups were still severe on average (Table S1). At baseline, only the prevalence of apneas was nominally lower in those with persistent sleepiness compared to those without (76.2% versus 86.4%, $p = 0.022$; Table S1). At the 2-year follow-up, subjects with persistent sleepiness more often reported persistence of other sleep apnea symptoms, including snoring (30.8% versus 12.0%, $p < 0.001$), witnessed apneas (29.0% versus 12.7%, $p < 0.001$), and nocturnal sweating (19.2% versus 8.0%, $p = 0.004$; Table 4). At baseline, insomnia symptoms were similar between those with and without persistent sleepiness (Table S1). However, at the 2-year follow-up there was a significant difference in insomnia symptoms, where those with persistent sleepiness more often reported difficulties maintaining sleep ($p = 0.001$) and early morning awakening ($p = 0.005$) (Table 4). At baseline, mental ($p = 0.096$) and physical ($p = 0.133$) QoL measurements were similar between those with and without persistent sleepiness (Table S1). At follow-up, a nominal difference in QoL was seen, with lower physical component score among those with persistent sleepiness compared to those whose sleepiness improved (mean [*SD*] 41.7 [11.1] versus 44.4 [11.5]; $p = 0.040$).

4 | DISCUSSION

The present study indicates that the most common way to clinically determine sleepiness in adults with OSA, namely by assessing the risk of dozing using the ESS, captures only one important dimension of their sleepiness symptoms. By adding a single question from the BNSQ, "Do you feel sleepy during the day?", we found an additional 24.7% of our cohort experienced frequent sleepiness. Importantly, these "feeling sleepy" subjects had similar OSA severity as those "at risk of dozing", suggesting differences in their sleepiness symptoms could not be explained by common measures of disease severity. Compared to the non-sleepy participants, the participants only "feeling sleepy" had significantly lower mental and physical QoL, and more often reported sleepiness symptoms such as feeling tired, taking a nap during the day, falling asleep when relaxing, and not feeling rested upon waking in the morning. They were also more likely than

TABLE 4 Demographics and characteristics of subjects with and without persistent sleepiness at the 2-year follow-up

Measurement	All	Improved sleepiness[a]	Persistent sleepiness[b]	*p**
Characteristics and habits[†]				
N (%)	305 (100)	176 (57.7)	129 (42.3)	–
Male, %	81.4	79.0	84.7	0.200
Age, years, mean (*SD*)	57.0 (10.7)	57.5 (10.4)	56.3 (11.0)	0.342
Body mass index, kg/m^2, mean (*SD*)	35.1 (5.6)	35.7 (5.6)	34.2 (5.6)	0.020
Large waist[c], %	92.5	92.6	92.2	0.905
Neck circumference, cm, mean (*SD*)	43.5 (3.6)	44.0 (4.2)	42.9 (3.6)	0.023
Smoking history, %				
Never	25.6	26.9	23.9	0.577
Past	54.7	55.4	53.8	
Current	19.7	17.7	22.3	
Heavy alcohol use %	2.6	2.3	3.1	0.683
Current regular exercise, %	66.6	67.5	65.3	0.702
Medical disorders and medication use[‡], %				
Hypertension	49.0	51.7	45.4	0.274
Cardiovascular disease	16.9	14.8	19.8	0.241
Type 2 diabetes	12.5	9.8	16.2	0.096
Metabolic syndrome	74.7	75.4	73.6	0.724
Hypothyroidism	6.9	8.0	5.4	0.372
Obstructive lung disease	16.9	18.2	15.3	0.501
Use of antidepressant	19.6	18.8	20.8	0.660
Use of hypnotics	11.8	13.1	10.0	0.410
Use of anti-hypertensives	57.2	59.1	55.4	0.517
PAP use				
PAP use/night, hr, mean (*SD*)	6.9 (1.2)	7.1 (1.1)	6.6 (1.3)	**0.004**
Sleep-related symptoms[°], %				
Restless legs syndrome	21.8	18.2	26.7	0.073
Snoring ≥3 nights/week	19.7	12.0	30.8	**<0.001**
Witnessed apneas ≥1 night/week	19.7	12.7	29.0	**<0.001**
Sweating during sleep ≥3 nights/week	12.7	8.0	19.2	**0.004**
nGER ≥1 night/week	4.3	3.4	5.4	0.403
Chronotype[§]				
Horne–Ostberg total score, mean (*SD*)	58.1 (10.4)	59.1 (9.4)	56.8 (11.6)	0.071
Morning type[d], %	55.3	58.6	50.8	0.125
Evening type[e], %	7.2	4.7	10.5	
Neither[f], %	37.5	36.7	38.7	
Insomnia symptoms[¢], %				
Difficulties initiating sleep, ≥3 nights/week	7.8	8.0	7.6	0.917
Difficulties maintaining sleep, ≥3 nights/week	29.4	22.2	39.2	**0.001**
Early morning awakening, ≥3 nights/week	20.3	14.8	27.7	**0.005**
Quality of life[§], mean (*SD*)				
SF-12 mental component score	51.2 (10.2)	52.1 (9.7)	50.0 (10.9)	0.079

(Continues)

TABLE 4 (Continued)

Measurement	All	Improved sleepiness[a]	Persistent sleepiness[b]	p*
SF-12 physical component score	43.3 (11.4)	44.4 (11.5)	41.7 (11.1)	0.040

AHI, apnea–hypopnea index; minSaO_2, minimum oxygen saturation; nGER, nocturnal gastro-oesophageal reflux; ODI, Oxygen Desaturation Index; OSA, obstructive sleep apnea; SF-12, Short Form (12) Health Survey.

[a]Epworth Sleepiness Scale (ESS) score >10, reporting feeling sleepy ≥3 times/week or both at baseline but non-sleepy (ESS score ≤10 and reporting feeling sleepy <3 times/week) at follow-up.

[b]ESS score >10, reporting feeling sleepy ≥3 times/week or both at baseline and follow up.

[c]Waist circumference ≥102 cm in males, ≥88 cm in females.

[d]Horn–Ostberg score ≥59.

[e]Horn–Ostberg score ≤41.

[f]Horn–Ostberg score 41–59.

*p values from chi-squared test (categorical variables) and t test (continuous variables). Significant p values after Bonferroni correction are in bold.

†Bonferroni corrected significance level: $p < 0.0063$.

‡Bonferroni corrected significance level: $p < 0.0056$.

°Bonferroni corrected significance level: $p < 0.01$.

§Bonferroni corrected significance level: $p < 0.025$.

¢Bonferroni corrected significance level: $p < 0.0167$.

non-sleepy participants to report evening chronotype and insomnia symptoms, which are known risk factors for short sleep and daytime impairment (Hidalgo, de Souza, Zanette, & Nunes, 2003; Riedel & Lichstein, 2000). Therefore, individuals with OSA experiencing the general feeling of sleepiness without risk of dozing should not be characterised as non-sleepy, as is the case when only using the ESS to measure sleepiness. Importantly, a single approach does not adequately measure sleepiness in individuals with OSA. Our present results show the importance of a multi-dimensional approach to defining sleepiness by measuring both the general feeling of sleepiness and the risk of dozing.

4.1 | QoL, chronotype and comorbidities

We found that compared to non-sleepy subjects, QoL was significantly worse in patients with OSA feeling sleepy, but not among those at risk of dozing. This finding is consistent with our results in the general population (Thorarinsdottir et al., 2019). Those feeling sleepy were more likely to identify as evening chronotypes compared to non-sleepy subjects (Thorarinsdottir et al., 2019). Subjects belonging to the evening chronotype are more alert during the evening hours and, therefore, more often have difficulties falling asleep in the evening (Adan et al., 2012). This can lead to shorter sleep duration and sleepiness (Li et al., 2018). Therefore, patients with OSA with a general feeling of sleepiness without risk of dozing might need further evaluation of other contributing factors for sleepiness, such as insomnia and evening chronotype, before starting PAP treatment.

We found that the non-sleepy phenotype had the highest proportion of cardiovascular disease. This might indicate a referral bias in our present cohort and reflect the tendency of healthcare workers to ask questions about OSA symptoms in patients they encounter with cardiovascular disease. As such, individuals that are referred for OSA testing and ultimately diagnosed despite a lack of traditional symptoms are more likely to have other underlying comorbidities. A similar result was noted in our prior publication on symptom-based subtypes (Ye et al., 2014).

4.2 | Symptoms of insomnia

Insomnia symptoms among individuals with OSA, especially difficulty maintaining sleep, are more prevalent than in the general population (Björnsdóttir et al., 2012; Krakow et al., 2001) and treatment with PAP is particularly effective at reducing complaints of difficulties maintaining sleep (Björnsdóttir et al., 2013). We found that both reports of insomnia and improvement in insomnia symptoms were related to baseline sleepiness phenotype. The phenotype both at risk of dozing and feeling sleepy had the highest incidence of reporting difficulties maintaining sleep and early morning awakenings at the time of diagnosis. This was also the only phenotype that showed significant improvement of insomnia symptoms with adherence to PAP. We also found that the feeling sleepy only phenotype was more likely than other phenotypes to have difficulties initiating sleep. However, PAP adherence was not related to resolution of this symptom. Additional therapies targeting insomnia are warranted in patients endorsing these symptoms.

4.3 | Change in sleepiness phenotypes and residual sleepiness with PAP

In general, we found that subjects with risk of dozing at baseline had greater improvement of sleepiness symptoms with PAP treatment than those only feeling sleepy. Given this increased benefit of PAP, one might expect that the phenotype “at risk of dozing” would be more likely to be adherent to treatment. However, we did not find that PAP adherence significantly differed between the four sleepiness phenotypes. The reason for this lack of difference in adherence is not immediately clear, but could reflect

other perceived benefits of therapy, not all of which are captured in the present study. Although the phenotype both at risk of dozing and feeling sleepy was the only phenotype that showed significant change in sleepiness phenotype distribution with PAP treatment (54.1% of PAP users became non-sleepy compared to 19.2% of non-PAP users), similar trends were seen among the other phenotypes, including those only feeling sleepy (55.2% of PAP users became non-sleepy after 2 years compared to 26.3% of non-PAP users). Current recommendations are to use the ESS to screen for daytime sleepiness in patients being evaluated for OSA (Patil et al., 2019), and clinicians use the ESS score in combination with the AHI when deciding whether or not to recommend treatment. These results indicate that using only the ESS as a measure of sleepiness may result in undertreatment of patients that would potentially benefit from PAP therapy.

Using our expanded sleepiness characterisations, nearly 43% of patients' adherent to PAP therapy had persistent sleepiness symptoms. In contrast, 26% of participants had persistent sleepiness based solely on an ESS score of >10, which is in agreement with results from a recent multicentre study on 4,852 PAP-treated patients with OSA reporting 28.2% of the population had persistent sleepiness (Bonsignore et al., 2021). Two other recent prospective studies on persistent sleepiness found a lower proportion, with only 12%–13% of the study populations having an ESS score of >10 (Gasa et al., 2013; Pépin et al., 2009). However, these previous studies excluded subjects with other contributing factors for sleepiness, such as depression, chronic sleep deprivation and a residual AHI of >15 events/hr, which would lower the prevalence of persistent sleepiness.

As reported previously (Gasa et al., 2013; Koutsourelakis et al., 2009), subjects with persistent sleepiness in our present study had significantly less severe OSA at baseline compared to those in whom sleepiness improved. One explanation might be that individuals with significant sleepiness are more likely to seek medical help, but they are also more likely to have other conditions contributing to their sleepiness independent of OSA. In the absence of diagnosis and treatment for other contributing conditions, PAP does not resolve their sleepiness complaints. Our present results indicate that insomnia might be one such contributing factor. Subjects with persistent sleepiness also more often reported persistence of OSA symptoms at the 2-year follow-up. This might indicate that they were less adequately treated with PAP despite meeting adherence criteria.

4.4 | Strength and limitations

The strengths of the present study include the large, well-characterised clinical sample of patients with OSA that underwent a detailed investigation. The study had high participation rates and included >90% of patients diagnosed with moderate–severe OSA in Iceland who were referred for PAP treatment. Limitations include the lack of data on short sleep length and depression, which are both known risk factor for EDS. Also, we did not have information on residual AHI at follow-up from PAP devices and did not do a repeat sleep study on treatment. At the time of the ISAC study, older versions of PAP devices were in use and readings on residual AHI from memory cards were not available. One might also keep in mind that our present cohort is a clinical cohort and does not represent all patients with OSA in the general population who are more likely to be less symptomatic (Arnardottir, Bjornsdottir, Olafsdottir, Benediktsdottir, & Gislason, 2016).

5 | CONCLUSIONS

In conclusion, among patients with moderate–severe OSA we found four phenotypes based on the risk of dozing and feeling of sleepiness. Of these, ~25% report feeling sleepy but are not at risk of dozing based on the ESS. These patients are not considered sleepy using traditional approaches. Our present results highlight the importance of characterising these patients as sleepy, as they endorse a number of relevant symptoms like insomnia and evening chronotype. Also, these patients report worse QoL compared to non-sleepy subjects. Patients feeling sleepy only were less likely to respond to PAP treatment when compared to those at risk of dozing. They may require further evaluation of other risk factors for sleepiness. Utilising a multi-dimensional approach to evaluate sleepiness among patient's adherent to PAP greatly increases the prevalence of persistent sleepiness, emphasising the broad scope of this problem among clinical patients.

CONFLICT OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

All authors have made substantial contributions to design, acquisition, and analysis of data for this article. Calculations were done by EHT with help from BTK and TA. EHT was mainly responsible for drafting the paper and co-authors revised the article for important intellectual content. All authors have approved this version to be published.

DATA AVAILABILITY STATEMENT

Data subject to third party restrictions.

ORCID

Elin H. Thorarinsdottir https://orcid.org/0000-0001-6561-3746

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SUPPORTING INFORMATION

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Paper III

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Research Letter

Research Letter

Evaluation of excessive daytime sleepiness in obstructive sleep apnea across international sleep centers

Elin H. Thorarinsdottir[1,2,*], Thorarinn Gislason[2,3], Allan I. Pack[4], Samuel T. Kuna[5], Thomas Penzel[6], Fang Han[7], Qing Yun Li[8], Peter A. Cistulli[9,10], Ulysses J. Magalang[11], Nigel McArdle[12,13], Bhajan Singh[12,13] and Brendan T. Keenan[4]

[1]Primary Health Care of the Capital Area, Reykjavik, Iceland,
[2]Faculty of Medicine, University of Iceland, Reykjavik, Iceland,
[3]Sleep Department, Landspitali, The National University Hospital of Iceland, Reykjavik, Iceland,
[4]Division of Sleep Medicine, Department of Medicine, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA,
[5]Department of Medicine, Corporal Michael J. Crescenz VA Medical Center, Philadelphia, PA, USA,
[6]Interdisciplinary Center of Sleep Medicine, Charité University Hospital, Berlin, Germany,
[7]Department of Respiratory Medicine, Peking University People's Hospital, Beijing, China,
[8]Department of Respiratory and Critical Care Medicine, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China,
[9]Department of Respiratory and Sleep Medicine, Royal North Shore Hospital, St Leonards NSW, Australia,
[10]Northern Clinical School and Charles Perkins Centre, University of Sydney, Camperdown NSW, Australia,
[11]Division of Pulmonary, Critical Care, and Sleep Medicine, The Ohio State Wexner Medical Center, Columbus, OH, USA,
[12]Sir Charles Gairdner Hospital, Western Australian Sleep Disorders Research Institute, Nedlands, Western Australia, Australia and
[13]Faculty of Human Sciences, University of Western Australia, Crawley, Western Australia, Australia

*Corresponding author. Elin Helga Thorarinsdottir, Faculty of Medicine, University of Iceland and Primary Health Care of the Capital Area, 108 Reykjavik, Iceland. 108 Reykjavik, Iceland. Email: eth32@hi.is.
The institution at which the work was performed: Primary Health Care of the Capital Area, Reykjavik, Iceland, and Landspitali, The National University Hospital of Iceland. Center for Sleep and Respiratory Neurobiology and Division of Sleep Medicine/Department of Medicine, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania.

Introduction

The lack of a definitive measurement of excessive daytime sleepiness (EDS) represents a key challenge in studying this important symptom. The most common approach in research and clinical practice is to utilize the Epworth Sleepiness Scale (ESS), a brief questionnaire measuring the tendency to doze off in eight common situations [1]. However, the ESS correlates poorly with objective tests of EDS and with severity of obstructive sleep apnea (OSA) [2]. Among adults from Iceland [3, 4], we previously applied a multi-dimensional EDS definition including both the ESS (>10 points defined as "risk of dozing") and the question "Do you feel sleepy during the day?" (≥3 times/week defined as "feeling sleepy"). Based on these questions, participants were classified as non-sleepy, risk of dozing only, feeling sleepy only, and presence of both symptoms. In the general population [4] and among OSA patients [3], nearly 25% of subjects reported feeling sleepy during the day despite not having an elevated ESS. Moreover, these patients had significantly lower quality of life and more often reported other sleepiness-related symptoms, insomnia, and evening chronotype [3]. These results suggest that patients experiencing the general feeling of sleepiness without reported risk of dozing (ESS ≤ 10) should still be characterized as having EDS. The aim of this report was to similarly evaluate these four sleepiness phenotypes in a large diverse international cohort.

Methods

Subjects were participants in the international Sleep Apnea Global Interdisciplinary Consortium (SAGIC), which has been previously described [5]. Similar to our previous study in the Icelandic Sleep Apnea Cohort, we included 2352 participants with moderate-severe OSA (defined as an apnea-hypopnea index [AHI] ≥ 15 events/hour); 2048 (87.1%) were diagnosed using laboratory-based polysomnography and 304 (12.9%) with home-based studies. For further details on sleep studies and scoring, see [5]. Questionnaires were translated into the languages of each site using forward and backward translation to ensure accuracy [6, 7]. EDS phenotypes of non-sleepy (ESS ≤ 10 and feeling sleepy <3 times/week), risk of dozing (ESS > 10 and feeling sleepy <3 times/week), feeling sleepy (ESS ≤ 10 and feeling sleepy ≥3 times/week) and both risk of dozing and feeling sleepy (ESS > 10 and feeling sleepy ≥3 times/week) were defined as in our prior papers [3, 4]. Categorical variables were summarized using frequencies and percentages and compared among sleepiness phenotypes using chi-squared tests. Continuous variables were summarized using

Table 1. Demographics and characteristics of the four sleepiness phenotypes

	Available data, *n*	Non-sleepy[a]	Risk of dozing off[b]	Feeling sleepy[c]	Both risk of dozing and feeling sleepy[d]	*p*-value*	Effect size**
General characteristics†							
n, %	2352	975 (41.5)	640 (27.1)	153 (6.5)	584 (24.8)	–	–
Male, %	2352	74.2	79.8	75.2	77.7	.055	
Age, years, mean (SD)	2352	52.2 ± 13.9[f,g,h]	49.3 ± 12.4[e,h]	47.6 ± 14.5[e]	47.6 ± 12.2[e,f]	**<.001**	0.022
Body mass index, kg/m^2, mean (SD)	2319	30.8 ± 7.0[f,g,h]	29.9 ± 5.4[e,g,h]	32.8 ± 8.2[e,f]	32.4 ± 7.6[e,f]	**<.001**	0.022
Large waist‡, %	2352	67.4[g,h]	68.7[h]	76.0[e]	77.9[e,f]	**<.001**	0.057
Neck circumference, cm, mean (SD)	2013	40.9 ± 4.4[g,h]	40.6 ± 3.8[g,h]	41.8 ± 4.0[e,f]	41.9 ± 4.4[e,f]	**<.001**	0.015
Shift work (%)	2100	6.6	6.5	9.8	10.1	.046	–
Investigating site (%)	2352					**<.001**	0.053
Germany		37.0	17.4	13.0	32.6		
Brazil		43.0	20.4	5.8	30.8		
Iceland		39.2	27.1	8.9	24.8		
Ohio State		46.3	17.0	10.2	26.5		
U Penn		48.4	11.9	15.1	24.6		
Perth		51.7	12.1	12.1	24.1		
Sydney		61.0	8.9	13.0	17.1		
Taiwan		54.6	22.7	2.6	20.1		
Beijing		35.0	36.8	3.4	24.8		
Shanghai		41.6	30.0	5.3	23.1		
Race/Ethnicity (%)	2262					**<.001**	0.061
White		44.9	18.0	10.1	27.0		
African/African American		39.1	15.9	17.4	27.6		
Asian		38.6	33.4	4.0	24.0		
Central/South American		47.6	18.1	7.6	26.7		
Other		58.8	11.8	11.8	17.6		
Epworth sleepiness scale score, mean (SD)	2352	6.0 ± 2.9	14.0 ± 2.6	7.3 ± 2.6	16.5 ± 3.5	–	–
Medical disorders and medication use‡							
Hypertension, %	2313	51.8	50.4	52.3	49.7	.852	–
Cardiovascular disease, %	2299	11.6	8.9	9.9	8.1	.114	–
Type 2 diabetes, %	2309	14.1	12.5	15.2	12.7	.702	–
Use of hypnotics, %	2270	8.4[f,g]	4.6[e,g]	19.7[e,f,h]	5.8[g]	**<.001**	0.078
OSA severity‡							
AHI, events/h, mean (SD)	2352	40.6 ± 22.2[f,h]	43.8 ± 23.7[e,h]	42.8 ± 26.7[h]	48.7 ± 27.6[e,f,g]	**<.001**	0.017
ODI, events/h, mean (SD)	2333	36.2 ± 25.8[f,h]	40.8 ± 28.6[e,h]	39.3 ± 31.4[h]	45.5 ± 28.5[e,f,g]	**<.001**	0.018
MinSaO_2, %, mean (SD)	2214	77.4 ± 8.8[f,h]	74.5 ± 9.5[e,g]	76.3 ± 9.6[f,h]	73.8 ± 10.2[e,g]	**<.001**	0.027
% Time spent at SaO_2 <90%, mean (SD)	2352	12.5 ± 17.6[f,h]	16.3 ± 19.5[e,h]	14.5 ± 19.6[h]	20.5 ± 23.2[e,f,g]	**<.001**	0.025
Arousal index, events/h, mean (SD)	2025	36.8 ± 23.0[h]	38.2 ± 23.9	40.2 ± 26.0	41.0 ± 25.8[e]	**.017**	0.005
Sleep-related symptoms*							
Restless leg syndrome	2235	5.4[g,h]	4.9[g,h]	14.9[e,f]	10.8[e,f]	**<.001**	0.070
Snoring ≥ 3 nights/week	2348	78.1[f,h]	89.8[e,g]	78.4[f,h]	90.4[e,g]	**<.001**	0.093
Witnessed apneas ≥1 night/week	2165	72.0[f,h]	80.4[e]	75.4[h]	84.5[e,g]	**<.001**	0.072
Sweating during sleep ≥3 nights/week	2352	22.7[f,g,h]	30.8[e,g,h]	39.5[e,f]	45.4[e,f]	**<.001**	0.114

Table 1. Continued

	Available data, *n*	Non-sleepy[a]	Risk of dozing off[b]	Feeling sleepy[c]	Both risk of dozing and feeling sleepy[d]	*p*-value*	Effect size**
Average self-reported sleep length (h)	2184	6.8 ± 1.2[g,h]	6.7 ± 1.2[g]	6.2 ± 1.5[e,f,h]	6.5 ± 1.3[e,g]	**<.001**	0.016
Chronotype							
Definitely a morning type	2086	25.9	23.0	21.4	19.0	**<.001**	0.058
More a morning type than an evening type		34.2	27.5	17.1	25.3		
More an evening than a morning type		29.9	40.0	39.3	38.9		
Definitely an evening type		10.1	9.6	22.1	16.9		
Insomnia symptoms[e]							
Difficulties initiating sleep, ≥3 nights/week, %	2333	14.0[f,g,h]	9.5[e,g,h]	28.8[e,f,h]	18.7[e,f,g]	**<.001**	0.081
Difficulties maintaining sleep, ≥3 nights/week, %	2310	20.1[g,h]	20.5[g,h]	43.3[e,f]	39.3[e,f]	**<.001**	0.121
Early morning awakening, ≥3 nights/week, %	2308	12.6[g,h]	11.1[g,h]	31.1[e,f,h]	20.9[e,f,g]	**<.001**	0.091

SD, Standard deviation; OSA, obstructive sleep apnea; AHI, apnea-hypopnea index; ODI, oxygen desaturation index; $minSaO_2$, minimum oxygen saturation.
*p-Value from Pearson's chi-square test (categorical variables) and one-way analysis of variance (continuous variables. Significant p-values after Bonferroni correction are in bold).
**Effect size was calculated as eta-squared for continuous variables (0.01 = small effect, 0.06 = medium effect, 0.14 = large effect) and as Cramer's V for categorical variables (0.06–0.17 = small effect, 0.17–0.29 = medium effect, >0.29 = large effect).
[a]ESS score ≤10 and reporting feeling sleepy <3 times per week.
[b]ESS score >10 but reporting feeling sleepy <3 times per week.
[c]ESS score ≤10 but reporting feeling sleepy ≥3 times per week.
[d]ESS score > 10 and reporting feeling sleepy ≥3 times per week.
[e]$p < .05$ (significantly different from non-sleepy).
[f]$p < .05$ (significantly different from risk of dozing off).
[g]$p < .05$ (significantly different from feeling sleepy).
[h]$p < .05$ (significantly different from the group both risk of dozing off and feeling sleepy).
[i]Waist circumference ≥102 cm among males, ≥88 cm among females.
†Bonferroni corrected significance level: $p < .007$.
‡Bonferroni corrected significance level: $p < .0125$.
*Bonferroni corrected significance level: $p < .01$.
¶Bonferroni corrected significance level: $p < .0167$.

means and standard deviations and compared using analysis of variance (ANOVA); results were similar when using non-parametric Kruskal–Wallis tests. Pairwise comparisons were performed if differences among groups were significant after Bonferroni correction. Standardized effect sizes were calculated to understand the relative magnitude of differences in variables among phenotypes, including eta-squared for continuous variables (η^2; 0.01 = small, 0.06 = medium, 0.14 = large) and Cramer's V for categorical variables ($\frac{0.1}{\sqrt{df}}$= small, $\frac{0.3}{\sqrt{df}}$ = medium, $\frac{0.5}{\sqrt{df}}$ = large, where df for a given contingency table equals [rows – 1] * [columns – 1]) [8].

Results

Of the 2352 adults with moderate-to-severe OSA evaluated, 41.5% (n = 975) were non-sleepy, 27.1% (n = 640) were at risk of dozing only, 6.5% (n = 153) were feeling sleepy only, and 24.8% (n = 584) were both at risk of dozing and feeling sleepy. Characteristics of the phenotypes are presented in Table 1. Non-sleepy subjects were older with slightly less severe OSA than other phenotypes. They were also less symptomatic, reporting symptoms of Restless Legs Syndrome (RLS), snoring, apneas, and night sweats less often. The phenotype only at risk of dozing had lower Body Mass Index (BMI) and was the least likely to use hypnotics, but had comparable frequencies of definite evening chronotype and insomnia symptoms as those who were non-sleepy. Those feeling sleepy were on average younger and more obese than non-sleepy and risk of dozing off only individuals and were significantly more likely to use hypnotics and report RLS symptoms, shorter sleep length and definite evening chronotype. Also, those feeling sleepy (with and without risk of dozing) most often reported insomnia symptoms. The phenotype reporting both risk of dozing and feeling sleepy had slightly more severe OSA, a higher arousal index than the non-sleepy, and was generally more likely to report symptoms of RLS, snoring, apneas, and insomnia. This group was also more likely than non-sleepy and at risk of dozing only individuals to report a definite evening chronotype. Altogether, 60.6% of the cohort was Asian, 30.2% White, 4.6% Central/South American, 3.1% African/African American, and 1.5% defined their race/ethnicity as other. There was a significant difference in self-reported race/ethnicity among the sleepiness phenotypes; African/African Americans more often reported feeling sleepy without risk of dozing and Asians more often reported risk of dozing only. Similar results were seen when comparing results site, given the strong relationship with race/ethnicity. While there was strong statistical significance, effects size estimates suggested small to moderate differences in these characteristics among sleepiness phenotypes.

Discussion

Our prior research within population and clinical samples from Iceland emphasized the importance of considering more than just the ESS when defining EDS. Here, we extend this observation to an international sample of clinical patients with

moderate-to-severe OSA. Overall, 153 subjects (6.5%) reported only feeling sleepy and, therefore, would have been diagnosed as non-sleepy when using only the ESS. However, these patients more often reported known risk factors for daytime impairment, including insomnia, RLS, and evening chronotype, and were the most likely to use hypnotics to help them sleep. Therefore, identification of patients only reporting feeling sleepy is important for improved clinical management. Additionally, results show clear differences in symptom burden among those with ESS > 10 with and without reporting feeling sleepy; those at risk of dozing off without feeling sleepy were more similar to non-sleepy subjects than those both reporting feeling sleepy and at risk of dozing off. Thus, reliance only on the ESS may be diagnosing subjects with EDS who are not otherwise significantly impaired.

Similar to our previous study in Iceland [3], we found that sleepiness phenotypes were not related to sex or medical disorders such as hypertension, cardiovascular disease, and diabetes. Subjects feeling sleepy more often reported insomnia symptoms and evening chronotype in both studies [3]. Additionally, those feeling sleepy in SAGIC were more likely to use hypnotics. Similar trends were seen in Iceland (although did not reach statistical significance); whether hypnotics cause sleepiness or subjects that feel sleepy are more prone to use hypnotics is unclear.

Interestingly, complaints of sleepiness were less common in the diverse international cohort. Here, 41.5% of patients did not report either sleepiness symptom, compared to only 17.7% in our prior clinical study [3]. Relatedly, only 24.8% of participants in the current study reported both sleepiness symptoms, compared to almost half (49.9%) of the patients in Iceland [3]. The reasons for these differences are not immediately clear, but likely include several factors such as referral patterns, awareness of OSA symptoms, underlying comorbidities, regional and cultural differences in the practice of sleep medicine, and the different timeframes during which patients were recruited (2005–2009 in Iceland compared to 2013–2022 in SAGIC). Another possible explanation is ethnic differences in how sleepiness is reported. We found significant difference in sleepiness phenotypes by ethnicity, with Whites more likely to report general feeling of sleepiness than Asians, who were comparatively more likely to report risk of dozing off. As 61% of participants were of Asian descent in SAGIC, compared to 100% White in ISAC, this could, in part, explain these differences. Future studies incorporating both objective and subjective measures of sleepiness may provide insights regarding differences due to subjective reporting, as well as facilitate evaluations of whether patients with both objective and subjective sleepiness have worse characteristics or outcomes.

Overall, results of this study extend the generalizability of prior evidence on the importance of considering a multi-dimensional definition of EDS to an international population of patients with moderate-to-severe OSA. Incorporating these definitions into future research and clinical applications represents an important next step.

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Data Availability Policy

The data underlying this article will be shared on reasonable request to the corresponding author.

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Paper IV

Polysomnographic characteristics of excessive daytime sleepiness phenotypes in obstructive sleep apnea: Results from the international Sleep Apnea Global Interdisciplinary Consortium (SAGIC)

Elin H. Thorarinsdottir [1,2], Allan I. Pack [3], Thorarinn Gislason [2,4], Samuel T. Kuna [5], Thomas Penzel [6], Qing Yun Li [7], Peter A. Cistulli [8,9], Ulysses J Magalang [10], Nigel McArdle [11,12], Bhajan Singh [11,12], Christer Janson [13], Thor Aspelund [2, 14], Magdy Younes [15], Philip de Chazal [16], Sergio Tufik [17], Brendan T. Keenan [3]

[1]Primary Health Care of the Capital Area, Reykjavik, Iceland.
[2]Faculty of Medicine, University of Iceland, Reykjavik, Iceland.
[3]Division of Sleep Medicine, Department of Medicine, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania.
[4]Sleep Department, Landspitali - The National University Hospital of Iceland, Reykjavik, Iceland.
[5]Department of Medicine, Corporal Michael J. Crescenz VA Medical Center, Philadelphia, Pennsylvania.
[6]Interdisciplinary Center of Sleep Medicine, Charité University Hospital, Berlin, Germany.
[7]Department of Respiratory and Critical Care Medicine, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China.
[8]Charles Perkins Centre, Faculty of Medicine and Health, University of Sydney, Sydney, Australia,
[9]Department of Respiratory and Sleep Medicine, Royal North Shore Hospital, Australia.
[10]Division of Pulmonary, Critical Care, and Sleep Medicine, The Ohio State University Wexner Medical Center, Columbus, Ohio, USA
[11]Western Australian Sleep Disorders Research Institute, Sir Charles Gairdner Hospital, Nedlands, Western Australia, Australia.
[12]Department of Pulmonary Physiology and Sleep Medicine, Sir Charles Gairdner Hospital, Nedlands, Western Australia, Australia.
[13]Department of Medical Sciences: Respiratory, Allergy and Sleep Research, Uppsala University, Uppsala, Sweden.
[14]Icelandic Heart Association, Kopavogur, Iceland.
[15]Sleep disorders center, Department of Medicine, University of Manitoba, Winnipeg, Manitoba, Canada.
[16]Charles Perkins Centre, Faculty of Engineering, University of Sydney, Sydney, Australia.
[17]Department of Psychobiology, Universidade Federal de São Paulo, São Paulo, Brazil.

Corresponding author:
Elin Helga Thorarinsdottir, MD
Faculty of Medicine, University of Iceland and Primary Health Care of the Capital Area, Reykjavik, Iceland. 108 Reykjavik, Iceland. tel: + 354- 5431000, fax: + 354-5436568, e-mail: eth32@hi.is

The institution at which the work was performed: Primary Health Care of the Capital Area, Reykjavik, Iceland. Landspitali - The National University Hospital of Iceland and University if Iceland. Division of Sleep Medicine/Department of Medicine, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania.

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ABSTRACT

Study objectives: Excessive daytime sleepiness (EDS) is a major symptom of obstructive sleep apnea (OSA). Traditional polysomnographic (PSG) measures only partially explain EDS in OSA. This study analyzed traditional and novel PSG characteristics of two different measures of EDS among OSA patients.

Methods: Sleepiness was assessed using the Epworth Sleepiness Scale (>10 points defined as "risk of dozing") and a measure of general sleepiness (feeling sleepy ≥3 times/week defined as "feeling sleepy"). Four sleepiness phenotypes were identified: "non-sleepy", "risk of dozing only", "feeling sleepy only" and "both at risk of dozing and feeling sleepy".

Results: Altogether, 2097 OSA patients (68% male) with an apnea-hypopnea index (AHI) ≥5 events/hour were studied. Of them, 48% were "non-sleepy", 20% at "risk of dozing only", 9% were "feeling sleepy only" and 23% reported both. The two phenotypes at "risk of dozing" had higher AHI and more severe hypoxemia as measured by oxygen desaturation index, minimum and average oxygen saturation (SpO2) and time spent <90% SpO2 and spent less time awake than "non-sleepy" and "feeling sleepy only" phenotypes. Overall, effect sizes were small. Sleep stages, odds ratio product, frequency and intensity of arousals, sleep latency, wake after sleep onset and limb movement did not differ between sleepiness phenotypes after adjusting for confounders.

Conclusions: In a large international group of OSA patients, PSG characteristics were weakly associated with EDS. Measures of hypoxemia, AHI and time awake differed among individuals characterized at "risk of dozing" or "non-sleepy" while "feeling sleepy only" did not differ from "non-sleepy" individuals.

INTRODUCTION

Excessive daytime sleepiness (EDS) is a cardinal symptom of obstructive sleep apnea (OSA) and an important factor when considering treatment.[1] However, there are great interindividual differences in sleepiness among patients with OSA, and it has been reported that less than 50% of patients with moderate-to-severe disease in clinical cohorts have EDS.[2] Furthermore, although sleep disordered breathing is frequently associated with sleepiness, population-based studies indicate that the majority of individuals with significant sleep disordered breathing do not report sleepiness.[3-5] The determinants of EDS in OSA are poorly understood. Several studies have shown that the apnea-hypopnea index (AHI), average and minimum oxygen saturation (SpO_2), and hypoxic burden are associated with subjective EDS in patients with OSA.[4,6-10] However, these associations are generally weak and often inconsistent across studies.[11,12] The presence of EDS has been attributed to impaired sleep quality due to obstructive events. In this regard, higher sleep efficiency, shorter sleep latency and higher arousal and microarousal indices have been associated with EDS in OSA.[11,13-18] Some studies have found a significant difference in sleep architecture, with sleepy OSA patients having increased "light sleep" indicated by a higher proportion of non-rapid eye movement (NREM) stage 1 (N1) sleep and a decrease in stage 3 (N3) sleep compared to non-sleepy subjects.[16,17] However, this is an inconsistent finding.[7,8,19]

The inconsistent findings regarding the association between polysomnography (PSG) measures and EDS in OSA might be in part due to differences in definitions and methods of measuring EDS across studies. Most studies measure sleepiness based on the Epworth Sleepiness Scale (ESS), which measures the tendency to doze off in eight situations most people encounter in their daily lives.[20] In previous studies of the general population[21] and among patients with OSA,[22,23] we have presented a multi-dimensional definition of EDS based on an ESS score >10 (e.g., at "risk of dozing") and/or self-reported frequency of ≥ 3 times/week in response to the question "Do you feel sleepy during the day?" (e.g., "feeling sleepy").[24]

Using these two definitions we defined 4 different sleepiness phenotypes: “non-sleepy”, “risk of dozing only”, “feeling sleepy only”, and “both at risk of dozing and feeling sleepy”. Using these phenotypes, we found that 7–25% of OSA patients would be misdiagnosed as “non-sleepy” when using only the ESS. These patients had higher prevalence of known risk factors for sleepiness, such as short sleep, evening chronotype and insomnia than “non-sleepy” patients by both criteria. Thus, it is important to also consider subjects with OSA who endorse “feeling sleepy only” without “risk of dozing” as having EDS.

The aim of this research was to examine the PSG characteristics of these 4 different phenotypes of sleepiness, using a large, multi-center, international cohort of newly diagnosed and untreated OSA patients with mild-to-severe disease. We hypothesized that leveraging this multi-dimensional definition of sleepiness would help to better distinguish sleepy subjects and identify stronger relationships between PSG traits and EDS in OSA.

MATERIALS AND METHODS

Participants

The OSA subjects were members of the Sleep Apnea Global Interdisciplinary Consortium (SAGIC, http://www.med.upenn.edu/sleepctr/sagic.htm). SAGIC is a collaborative effort of international sleep centers to recruit a multinational clinical cohort of patients undergoing sleep studies for suspected OSA. This current study included data from individuals with OSA (AHI $\geq$5) from 9 centers in 7 countries, including the United States (University of Pennsylvania and The Ohio State University), Australia (Royal North Shore Hospital, Sydney and Sir Charles Gairdner Hospital, Perth), Germany (Charité University Hospital), Brazil (Médicado Instituto do Sono), Taiwan (Chang Gung Memorial Hospital), China (Ruijin Hospital, Shanghai) and Iceland (Landspitali—The National University Hospital of Iceland). The study protocol was approved by the Institutional Review Board at the University of Pennsylvania and additional approvals were obtained at each site. Informed consent was obtained from all participants.

Measurements

Participants completed the SAGIC questionnaire containing detailed questions on demographics, ethnicity, sleep-related symptoms, sleepiness, comorbidities, and medications. Questionnaires were initially written in English and then translated into languages of the participating sites, including Icelandic, German, Portuguese and Mandarin, using forward and backward translation to ensure accuracy.[25,26] Standardized methods were used to measure height and weight, and body mass index (BMI) was calculated as kg/m^2.

Assessment of sleepiness phenotypes

Similar to our previous research[22,27,28] we used two different subjective methods to define EDS; the ESS score of >10 was considered as having “risk of dozing” and answering the statement “I feel sleepy during the day” 3 or more times per week (scores 4 and 5 on a 5 point scale) was considered as “feeling sleepy”. Based on the presence or absence of these symptoms, participants were categorized into 4 sleepiness phenotypes:

1. **Non-sleepy**: ESS score $\leq$10 and reporting feeling sleepy <3 times per week (n=1001)
2. **Risk of dozing only**: ESS score >10 and reporting feeling sleepy <3 times per week (n=422)
3. **Feeling sleepy only**: ESS score $\leq$10 and reporting feeling sleepy $\geq$3 times per week (n=190)
4. **Both at risk of dozing and feeling sleepy**: ESS score >10 and reporting feeling sleepy $\geq$3 times per week (n=484)

Sleep studies

Among the study participants included in this research, OSA was diagnosed using in-laboratory full-night diagnostic PSG in 1513 participants (72%), in-laboratory split-night PSG in 102 (5%) and home sleep apnea test (HSAT) in 482 (23%) (see **Table 1**). To ensure uniform data collection, standard operating procedures were implemented at each site. The reliability of scoring between the centers for both in-laboratory PSG and HSATs have been tested and have shown strong inter-rater agreement for common metrics of OSA severity.[29,30] As physiological measures evaluated include both clinically-obtained data and measures derived directly from the in-laboratory PSG using specialized software, the total sample size differed across specific traits.

Apneas were defined as an absence of airflow on the nasal pressure cannula or oronasal thermistor for ≥10 seconds. Hypopneas were defined as a ≥30% reduction from baseline in airflow for ≥10 s associated with at least a 4% oxygen desaturation. The AHI was calculated as the mean apneas and hypopneas per hour. The oxygen desaturation index (ODI) was defined as the number of oxygen desaturations ≥ 4% per hour. Minimum and average SpO_2 were evaluated as well as the total time spent at SpO_2 less than 90% (TST90). For PSG studies, AHI, ODI and TST90 were calculated based on total sleep time while for HSATs, calculations were based on total analysis time defined as the time between "lights-off" and "lights-on" minus any artifact time (if artifacts were present in the study). Detailed information on scoring of traditional PSG variables in SAGIC has been published previously.[30] Hypoxic burden was defined using methods consistent with those previously described (MATLAB code implementing hypoxic burden is available at https://github.com/pdechazal/Hypoxic-Burden).[31]

For participants undergoing an in-laboratory or slit-night PSG, sleep stages, arousal index, arousal intensity, periodic limb movement index (PLMI) were assessed by the American Academy of Sleep Medicine standards.[32] Both absolute (minutes) and relative (percent) of NREM sleep stages N1, 2 (N2), N3 and rapid eye movement (REM) sleep were evaluated. Two markers of arousal intensity were assessed. First, arousal intensity was assessed using a validated automated wavelet transformation and scaled from 1 to 9 according to increasing intensity.[33-35] Second, average increase in heart rate (HR) in response to arousal was assessed and expressed as average HR in response to arousal, which has been directly correlated with arousal intensity in previous research.[33] Sleep latency was defined as the duration in minutes from "lights-off" to the first epoch of sleep and wake after sleep onset (WASO) as the time spent awake (in minutes) after initially falling asleep during the study.

The odds ratio product (ORP) was used as a continous marker of sleep depth.[36-38]. The method for calculating ORP has been described in detail.[37] In brief, ORP is calculated every 3 seconds from the power spectrum of the electroencephalography (EEG) (in contrast to the 30 seconds epochs used for traditional sleep staging). Total power in each of 4 frequency ranges (0-2.33 Hz, 2.34-6.67 Hz, 6.68-14.0 Hz, 14.1-35.0 Hz) was calculated and assigned a rank from 0 to 9, resulting in 10,000 possible 4-digit signatures (ranging from 0000 to 9999) for each 3-second epoch describing the relative powers in the 4 frequency bands. The probability of any pattern occurring during arousals or in epochs manually scored as wake was determined by reference to a look-up table. This probability (0-100%) was then divided by 40 to derive the ORP value (range from 0 [deep sleep] to 2.5 [fully awake]). ORP was summarized using the average value in wake and in different stages of sleep (NREM and REM) and the distribution of ORP values across the night was summarized as the proportion of all epochs with ORP values in 10 bins of size 0.25 (i.e., 0.00-0.25, 0.25-0.50, …, 2.25-2.25). As described in a recent publication,[39] each participant was also assigned one of nine 2-digit phenotypes based on the relative proportion of ORP values in deep sleep (ORP<0.50) and in full wakefulness (ORP>2.25). Using distributions observed in the Sleep Heart Health Study,[39] the

first digit was assigned as "1" if the percentage of epochs in deep sleep (ORP<0.50) was in the bottom quartile (defined as <10.2%), "2" if this percentage was in the interquartile range (defined as 10-2-28.5%), and "3" if this percentage was in the top quartile (defined as >28.5%). Similarly, the second digit was assigned as "1" if the percentage of epochs with ORP in full wakefulness (ORP>2.25) was first quartile (i.e., <3.4%), "2" if in the interquartile range (i.e., 3.4-12.5%), and "3" if in the upper quartile (i.e., >12.5%). Thus, for example, a person with type "1,1" has a percentage of ORP value in both deep sleep and full wakefulness that fall within the bottom quartiles. Further details on the ORP type are provided in the article by Younes et al.[39] In addition, ORP-9 was assessed as the ORP in the immediate 9 seconds after arousal, reflecting the speed at which a person returns to sleep after arousal.[40] A lower ORP-9 value indicates a quicker return to sleep and, therefore, a stronger sleep drive. Finally, the intra-class correlation coefficient for the relationship between the average ORP in 30 second epochs of the right and left EEG signals was also assessed for the entire PSG (right/left ORP correlation)[41] since lower values have been associated with driving safety in individuals with OSA and to be a marker of accumulated sleep loss.[42]

Statistical methods

Statistical analyses were done using STATA 16.0 software (Stata Corporation, College Station, Texas). Categorical variables were summarized using frequencies and percentages and compared among sleepiness phenotypes using chi-squared tests. Continuous variables were summarized using means ± standard deviation (SD) and compared between phenotypes using an analysis of variance (ANOVA). If variables did not follow a normal distribution, natural log- or square root transformations were applied prior to parametric analysis. Additionally, medians and interquartile ranges (IQR) were calculated for all continuous PSG variables and compared between sleepiness phenotypes using a Kruskal-Wallis test (see **Supplementary Table S1**). A Hochberg "step-up" approach was used to control for the family-wise error rate at 5% within three physiological domains of interest – measures of OSA severity/hypoxemia, sleep stages/arousals, and ORP metrics.[43,44] A p-value <0.05 was considered nominally significant. Pairwise comparisons among phenotypes were performed if differences among groups achieved nominal significance.

To understand the relative magnitude of differences in the PSG variables among phenotypes, standardized effect sizes were calculated using two methods (see **Supplementary Table S2**). First, eta-squared was calculated to measure the proportion of variance in the PSG variables that can be explained by the sleepiness phenotypes (η^2; 0.01 = small, 0.06 = medium, 0.14 = large effect).[45] Second, Cohen's d was calculated between each pair of sleepiness phenotypes (0.2 = small, 0.5 = medium, 0.8 = large).[45] Given the higher likelihood of causes of sleepiness other than OSA among those with only mild disease (e.g., AHI 5-15), a sensitivity analysis was performed restricted to patients with at least moderate OSA (AHI ≥15, n=1372).

RESULTS

Sample Characteristics

Altogether, 2141 participants had an AHI of ≥5 and answered both sleepiness questions; 44 answered the question on general feeling of sleepiness as "don't know" and were excluded, resulting in a final sample of 2097 subjects (68% males, 32% females). As shown in **Table 1 and S1**, on average, participants were middle aged (51.5±13.4 years) and obese (32.1±7.8 kg/m^2), and the majority of the sample were either White (n=1076, 51%) or Asian (n=544, 26%).

Table 1. *General characteristics and type of sleep study used for OSA diagnosis compared between the sleepiness phenotypes.*

Characteristic	Available data	Overall	Sleepiness phenotypes				p-value*
			Non-sleepy[a]	Risk of dozing only[b]	Feeling sleepy only[c]	Both at risk of dozing and feeling sleepy[d]	
N (%)	2097	2097 (100)	1001 (47.7)	422 (20.1)	190 (9.1)	484 (23.1)	-
Age, years ± SD	2097	51.5 ± 13.4	53.3 ± 13.7	51.8 ± 12.8	48.3 ± 14.5	48.9 ± 12.0	**<0.001**
Male, %	2097	68.1	69.7	69.0	66.3	64.9	0.266
Body mass index, kg/m2, mean± SD	2081	32.1 ± 7.8	31.5 ± 7.8	31.4 ± 6.6	32.7 ± 8.1	33.4 ± 8.3	**<0.001**
Investigating site, %	2097						**<0.001**
Germany	237	11.3	42.2	19.0	10.1	28.7	
Brazil	299	14.3	45.8	23.4	4.4	26.4	
Iceland	316	15.1	36.7	27.2	9.5	26.6	
United States	422	20.1	49.5	14.2	12.8	23.5	
Australia	318	15.2	59.1	10.1	14.5	16.4	
Taiwan	217	10.3	53.5	22.6	4.6	19.3	
Shanghai	288	13.7	46.9	27.8	4.5	20.8	
Ethnicity, %	2088						**0.001**
White	1076	51.5	46.7	17.6	10.8	24.9	
African/African American	101	4.8	44.6	17.8	14.8	22.8	
Asian	544	26.1	49.6	24.8	5.7	19.9	
Central/South American	191	9.2	47.1	23.1	5.2	24.6	
Other	176	8.4	50.0	19.3	9.1	21.6	
Type of sleep study, %	2097						**0.002**
In-lab PSG	1513	72.1	76.6	69.4	65.3	68.0	
Split-night PSG	102	4.9	3.9	5.2	5.3	6.4	
Home sleep apnea test	482	23.0	19.5	25.4	29.5	25.6	

p values from chi-square test (categorical variables) and one-way analysis of variance (continuous variables). Significant differences (p<0.05) are shown in* ***bold**. [a]ESS score ≤10 and reporting feeling sleepy <3 times per week; [b]ESS score >10 but reporting feeling sleepy <3 times per week; [c]ESS score ≤10 but reporting feeling sleepy ≥3 times per week; [d]ESS score >10 and reporting feeling sleepy ≥3 times per week. Abbreviations: SD = Standard deviation, PSG = polysomnography*

Females were on average 5 years older than males (54.6±12.5 vs. 50.1±13.6 respectively, p<0.001), they had less severe OSA (median AHI 17.2 (IQR 9.8-31.0) vs 26.0 (IQR13.5-49.8) respectively, p<0.001) and were more obese (mean BMI 34.1±9.4 vs. 31.1±6.7 respectively, p<0.001). Overall, 32.2% reported feeling sleepy ≥3 times per week and 43.2% had an ESS score >10. The categorization of subjects based on their sleepiness phenotype was distributed as follows: 47.7% were "non-sleepy", 20.1% had "risk of dozing only", 9.1% were "feeling sleepy only" and 23.1% were "both at risk of dozing and feeling sleepy" (**Table 1**). No significant differences were found between females and males in the prevalence of having an ESS score >10 (42.3% vs. 45.1% respectively, p=0.241), feeling sleepy ≥3 times per week (30.8% vs 35.0%, p=0.053) or in the distribution of the sleepiness phenotypes (p=0.266).

General characteristics of the sleepiness phenotypes

Characteristics of the sleepiness phenotypes are shown in **Table 1**. The two phenotypes "feeling sleepy" (with or without risk of dozing) were on average younger and had higher BMI. There was a significant difference in the type of study used for OSA diagnosis between the sleepiness phenotypes, where the "non-sleepy" were more likely to have undergone an in-laboratory PSG and less likely to have had a HSAT.

OSA severity and measures of hypoxemia

Overall, the participants had moderate-to-severe OSA, with a mean AHI of 31.9 ± 26.4 events/h and a median AHI of 22.4 (IQR 12.0-44.1) events/h. As shown in **Table 2**, there were significant differences among the sleepiness phenotypes in AHI and all assessed markers of hypoxemia, including ODI, average SpO_2, minimum SpO_2, TST90 and hypoxic burden.

Table 2. *Unadjusted analysis comparing polysomnographic parameters between the sleepiness phenotypes.*

Characteristic	Available data	Overall	Sleepiness phenotypes				p-value*
			Non-sleepy[a]	Risk of dozing only[b]	Feeling sleepy only[c]	Both at risk of dozing and feeling sleepy[d]	
Measures of OSA severity and hypoxemia							
AHI, h^{-1}	2097	31.9 ± 26.4	30.2 ± 24.2	32.3 ± 25.9	29.0 ± 26.5	36.0 ± 30.4	**0.004**†
ODI, h^{-1}	2036	30.2 ± 29.1	28.3 ± 26.9	32.0 ± 31.9	26.0 ± 29.2	34.4 ± 30.4	**<0.001**†
Average SpO_2, %	1922	92.9 ± 3.2	93.2 ± 2.9	92.8 ± 3.1	93.1 ± 3.1	92.3 ± 3.8	**<0.001**
Minimum SpO2, %	1977	79.0 ± 8.9	79.9 ± 8.5	78.1 ± 8.9	80.1 ± 8.3	77.5 ± 9.8	**<0.001**
TST90, %	1936	11.7 ± 18.8	10.2 ± 16.9	13.1 ± 19.5	8.5 ± 15.5	14.9 ± 22.2	**<0.001**†
Hypoxic Burden, %min/h	933	110 ± 137	112 ± 137	104 ± 125	66.7 ± 81.2	126 ± 157	**0.007**†
Sleep stages, %							
Wake	802	22.8 ± 14.7	24.8 ± 15.2	20.7 ± 13.6	23.8 ± 15.5	19.5 ± 13.6	**<0.001**†
NREM Stage N1	802	17.1 ± 9.9	17.1 ± 9.8	17.8 ± 9.5	16.3 ± 9.2	16.6 ± 10.7	0.516†
NREM Stage N2	802	42.2 ± 12.2	41.5 ± 11.9	43.0 ± 12.4	41.1 ± 11.1	43.4 ± 12.8	0.215
NREM Stage N3	802	6.1 ± 7.2	5.5 ± 6.3	6.0 ± 6.8	7.2 ± 8.7	7.4 ± 8.9	0.276†
REM	802	8.8 ± 6.9	8.3 ± 6.8	9.0 ± 6.3	7.9 ± 8.2	10.2 ± 7.1	**0.012**†
Sleep latency, arousals, and limb movements							
Sleep latency, min	1593	20.7 ± 31.3	22.9 ± 36.0	18.7 ± 28.3	20.5 ± 23.7	17.5 ± 23.3	**0.003**†
WASO, min	1480	82.4 ± 59.3	86.0 ± 59.6	86.0 ± 63.0	85.9 ± 58.7	69.9 ± 53.7	**<0.001**†
Arousal Index, h^{-1}	1554	34.4 ± 24.8	33.5 ± 22.5	34.8 ± 27.6	33.7 ± 24.7	36.5 ± 27.2	0.554†
Arousal intensity, 1-9	796	3.2 ± 0.6	3.2 ± 0.5	3.2 ± 0.6	3.1 ± 0.6	3.3 ± 0.7	**0.030**†
HR response to arousals, beats/min	693	2.8 ± 1.3	2.7 ± 1.3	2.7 ± 1.2	2.6 ± 1.4	2.9 ± 1.3	0.106
PLMI, h^{-1}	802	15.8 ± 22.0	15.3 ± 21.5	17.6 ± 20.5	20.2 ± 29.3	14.0 ± 21.7	0.063†
Odds ratio product							
Avg. ORP	802	1.27 ± 0.31	1.31 ± 0.31	1.25 ± 0.29	1.28 ± 0.35	1.22 ± 0.31	**0.017**
Avg. Wake ORP	801	2.11 ± 0.14	2.13 ± 0.14	2.11 ± 0.15	2.10 ± 0.14	2.10 ± 0.15	0.092
Avg. NREM ORP	802	0.98 ± 0.26	0.99 ± 0.26	0.97 ± 0.24	0.99 ± 0.31	0.97 ± 0.27	0.778
Avg. REM ORP	688	1.30 ± 0.31	1.33 ± 0.32	1.30 ± 0.26	1.21 ± 0.34	1.28 ± 0.30	0.088
Avg. ORP-9	794	1.19 ± 0.29	1.22 ± 0.29	1.17 ± 0.26	1.21 ± 0.32	1.16 ± 0.29	0.066
Right/Left ORP Correlation	695	0.83 ± 0.10	0.84 ± 0.09	0.82 ± 0.10	0.83 ± 0.08	0.80 ± 0.11	**<0.001**

*Data are presented as mean ± standard deviation; *p-values from one-way analysis of variance (ANOVA) comparing mean values between sleepiness phenotypes, †p values from ANOVA comparing log or square root transformed values between sleepiness phenotypes. Abbreviations: OSA = Obstructive Sleep Apnea, AHI = Apnea Hypopnea Index, ODI = Oxygen Desaturation Index, SpO2 = Oxygen Saturation, TST90 = Total Sleep Time Spend Under 90% SpO_2, NREM = Non-Rapid Eye Movement; REM = Rapid Eye Movement, WASO = Wake After Sleep Onset; HR = Heart Rate, PLMI = Periodic Limb Movement Index, ORP = Odds Ratio Product, ORP-9 = ORP in the immediate 9 seconds after arousal, min = Minute, h = Hour.*

These differences remained significant after adjusting for age, gender, BMI and ethnicity (**Table 3**). In general, the two phenotypes at "risk of dozing" had more severe markers of hypoxemia than "non-sleepy" and "feeling sleepy only". **Figure 1** shows the distribution of OSA severity as defined by traditional AHI cut-offs among the sleepiness phenotypes. There was a significant difference between sleepiness phenotypes and AHI categories (p=0.028) where the phenotype "both at risk of dozing and feeling sleepy" had the highest proportion of subjects with severe OSA (AHI≥30 events/h). While statistically significant, the eta-squared values were all near 0.01 (range 0.009 to 0.015), indicating that the sleepiness phenotypes had a small effect on the variance of the AHI and hypoxemia variables (see **Supplementary Table S2**). The greatest differences in AHI and measures of hypoxemia were observed between the phenotypes "feeling sleepy only" and "both at risk of dozing and feeling sleepy" with a Cohen´s d ranging from 0.212-0.419 indicating a small-to-medium effect (see **Supplementary Table S2**).

Table 3. *Adjusted* analysis comparing polysomnographic parameters of OSA severity and hypoxemia between the sleepiness phenotypes.*

Sleep Study Metric	Available data	Non-sleepy [a]	Risk of dozing only[b]	Feeling sleepy only[c]	Both at risk of dozing and feeling sleepy[d]	P[†]
AHI, h^{-1}	2072	30.2 (28.7, 31.7)[h]	31.8 (29.5, 34.1)[h]	30.7 (27.3, 34.2)[h]	35.8 (33.6, 37.9)[e,f,g]	**0.002**[‡]
ODI, h^{-1}	2011	28.3 (26.6, 29.9)[f,h]	31.2 (28.7, 33.8)[e,g]	28.5 (24.6, 32.3)[f,h]	34.1 (31.8, 36.5)[e,g]	**<0.001**[‡]
Average SpO_2, %	1905	93.2 (93.0, 93.4)[f,h]	92.7 (92.4, 93.0)[e]	93.1 (92.6, 93.5)[h]	92.4 (92.1, 92.6)[e,g]	**<0.001**
Minimum SpO_2, %	1956	79.9 (79.4, 80.5)[f,h]	78.2 (77.4, 79.0)[e,g]	79.7 (78.5, 80.9)[f,h]	77.5 (76.8, 78.3)[e,g]	**<0.001**
TST90, %	1913	10.2 (9.1, 11.4)[f,h]	12.9 (11.2, 14.7)[e,g]	9.3 (6.6, 12.0)[f,h]	14.7 (13.1, 16.4)[e,g]	**<0.001**
Hypoxic Burden, %min/h	927	106 (95.3, 118)[g]	107 (88.7, 125)[g]	77.0 (49.6, 104)[e,f,h]	129 (113, 145)[g]	**0.014**[‡]

Adjusted for age, gender, body mass index and ethnicity; Data presented as means (95% confidence intervals), with p-values statistically significant after Hochberg step-up correction shown in* ***bold**; [†]Adjusted p-value from ANOVA comparing mean values between the sleepiness phenotypes, controlling for age, gender, body mass index and ethnicity, [‡]p values using log or square root transformed values; [a]p <0.05 (significantly different from "non-sleepy"); [b]p<0.05 (significantly different from "risk of dozing only"); [c]p<0.05 (significantly different from "feeling sleepy only");[d]p<0.05 (significantly different from "both at risk of dozing and feeling sleepy"); Abbreviations: AHI = Apnea Hypopnea Index, ODI = Oxygen Desaturation Index, SpO2 = Oxygen Saturation, TST90 = Total Sleep Time Spend Under 90% SpO_2, min = Minute, h = Hour.*

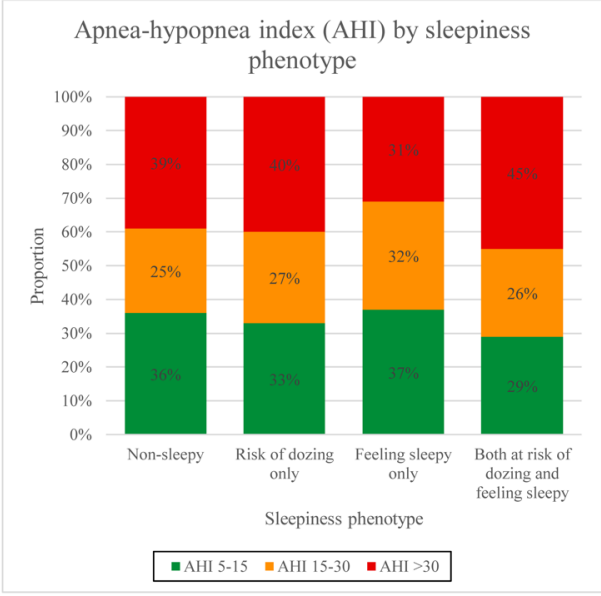

Figure 1*. Association between OSA severity as defined by the traditional AHI cut offs and sleepiness phenotypes. The phenotype "both at risk of dozing and feeling sleepy" had a greater proportion of subjects with severe OSA. Abbreviations: AHI = Apnea Hypopnea index, OSA = Obstructive sleep apnea.*

Sleep stages, sleep latency, WASO, arousals, and PLMI

Compared to the two phenotypes at "risk of dozing", the "non-sleepy" phenotype had the longest sleep latency and spent more time awake on average (see **Table 2**). This difference remained significant for total wake (in minutes and percentage of total recording time) in covariate adjusted analyses (see **Table 4**). Similar to measures of hypoxemia, the eta-squared values indicated that the sleepiness phenotypes had a small effect on the variance of the absolute (minutes) and relative (percentage) wake time (see **Supplementary Table S2**). When comparing the "feeling sleepy only" phenotype to those "both at risk of dozing and feeling sleepy", small to medium effects sizes were observed (Cohen's d ~0.30) (see **Supplementary Table S2**). The phenotype "both at risk of dozing and feeling sleepy" also had the longest average time in REM and highest arousal intensity of the four sleepiness phenotypes, but these differences were not significant after adjusting for confounders (see **Tables 2 and 4**). There was no difference in NREM sleep stages, arousal index, HR response to arousals or PLMI between the sleepiness phenotypes (see **Tables 2 and 4**).

Table 4. *Adjusted* analysis comparing sleep stages, sleep latency, arousals and limb movements between sleepiness phenotypes.*

Sleep Study Metric	Available data	Non-sleepy [a]	Risk of dozing only [b]	Feeling sleepy only [c]	Both at risk of dozing and feeling sleepy [d]	p†
Sleep stages, min						
Wake	796	107 (101, 113)[f,h]	91.5 (81.9, 101)[e]	100 (84.3, 116)	89.9 (80.9, 98.9)[e]	**0.002**‡
NREM Stage N1	796	71.7 (67.8, 75.6)	76.5 (70.0, 83.0)	73.9 (63.2, 84.5)	72.4 (66.5, 78.3)	0.308‡
NREM Stage N2	796	180 (175, 186)	182 (173, 191)	180 (166, 195)	184 (176, 192)	0.895
NREM Stage N3	796	25.4 (22.6, 28.1)	25.4 (20.9, 29.9)	28.9 (21.4, 36.3)	28.9 (24.7, 33.1)	0.812‡
REM	796	36.6 (33.7, 39.4)	37.7 (32.9, 42.4)	35.4 (27.6, 43.2)	42.5 (38.1, 46.8)	0.174‡
Sleep stages, %						
Wake	796	24.2 (22.9, 25.5)[f,h]	21.0 (18.8, 23.1)[e]	23.4 (19.9, 27.0)	20.7 (18.8, 22.7)[e]	**0.003**‡
NREM Stage N1	796	16.7 (15.8, 17.6)	17.9 (16.5, 19.4)	17.2 (14.8, 19.6)	16.9 (15.6, 18.3)	0.399‡
NREM Stage N2	796	41.9 (40.8, 43.0)	42.4 (40.5, 44.3)	41.5 (38.4, 44.5)	42.9 (41.2, 44.6)	0.737
NREM Stage N3	796	5.9 (5.3, 6.5)	6.1 (5.0, 7.1)	6.5 (4.8, 8.2)	6.6 (5.6, 7.6)	0.872‡
REM	796	8.5 (7.8, 9.1)	8.7 (7.7, 9.8)	8.2 (6.4, 9.9)	9.9 (8.9, 10.9)	0.107‡
Sleep latency, arousals and limb movements						
Sleep latency, min	1570	22.8 (20.7, 25.0)[f,h]	19.8 (16.4, 23.3)[e]	19.2 (13.8, 24.6)	16.8 (13.5, 20.0)[e]	0.006‡
WASO, min	1446	83.6 (79.6, 87.5)[h]	83.4 (77.0, 89.8)[g]	94.7 (84.7, 105)[f,h]	75.7 (69.7, 81.7)[e,g]	0.017‡
Arousal Index, h^{-1}	1507	33.2 (31.6, 34.9)	34.7 (32.0, 37.4)	34.1 (29.9, 38.3)	36.6 (34.1, 39.2)	0.768‡
Arousal intensity, 0-9	790	3.21 (3.15, 3.26)	3.25 (3.16, 3.34)	3.08 (2.94, 3.23)	3.28 (3.20, 3.36)	0.134‡
HR response to arousals, beats/min	687	2.74 (2.62, 2.87)	2.67 (2.46, 3.11)	2.76 (2.41, 3.11)	2.91 (2.72, 3.10)	0.195‡
PLMI, h^{-1}	599	14.8 (12.8, 16.8)	17.2 (13.8, 20.6)	21.5 (16.0, 27.1)	14.9 (11.8, 18.0)	0.095‡

Adjusted for age, sex, body mass index and ethnicity; Data presented as means (95% confidence intervals), with p-values statistically significant after Hochberg step-up correction shown in* ***bold**; †Adjusted p-value from ANOVA comparing mean values between the sleepiness phenotypes, controlling for age, sex, BMI and ethnicity, ‡p values using log-or square root transformed values, [a]p <0.05 (significantly different from non-sleepy); [b]p<0.05 (significantly different from risk of dozing); [c]p<0.05 (significantly different from feeling sleepy);[d]p<0.05 (significantly different from the group both at risk of dozing and feeling sleepy). Abbreviations: NREM = Non-Rapid Eye Movement, REM = Rapid Eye Movement, WASO = Wake After Sleep Onset, HR = Heart Rate, PLMI = Periodic Limb Movement Index.*

ORP characteristics

In unadjusted analysis (see **Table 2**) there was a difference in average ORP between sleepiness phenotypes, with the "non-sleepy" phenotype having the highest average ORP and those "both at risk of dozing and feeling sleepy" having the lowest. Right/Left ORP correlation was also highest in those "non-sleepy" and lowest in those "both at risk of dozing and feeling sleepy". In general, there were no significant differences between the sleepiness phenotypes in the ORP metrics after covariate adjustments (see **Table 5**), except that "non-sleepy" phenotype was more likely to have ORP in the ranges of 2.25-2.50, indicating that they

spent more time fully awake. Calculated effect sizes indicated that the effect of the sleepiness phenotypes on the proportion of ORP values from 2.25-2.50 was small (eta-squared = 0.010), with the largest difference being between "non-sleepy" and "both at risk of dozing and feeling sleepy" phenotypes (small-to-medium Cohen's d of 0.316).

Table 5. *Adjusted* analysis comparing odds ratio product characteristics between the sleepiness phenotypes.*

ORP Metric	Available data	Non-sleepy [a]	Risk of dozing only [b]	Feeling sleepy only [c]	Both at risk of dozing and feeling sleepy [d]	p[†]
Avg. ORP	796	1.30 (1.27, 1.33)	1.25 (1.21, 1.30)	1.27 (1.19, 1.34)	1.24 (1.20, 1.28)	0.113
Avg. Wake ORP	795	2.13 (2.11, 2.14)	2.11 (2.09, 2.14)	2.09 (2.06, 2.12)	2.10 (2.08, 2.12)	0.068
Avg. NREM ORP	796	0.99 (0.96, 1.01)	0.97 (0.93, 1.01)	0.98 (0.92, 1.05)	0.97 (0.93, 1.01)	0.902
Avg. REM ORP	682	1.32 (1.29, 1.35)	1.28 (1.23, 1.33)	1.22 (1.13, 1.32)	1.30 (1.25, 1.34)	0.220
Avg. ORP-9	788	1.22 (1.19, 1.25)	1.17 (1.12, 1.21)	1.20 (1.13, 1.27)	1.16 (1.12, 1.21)	0.094
Right/Left ORP Correlation	689	0.84 (0.83, 0.85)[b,h]	0.82 (0.81, 0.84)	0.83 (0.81, 0.86)	0.81 (0.80, 0.83)[e]	0.017
ORP type, n (%)						
Type 1,1	802	42 (10.1)	23 (15.2)	6 (10.9)	21 (11.7)	0.147[¥]
Type 1,2		81 (19.4)	30 (20.0)	11 (20.0)	36 (20.1)	
Type 1,3		103 (24.7)	32 (21.2)	11 (20.0)	31 (17.3)	
Type 2,1		37 (8.9)	13 (8.6)	8 (14.6)	24 (13.4)	
Type 2,2		55 (13.2)	26 (17.2)	6 (10.9)	33 (18.4)	
Type 2,3		51 (12.2)	10 (6.6)	5 (9.1)	13 (7.3)	
Type 3,1		25 (6.0)	12 (8.0)	5 (9.1)	18 (10.1)	
Type 3,2		20 (4.8)	4 (2.7)	3 (5.5)	3 (1.7)	
Type 3,3		3 (0.7)	1 (0.7)	0 (0.0)	0 (0.0)	
ORP Distribution (% epochs)						
0.00 - 0.25	796	1.59 (1.35, 1.84)	1.31 (0.99, 1.64)	1.77 (1.09, 2.46)	1.58 (1.23, 1.92)	0.917
0.25 - 0.50	796	7.50 (6.94, 8.06)	6.58 (5.84, 7.33)	8.01 (6.44, 9.57)	7.49 (6.70, 8.28)	0.695
0.50 - 0.75	796	11.2 (10.7, 11.8)	10.8 (10.2, 11.5)	11.2 (9.82, 12.7)	11.1 (10.4, 11.8)	0.403
0.75 - 1.00	796	12.5 (12.1, 12.9)[f]	13.1 (12.5, 13.6)[e]	12.1 (10.9, 13.3)	12.8 (12.2, 13.4)	0.037
1.00 - 1.25	796	12.8 (12.4, 13.2)	13.7 (13.2, 14.2)	12.1 (11.1, 13.1)	13.6 (13.0, 14.1)	0.149[‡]
1.25 - 1.50	796	12.4 (12.1, 12.8)	13.4 (12.9, 13.9)	11.8 (10.8, 12.8)	13.2 (12.6, 13.6)	0.366[‡]
1.50 - 1.75	796	11.1 (10.7, 11.4)	12.0 (11.5, 12.5)	11.0 (9.89, 12.0)	11.7 (11.0, 12.1)	0.802[‡]
1.75 - 2.00	796	9.56 (9.18, 9.95)	9.97 (9.46, 10.4)	10.0 (8.97, 11.1)	9.88 (9.33, 10.4)	0.087[‡]
2.00 - 2.25	796	9.25 (8.83, 9.66)[f]	8.95 (8.40, 9.50)[e]	9.95 (8.79, 11.10)	8.93 (8.34, 9.51)	0.044[‡]
2.25 - 2.50	796	12.0 (11.3, 12.8)[f,h]	10.2 (9.26, 11.2)[e]	12.0 (10.0, 14.0)	10.0 (9.04, 11.0)[e]	**0.002**[‡]

Adjusted for age, sex, body mass index and ethnicity; Data presented as means (95% confidence intervals) or number and percentages (for ORP types), with p-values statistically significant after Hochberg step-up correction shown in* ***bold**, [†]Adjusted p-value from ANOVA comparing mean values between the sleepiness phenotypes, controlling for age, sex, body mass index and ethnicity, [‡]p values using log or square root transformed values, [¥]p-value from Person's chi-square test, [a]p <0.05 (significantly different from "non-sleepy"); [b]p<0.05 (significantly different from "risk of dozing"); [c]p<0.05 (significantly different from "feeling sleepy");[d]p<0.05 (significantly different from the group "both at risk of dozing and feeling sleepy"). Type 1,1 = Little deep sleep (DS)-Little full wakefulness (FW), Type 1,2 = Little DS-Average FW, Type 1,3 = Little DS-Much FW, Type 2,1 = Average DS-Little FW, Type 2,2 = Average DS-Average FW, Type 2,3 = Average DS-much FW, Type 3,1 = Much DS-Little FW, Type 3,2 = Much DS-Average FW, Type 3,3 = Much DS-Much FW. Abbreviations: ORP = Odds Ratio Product; NREM = Non Rapid Eye Movement; REM = Rapid Eye Movement.*

Sensitivity analysis

Supplementary Tables S3-S5 show PSG characteristics of the sample restricted to participants with an AHI ≥15 events/h (n=1372). Overall, results for AHI and variables of hypoxemia were similar to primary analyses in all patients, with the two phenotypes at "risk of dozing" having significantly worse hypoxemia than "non-sleepy" and "feeling sleepy only" phenotypes (**Table S3**); results did not reach significance for AHI (p=0.089). When comparing wake and sleep stages (see **Table S4**), there was a significant difference in WASO between sleepiness phenotypes: WASO was highest in the "feeling sleepy only" phenotype (100.7 minutes [95% CI: 77.3, 114.0]) and lowest in the "both at risk of dozing and feeling sleepy" phenotype (78.0 minutes [95% CI: 70.7, 85.2]) (**Table S4**). Similar results were seen in the full cohort but

did not reach significance after Hochberg step up correction (p=0.017; see **Table 4**). No significant differences were observed in ORP characteristics in those with an AHI≥15 (**Table S5**)

DISCUSSION

The main finding of this study is that overall, there are only small differences in PSG characteristics between OSA patients with and without EDS. AHI and measures of hypoxemia did distinguish individuals at "risk of dozing" (with or without feeling sleepy) more effectively from those who were "non-sleepy" or "feeling sleepy only". Overall, those "feeling sleepy only" had the least severe PSG abnormalities, including significantly lower hypoxic burden than all other sleepiness phenotypes. Ultimately, our results suggest that other factors, which are not captured by the PSG, may have a greater influence on the manifestation of EDS among OSA patients.

In this present study, we found that reported "risk of dozing" in OSA patients was associated with higher AHI and more severe hypoxemia, including higher ODI and TST90 and lower minimum SpO_2 and average SpO_2. These findings are consistent with many previous studies that have found significantly higher AHI and worse hypoxemia among OSA patients with EDS.[4,6-8,10,46] There are several proposed mechanisms of how hypoxemia causes sleepiness in OSA. Murine studies show that the chronic intermittent hypoxemia seen in OSA causes inflammation, oxidative injury, neuronal damage, and cell loss in wake-promoting regions of the brain.[47-50] Inflammation has also been proposed as a link between OSA, EDS and increased risk of cardiovascular disease.[51] The exact pathophysiological mechanisms by which hypoxemia causes inflammation and EDS in OSA are however not yet known. We found that hypoxemia was more strongly associated with having a "risk of dozing", while those "feeling sleepy only" had similar or less severe hypoxemia than the "non-sleepy" phenotype. The reason for this is not clear but suggests that "feeling sleepy only" without a risk of dozing is caused by unmeasured factors unrelated to OSA. Consistent with this theory, our previous research among OSA patients with moderate-to-severe disease in the Icelandic Sleep Apnea Cohort[23] and in SAGIC[22] showed that those "feeling sleepy only" had higher prevalence of insomnia symptoms, evening chronotype and short sleep. Furthermore, in the Icelandic cohort, those "feeling sleepy only" showed less improvement of sleepiness with positive airway pressure treatment than the two sleepiness phenotypes at "risk of dozing". This again indicates that the "feeling sleepy only" phenotype has other additional causes of sleepiness independent of OSA. Therefore, "feeling sleepy only" subjects might need a more thorough investigation of the underlying causes of their sleepiness, including causes of disturbed sleep or insomnia, for better and more personalized clinical management.

We investigated two markers of sleep depth, the relative amounts of different sleep stages and the ORP. We found that the "non-sleepy" phenotype spent more time awake on average during the recording and had a greater proportion of ORP in the 2.20-2.25 range, indicating more wakefulness. This might simply reflect that those with "risk of dozing" had higher propensity for sleep than "non-sleepy" subjects. Our results, therefore, support previous studies[7,8,19] that have not found EDS among OSA patients to be a result of change in sleep architecture.

In the current study, we did not find a significant association between the arousal index and sleepiness in OSA. This is in agreement with many other studies,[7-9,19] although others have found a higher arousal index

to be associated with subjective sleepiness.[11,13,15,18] The arousal index represents number of arousals per hour, but it does not distinguish between arousals of different intensities. Therefore, in addition to the arousal index, we examined two markers of arousal intensity; an algorithm produced intensity score from 1-9[33-35] and the HR response to arousal, which has been directly correlated with arousal intensity.[33] Our results did not show a significant difference in either marker of arousal intensity between our sleepiness phenotypes after adjustments of confounders. Thus, sleepiness in OSA is more closely related to hypoxemia than sleep fragmentation, as measured in frequencies and intensities of arousals, although the differences are small.

Strength and limitations

Our present study represents an important follow-up to the original analysis of the sleepiness phenotypes performed in the Icelandic Sleep Apnea Cohort.[23] Exploring the PSG determinants of our sleepiness phenotypes is a crucial step towards understanding how the pathophysiology of OSA is associated with sleepiness experienced by patients. Other strengths of this study include the large and diverse sample size of patients from multiple international centers, as well as standardized data collection and uniform centralized analysis.

There are also limitations. Given the design of SAGIC, the OSA patients were recruited from clinical sleep centers and do not necessarily represent OSA patients found in the general population. Also, in this study we did not investigate the potential role of comorbidities on EDS in OSA. We have, however, previously described the characteristics, comorbidities, reports of sleep related symptoms, self-reported sleep length and chronotype among the sleepiness phenotypes in SAGIC.[22] Another limitation is that we do not have objective measures of sleepiness in our sample; it's possible that physiology may be more predictive of functional deficits related to sleepiness, such as those measured by psychomotor vigilance task.[52] Ultimately, more measures of sleepiness may provide new information on relevant sleepiness phenotypes in OSA and enable us to find PSG associations – if they are to be found.

CONCLUSIONS

EDS in OSA is multifactorial and only weakly associated with traditional and novel physiological characteristics. AHI and measures of hypoxemia are the most effective in differentiating those with "risk of dozing" from "non-sleepy" and those "feeling sleepy only", although effect sizes are small. Other parameters such as sleep stages, arousals, arousal intensity, limb movement, and sleep depth, were not associated with the sleepiness phenotypes studied here. Future studies aimed at exploring alternative mechanisms of EDS in OSA patients are needed.

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List of abbreviations:
AHI: Apnea Hypopnea Index
ANOVA: Analysis of Variance
BMI: Body Mass Index
EDS: Excessive Daytime Sleepiness
EEG: Electroencephalography
ESS: Epworth Sleepiness Scale
HR: Heart Rate
HSAT: Home Sleep Apnea Tests
IQR: Inter-quartile range
N1: NREM sleep stage 1
N2: NREM sleep stage 2
N3: NREM sleep stage 3
NREM: Non-rapid Eye Movement
ODI: Oxygen Desaturation Index
ORP: Odds Ratio Product
OSA: Obstructive Sleep Apnea
PLMI: Periodic Limb Movement
PSG: Polysomnography
REM: Rapid Eye Movement
SAGIC: Sleep Apnea Global Interdisciplinary Consortium
SD: Standard Deviation
SpO_2: Oxygen Saturation
TST90: Total Sleep Time spend under 90% SpO_2.
WASO: Wake After Sleep Onset

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Financial disclosure: MY is the inventor of ORP and has a patent on it. The technology is licensed to Cerebra Health and MY owns shares and receives royalties from Cerebra. Other authors have nothing to declare.
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SUPPLIMENTARY TABLES

Table S1. *Unadjusted analysis comparing means and medians of measures of OSA severity, hypoxemia and sleep stages between the sleepiness phenotypes*

Characteristic	Available data	Overall	Sleepiness phenotypes				p-value*
			Non-sleepy [a]	Risk of dozing only [b]	Feeling sleepy only [c]	Both at risk of dozing and feeling sleepy [d]	
Measures of OSA severity and hypoxemia							
AHI, h^{-1}	2097						
Mean ± SD		31.9 ± 26.4	30.2 ± 24.2	32.3 ± 25.9	29.0 ± 26.5	36.0 ± 30.4	**0.004**†
Median (IQR)		22.4 (12.0, 44.1)	21.9 (11.7, 42.3)	23.2 (12.2, 48.5)	18.7 (11.3, 36.6)	25.9 (13.1, 47.5)	**0.006**
ODI, h^{-1}	2036						
Mean ± SD		30.2 ± 29.1	28.3 ± 26.9	32.0 ± 31.9	26.0 ± 29.2	34.4 ± 30.4	**<0.001**†
Median (IQR)		19.9 (9.8, 42.4)	19.4 (9.2, 40.3)	22.3 (10.6, 44.4)	14.7 (7.6, 32.1)	22.9 (11.3, 47.2)	**<0.001**
Average SpO_2, %	1922						
Mean ± SD		92.9 ± 3.2	93.2 ± 2.9	92.8 ± 3.1	93.1 ± 3.1	92.3 ± 3.8	**<0.001**
Median (IQR)		93.3 (91.7, 95.0)	93.4 (92.0, 95.0)	93.3 (91.5, 95.0)	93.5 (92.0, 95.0)	93.0 (91.0, 94.8)	**0.003**
Minimum SpO_2, %	1977						
Mean ± SD		79.0 ± 8.9	79.9 ± 8.5	78.1 ± 8.9	80.1 ± 8.3	77.5 ± 9.8	**<0.001**
Median (IQR)		81.0 (74.0, 85.0)	82.0 (76.0, 86.0)	80.0 (74.0, 84.0)	82.0 (75.0, 86.0)	80.0 (72.0, 85.0)	**0.001**
TST90, %	1936						
Mean ± SD		11.7 ± 18.8	10.2 ± 16.9	13.1 ± 19.5	8.5 ± 15.5	14.9 ± 22.2	**<0.001**†
Median (IQR)		3.1 (0.4, 14.0)	2.6 (0.3, 12.5)	4.3 (0.6, 16.0)	1.7 (0.2, 8.6)	4.5 (0.7, 18.9)	**<0.001**
Hypoxic Burden, %min/h	933						
Mean ± SD		110.3 ± 137.0	112.3 ± 137.0	103.5 ± 124.7	66.7 ± 81.2	126.1 ± 157.0	**0.007**†
Median (IQR)		57.8 (28.6, 133.3)	59.5 (28.9, 140.8)	57.6 (28.6, 113.9)	36.5 (20.6, 71.3)	63.3 (32.6, 146.4)	**0.002**
Sleep stages, %							
Wake	802						
Mean ± SD		22.8 ± 14.7	24.8 ± 15.2	20.7 ± 13.6	23.8 ± 15.5	19.5 ± 13.6	**<0.001**†
Median (IQR)		20.0 (11.4, 31.1)	22.1 (13.4, 33.5)	18.7 (10.4, 27.4)	21.1 (10.9, 33.0)	16.0 (8.8, 27.1)	**<0.001**
NREM Stage N1	802						
Mean ± SD		17.1 ± 9.9	17.1 ± 9.8	17.8 ± 9.5	16.3 ± 9.2	16.6 ± 10.7	0.516†
Median (IQR)		14.5 (9.9, 15.0)	15.4 (9.7, 22.3)	15.4 (11.3, 22.1)	15.2 (9.9, 21.3)	13.6 (9.7, 20.8)	0.285
NREM Stage N2	802						
Mean ± SD		42.2 ± 12.2	41.5 ± 11.9	43.0 ± 12.4	41.1 ± 11.1	43.4 ± 12.8	0.215
Median (IQR)		42.9 (34.4, 51.2)	42.1 (34.1, 50.5)	43.6 (34.5, 51.6)	41.7 (34.3, 49.6)	45.7 (34.4, 53.9)	0.116
NREM Stage N3	802						
Mean ± SD		6.1 ± 7.2	5.5 ± 6.3	6.0 ± 6.8	7.2 ± 8.7	7.4 ± 8.9	0.276†
Median (IQR)		3.5 (0.23, 9.6)	3.3 (0.1, 9.0)	4.2 (0.3, 9.0)	4.6 (0.0, 14.4)	3.6 (0.4, 12.1)	0.220
REM	802						
Mean ± SD		8.8 ± 6.9	8.3 ± 6.8	9.0 ± 6.3	7.9 ± 8.2	10.2 ± 7.1	**0.012**†
Median (IQR)		8.0 (3.3, 13.6)	7.1 (2.9, 12.2)	8.4 (4.2, 13.6)	5.8 (0.0, 13.6)	10.0 (4.7, 15.1)	**0.004**

**p values from one-way analysis of variance (ANOVA) comparing mean values and Kruskal Wallis test comparing median values between sleepiness phenotypes, †p values from ANOVA comparing log or square root transformed mean values between sleepiness phenotypes. [a]ESS score ≤10 and reporting feeling sleepy <3 times per week; [b]ESS score >10 but reporting feeling sleepy <3 times per week; [c]ESS score ≤10 but reporting feeling sleepy ≥3 times per week; [d]ESS score >10 and reporting feeling sleepy ≥3 times per week. Abbreviations: SD = Standard deviation, IQR = Inter-quartile range, OSA = Obstructive sleep apnea, AHI = Apnea hypopnea index, ODI = Oxygen desaturation index, SpO2 = Oxygen saturation, TST90 = Total Sleep Time spend under 90% SpO_2, NREM = non-rapid eye movement; REM = Rapid eye movement, min = minute, h = hour*

Table S2. *Unadjusted analysis comparing means and medians of sleep latency, arousals, limb movements and ORP metrics between the sleepiness phenotypes*

Characteristic	Available data	Overall	Sleepiness phenotypes				
			Non-sleepy [a]	Risk of dozing only [b]	Feeling sleepy only [c]	Both at risk of dozing and feeling sleepy [d]	
Sleep latency, arousals, and limb movements							
Sleep latency, min	1593						
Mean ± SD		20.7 ± 31.3	22.9 ± 36.0	18.7 ± 28.3	20.5 ± 23.7	17.5 ± 23.3	**0.003**[†]
Median (IQR)		11.0 (4.5, 24.0)	12.5 (5.0, 25.4)	9.5 (3.5, 22.7)	13.0 (5.5, 27.0)	9.9 (4.0, 21.0)	**0.006**
WASO, min	1480						
Mean ± SD		82.4 ± 59.3	86.0 ± 59.6	86.0 ± 63.0	85.9 ± 58.7	69.9 ± 53.7	**<0.001**[†]
Median (IQR)		69.0 (37.1, 115.5)	71.5 (41.5, 119.0)	71.1 (37.5, 121.0)	76.5 (40.5, 127.0)	56.5 (30.5, 94.5)	**<0.001**
Arousal Index, h^{-1}	1554						
Mean ± SD		34.4 ± 24.8	33.5 ± 22.5	34.8 ± 27.6	33.7 ± 24.7	36.5 ± 27.2	0.554[‡]
Median (IQR)		27.7 (18.0, 45.7)	27.9 (17.5, 43.6)	28.4 (15.7, 48.5)	26.2 (17.1, 42.6)	27..8 (17.0, 50.5)	0.855
Arousal intensity, 1-9	796						
Mean ± SD		3.2 ± 0.6	3.2 ± 0.5	3.2 ± 0.6	3.1 ± 0.6	3.3 ± 0.7	**0.030**[‡]
Median (IQR)		3.1 (2.8, 3.5)	3.1 (2.8, 3.5)	3.2 (2.8, 3.6)	3.0 (2.7, 3.5)	3.2 (2.9, 3.7)	0.073
HR response to arousals, beats/min	693						
Mean ± SD		2.8 ± 1.3	2.7 ± 1.3	2.7 ± 1.2	2.6 ± 1.4	2.9 ± 1.3	0.106
Median (IQR)		2.6 (1.8, 3.4)	2.6 (1.7, 3.4)	2.5 (1.8, 3.2)	2.4 (1.6, 3.0)	2.7 (2.2, 3.6)	0.099
PLMI, h^{-1}	802						
Mean ± SD		15.8 ± 22.0	15.3 ± 21.5	17.6 ± 20.5	20.2 ± 29.3	14.0 ± 21.7	0.063[†]
Median (IQR)		6.8 (0.8, 23.2)	4.8 (0.0, 24.1)	8.2 (1.3, 27.4)	11.3 (2.3, 25.8)	5.4 (0.9, 17.7)	**0.032**
Odds ratio product							
Avg. ORP	802						
Mean ± SD		1.27 ± 0.31	1.31 ± 0.31	1.25 ± 0.29	1.28 ± 0.35	1.22 ± 0.31	**0.017**
Median (IQR)		1.25 (1.05, 1.48)	1.30 (1.08, 1.53)	1.23 (1.02, 1.44)	1.22 (1.03, 1.58)	1.22 (0.99, 1.40)	**0.018**
Avg. Wake ORP	801						
Mean ± SD		2.11 ± 0.14	2.13 ± 0.14	2.11 ± 0.15	2.10 ± 0.14	2.10 ± 0.15	0.092
Median (IQR)		2.13 (2.03, 2.22)	2.14 (2.04, 2.23)	2.12 (2.03, 2.23)	2.12 (2.00, 2.20)	2.13 (2.00, 2.21)	0.114
Avg. NREM ORP	802						
Mean ± SD		0.98 ± 0.26	0.99 ± 0.26	0.97 ± 0.24	0.99 ± 0.31	0.97 ± 0.27	0.778
Median (IQR)		0.96 (0.79, 1.14)	0.96 (0.81, 1.16)	0.95 (0.78, 1.13)	0.92 (0.75, 1.21)	0.95 (0.77, 1.12)	0.778
Avg. REM ORP	688						
Mean ± SD		1.30 ± 0.31	1.33 ± 0.32	1.30 ± 0.26	1.21 ± 0.34	1.28 ± 0.30	0.088
Median (IQR)		1.29 (1.09, 1.54)	1.31 (1.11, 1.57)	1.30 (1.07, 1.50)	1.14 (0.97, 1.46)	1.27 (1.07, 1.51)	0.091
Avg. ORP-9	794						
Mean ± SD		1.19 ± 0.29	1.22 ± 0.29	1.17 ± 0.26	1.21 ± 0.32	1.16 ± 0.29	0.066
Median (IQR)		1.18 (0.99, 1.38)	1.21 (1.01, 1.42)	1.16 (0.97, 1.34)	1.14 (0.96, 1.46)	1.16 (0.96, 1.33)	0.102
Right/Left ORP Correlation	695						
Mean ± SD		0.83 ± 0.10	0.84 ± 0.09	0.82 ± 0.10	0.83 ± 0.08	0.80 ± 0.11	**<0.001**
Median (IQR)		0.85 (0.78, 0.90)	0.86 (0.80, 0.90)	0.84 (0.77, 0.90)	0.85 (0.77, 0.90)	0.83 (0.76. 0.89)	**<0.001**

**p values from one-way analysis of variance (ANOVA) comparing mean values and Kruskal Wallis test comparing median values between sleepiness phenotypes, [†]p values from ANOVA comparing log or square root transformed mean values between sleepiness phenotypes. [a]ESS score ≤10 and reporting feeling sleepy <3 times per week; [b]ESS score >10 but reporting feeling sleepy <3 times per week; [c]ESS score ≤10 but reporting feeling sleepy ≥3 times per week; [d]ESS score >10 and reporting feeling sleepy ≥3 times per week. Abbreviations: SD = Standard deviation, IQR = Inter-quartile range, NREM = non-rapid eye movement; REM = Rapid eye movement, WASO = Wake after sleep onset; HR = Heart rate, PLMI = Periodic Limb Movement Index, ORP = Odds Ratio Product, ORP-9 = ORP in the immediate 9 seconds after arousal, min = minute, h = hour*

Table S3. *Calculated effect sizes of the relationship between the polysomnographic variables and sleepiness phenotypes overall (eta-squared) and between each pair of sleepiness phenotypes (Cohen´s d)*

	Cohen's d[‡]						Eta-squared [§]
	Non vs. RD	Non vs. FS	Non vs. FD	RD vs. FS	RD vs. FD	FS vs. FD	
Measures of OSA severity and hypoxemia							
AHI, h^{-1}	-0.083	0.050	-0.221	0.126	-0.133	-0.240	0.009
ODI, h^{-1}	-0.133	0.084	-0.219	0.195	-0.076	-0.281	0.009
Average SpO_2, %	0.138	0.034	0.268	-0.100	0.130	0.212	0.013
Minimum SpO_2, %	0.217	-0.022	0.274	-0.235	0.062	0.281	0.015
TST90, %	-0.160	0.103	-0.248	0.248	-0.087	-0.311	0.013
Hypoxic Burden, %min/h	0.066	0.349	-0.096	0.325	-0.157	-0.419	0.013
Sleep stages							
Wake, min	0.305	0.089	0.360	-0.231	0.060	0.289	0.016
Wake, %	0.281	0.067	0.363	-0.221	0.089	0.307	0.015
ORP metric							
ORP Distribution							
2.25 - 2.50	0.193	0.103	0.316	-0.091	0.130	0.226	0.010

[‡]Effect size calculated as Cohen's d quantifying standardized mean difference between each pair of sleepiness phenotypes (0.2=small effect, 0.5=medium effect, 0.8=large effect), [§]Effect size among sleepiness phenotypes calculated as eta-squared (0.01=small effect, 0.06=medium effect, 0.14=large effect). Abbreviations: Non = "Non-sleepy" phenotype, RD = "Risk of dozing only" phenotype, FS = "Feeling sleepy only" phenotype, FD = "Both at risk of dozing and feeling sleepy" phenotype, OSA = Obstructive sleep apnea, AHI = Apnea hypopnea index, ODI = Oxygen desaturation index, SpO2 = Oxygen saturation, TST90 = Total Sleep Time spend under 90% SpO_2, ORP = Odds ratio product, min = minute, h = hour

Table S4. *Adjusted[*] analysis comparing polysomnographic parameters of OSA severity and hypoxemia between the sleepiness phenotypes among subjects with an Apnea-Hypopnea Index ≥15*

Sleep Study Metric	Available data	Non-sleepy [a]	Risk of dozing only[b]	Feeling sleepy only[c]	Both at risk of dozing and feeling sleepy[d]	P[†]
AHI, h^{-1}	1372	42.1 (40.3, 43.9)	43.7 (41.0, 46.4)	40.5 (36.2, 44.7)	45.7 (43.2, 48.2)	0.089[‡]
ODI, h^{-1}	1331	39.5 (37.4, 41.7)	43.4 (40.1, 46.6)	38.2 (33.1, 43.2)	43.7 (40.8, 46.6)	**0.001**[‡]
Average SpO_2, %	1263	92.6 (92.3, 92.8)	91.9 (91.6, 92.3)	92.5 (91.9, 93.1)	91.8 (91.4, 92.1)	**0.001**
Minimum SpO_2, %	1278	77.0 (76.3, 77.7)	75.2 (74.1, 76.2)	77.6 (76.0, 79.2)	75.3 (74.3, 76.2)	**0.001**
TST90, %	1258	14.1 (12.5, 15.7)	17.9 (15.5, 20.3)	12.4 (8.6, 16.2)	19.1 (16.9, 21.3)	**<0.001**
Hypoxic Burden, %min/h	604	148 (133, 164)	151 (125, 177)	107 (67.1, 147)	168 (147, 189)	**0.015**[‡]

Adjusted for age, gender, body mass index and ethnicity; Data presented as means (95% confidence intervals), with p-values statistically significant after Hochberg step-up correction shown in **bold; [†]Adjusted p-value from ANOVA comparing mean values between the sleepiness phenotypes, controlling for age, gender, body mass index and ethnicity, [‡]p values using log or square root transformed values; [a]ESS score ≤10 and reporting feeling sleepy <3 times per week; [b]ESS score >10 but reporting feeling sleepy <3 times per week; [c]ESS score ≤10 but reporting feeling sleepy ≥3 times per week; [d]ESS score >10 and reporting feeling sleepy ≥3 times per week; [e]p <0.05 (significantly different from "non-sleepy"); [f]p<0.05 (significantly different from "risk of dozing only"); [g]p<0.05 (significantly different from "feeling sleepy only");[h]p<0.05 (significantly different from "both at risk of dozing and feeling sleepy"); Abbreviations: AHI = Apnea hypopnea index, ODI = Oxygen desaturation index, SpO2 = Oxygen saturation, TST90 = Total Sleep Time spend under 90% SpO_2, min = minute, h = hour.*

Table S5. *Adjusted[*] analysis comparing sleep stages, sleep latency, arousals, and limb movements between sleepiness phenotypes among subjects with an Apnea-Hypopnea Index ≥15*

Sleep Study Metric	Available data	Non-sleepy [a]	Risk of dozing only[b]	Feeling sleepy only [c]	Both at risk of dozing and feeling sleepy [d]	p[†]
Sleep stages, min						
Wake	519	99.7 (92.6, 107)	87.7 (75.5, 99.8)	91.3 (71.3, 111)	84.7 (74.3, 95.2)	0.058[‡]
NREM Stage N1	519	90.6 (75.2, 85.9)	84.7 (75.6, 93.8)	80.9 (65.9, 95.9)	79.4 (71.5, 87.2)	0.667[‡]
NREM Stage N2	519	172 (165, 179)	171 (159, 182)	178(159, 196)	179 (169, 189)	0.605
NREM Stage N3	519	23.7 (20.4, 27.0)	23.7 (18.0, 29.3)	26.9 (17.6, 36.2)	23.4 (18.6, 28.3)	0.659[‡]
REM	519	34.9 (31.4, 38.4)	25.1 (29.1, 41.1)	34.5 (24.6, 44.3)	39.5 (34.3, 44.7)	0.260[‡]
Sleep stages, %						
Wake	519	23.0 (21.4, 24.6)	20.7 (17.9, 23.4)	22.0 (17.4, 26.5)	20.1 (17.7, 22.4)	0.101[‡]
NREM Stage N1	519	19.1 (17.9, 20.3)	20.3 (18.2, 22.3)	19.4 (16.0, 22.8)	18.9 (17.2, 20.7)	0.601[‡]
NREM Stage N2	519	41.0 (39.6, 42.5)	40.7 (38.2, 43.2)	41.8 (37.7, 45.9)	42.9 (40.7, 45.0)	0.510
NREM Stage N3	519	5.7 (4.9, 6.5)	5.8 (4.4, 7.1)	6.0 (3.8, 8.2)	5.5 (4.3, 6.7)	0.713[‡]
REM	519	8.3 (7.5, 9.1)	8.3 (6.9, 9.7)	8.2 (5.9, 10.5)	9.5 (8.3, 10.7)	0.285[‡]
Sleep latency, arousals and limb movements						
Sleep latency, min	1050	21.7 (19.3, 24.2)	20.9 (17.2, 24.7)	14.8 (8.59, 20.9)	15.5 (12.1, 18.9)	0.012[‡]
WASO, min	972	85.8 (80.6, 91.0)	87.7 (79.6, 95.8)	101 (87.3, 114)	78.0 (70.7, 85.2)	0.021[‡]
Arousal Index, h^{-1}	1026	40.5 (38.3, 42.7)	41.8 (38.3, 45.3)	39.5 (33.8, 45.2)	42.1 (38.9, 45.3)	0.896[‡]
Arousal intensity, 1-9	517	3.19 (3.12, 3.25)	3.25 (3.15, 3.37)	3.07 (2.88, 3.25)	3.26 (3.16, 3.35)	0.272[‡]
HR response to arousals, beats/min	452	2.96 (2.81, 3.12)	2.98 (2.70, 3.25)	2.96 (2.52, 3.39)	3.08 (2.85, 3.32)	0.758[‡]
PLMI, h^{-1}	519	14.2 (12.0, 16.4)	16.1 (12.3, 19.8)	15.8 (9.7, 21.9)	12.6 (9.4, 15.8)	0.286[‡]

Adjusted for age, gender, body mass index and ethnicity; Data presented as means (95% confidence intervals), with p-values statistically significant after Hochberg step-up correction shown in **bold; [†]Adjusted p-value from analysis of variance (ANOVA) comparing mean values between the sleepiness phenotypes, controlling for age, gender, body mass index and ethnicity, [‡]p values using log-or square root transformed values; [a]ESS score ≤10 and reporting feeling sleepy <3 times per week; [b]ESS score >10 but reporting feeling sleepy <3 times per week; [c]ESS score ≤10 but reporting feeling sleepy ≥3 times per week; [d]ESS score >10 and reporting feeling sleepy ≥3 times per week, [e]p <0.05 (significantly different from "non-sleepy"); [f]p<0.05 (significantly different from "risk of dozing only"); [g]p<0.05 (significantly different from "feeling sleepy only");[h]p<0.05 (significantly different from "both at risk of dozing and feeling sleepy"); Abbreviations: NREM = Non-rapid eye movement, REM = Rapid eye movement, WASO = Wake after sleep onset, HR = Heart rate, PLMI = Periodic Limb Movement Index, min = minute, h = hour*

Table S5. *Adjusted[*] analysis comparing odds ratio product characteristics between sleepiness phenotypes among subjects with an Apnea-Hypopnea Index ≥15*

ORP Metric	Available data	Non-sleepy [a]	Risk of dozing only [b]	Feeling sleepy only [c]	Both at risk of dozing and feeling sleepy [d]	p[†]
Avg. ORP	519	1.30 (1.26, 1.33)	1.26 (1.20, 1.32)	1.26 (1.16, 1.36)	1.25 (1.20, 1.30)	0.446
Avg. Wake ORP	519	2.11 (2.10, 2.13)	2.09 (2.06, 2.12)	2.08 (2.03, 2.13)	2.08 (2.06, 2.10)	0.078
Avg. NREM ORP	519	1.01 (0.98, 1.04)	1.00 (0.95, 1.05)	0.99 (0.91, 1.08)	1.00 (0.96, 1.05)	0.981
Avg. REM ORP	446	1.31 (1.27, 1.35)	1.26 (1.20, 1.32)	1.24 (1.12, 1.36)	1.32 (1.26, 1.37)	0.362
Avg. ORP-9	515	1.22 (1.18, 1.25)	1.19 (1.13, 1.24)	1.22 (1.12, 1.31)	1.18 (1.13, 1.23)	0.573
Right/Left ORP Correlation	450	0.83 (0.82, 0.85)	0.82 (0.81, 0.88)	0.84 (0.81, 0.88)	0.81 (0.78, 0.82)	0.036
ORP type, n (%)						
Type 1,1	546	13.5	16.0	10.8	14.2	0.514
Type 1,2		19.2	22.3	21.6	21.6	
Type 1,3		22.8	20.2	18.9	13.4	
Type 2,1		10.3	9.6	18.9	11.9	
Type 2,2		12.1	16.0	2.7	16.4	
Type 2,3		9.3	4.3	5.4	6.0	
Type 3,1		6.1	8.5	8.1	8.2	
Type 3,2		3.2	2.1	5.4	1.5	
Type 3,3		0.4	0.0	0.0	0.0	
ORP Distribution (% epochs)						
0.00 - 0.25	519	1.98 (1.52, 2.45)	2.00 (1.21, 2.79)	2.03 (0.72, 3.34)	2.46 (1.77, 3.14)	0.715
0.25 - 0.50	519	9.46 (8.37, 10.5)	9.14 (7.29, 10.9)	10.2 (7.10, 13.2)	10.1 (8.49, 11.7)	0.858
0.50 - 0.75	519	13.0 (12.1, 13.9)	13.2 (11.7, 14.8)	13.9 (11.3, 16.4)	13.2 (11.9, 14.6)	0.938
0.75 - 1.00	519	13.7 (12.9, 14.4)	15.2 (13.9, 16.5)	13.7 (11.6, 15.7)	13.9 (12.8, 14.9)	0.203
1.00 - 1.25	519	13.1 (12.5, 13.8)	14.2 (13.1, 15.3)	13.3 (11.4, 15.1)	13.7 (12.8, 14.7)	0.429
1.25 - 1.50	519	11.7 (11.0, 12.3)	12.5 (11.4, 13.6)	11.7 (9.94, 13.6)	12.4 (11.5, 13.4)	0.602
1.50 - 1.75	519	9.69 (9.09, 10.3)	9.8 (8.82, 10.9)	9.78 (8.08, 11.5)	9.86 (8.97, 10.8)	0.985
1.75 - 2.00	519	8.09 (7.54, 8.64)	7.45 (6.51, 8.39)	8.40 (6.85, 9.95)	7.80 (6.99, 8.61)	0.580
2.00 - 2.25	519	8.19 (7.54, 8.83)	7.41 (6.31, 8.51)	7.92 (6.11, 9.73)	7.63 (6.68, 8.58)	0.451
2.25 - 2.50	519	11.1 (9.95, 12.3)	9.05 (7.08, 11.0)	9.17 (5.91, 12.4)	8.86 (7.16, 10.6)	0.049

Adjusted for age, gender, body mass index and ethnicity; Data presented as means (95% confidence intervals) or number and percentages (for ORP types), with p-values statistically significant after Hochberg step-up correction shown in* ***bold**; [†]Adjusted p-value from analysis of variance (ANOVA) comparing mean values between the sleepiness phenotypes, controlling for age, gender, body mass index and ethnicity, [‡]p values using log or square root transformed values, [¥]p-value from chi-square test; [a]ESS score ≤10 and reporting feeling sleepy <3 times per week; [b]ESS score >10 but reporting feeling sleepy <3 times per week; [c]ESS score ≤10 but reporting feeling sleepy ≥3 times per week; [d]ESS score >10 and reporting feeling sleepy ≥3 times per week, [e]p <0.05 (significantly different from "non-sleepy"); [f]p<0.05 (significantly different from "risk of dozing only"); [g]p<0.05 (significantly different from "feeling sleepy only");[h]p<0.05 (significantly different from "both at risk of dozing and feeling sleepy"); Type 1,1 = Little deep sleep (DS)-Little full wakefulness (FW), Type 1,2 = Little DS-Average FW, Type 1,3 = Little DS-Much FW, Type 2,1 = Average DS-Little FW, Type 2,2 = Average DS-Average FW, Type 2,3 = Average DS-much FW, Type 3,1 = Much DS-Little FW, Type 3,2 = Much DS-Average FW, Type 3,3 = Much DS-Much FW. Abbreviations: ORP = Odds Ratio Product; NREM = Non rapid eye movement; REM = Rapid eye movement*

Appendix A

Appendix 1 – Epworth Sleepiness Scale

Epworth Sleepiness Scale[11]

How likely are you to nod off or fall asleep in the following situations, in contrast to feeling just tired? This refers to your usual way of life in recent times.

Even if you haven't done some of these things recently, try to work out how they would have affected you. It is important that you answer each question as best you can.

Use the following scale to choose the most appropriate number for each situation.

	Would never nod off 0	Slight chance of nodding off 1	Moderate chance of nodding off 2	High chance of nodding off 3
Sitting and reading				
Watching TV				
Sitting, inactive, in a public place (e.g., in a meeting, theater, or dinner event)				
As a passenger in a car for an hour or more without stopping for a break				
Lying down to rest when circumstances permit				
Sitting and talking to someone				
Sitting quietly after a meal without alcohol				
In a car, while stopped for a few minutes in traffic or at a light				

Add up your points to get your total score. A score of 10 or greater raises concern: you may need to get more sleep, improve your sleep practices, or seek medical attention to determine why you are sleepy.

Appendix 2 — Basic Nordic Sleep Questionnaire

Basic Nordic Sleep Questionnaire

1. Have you had difficulties to fall asleep during the past three months?

1 never or less than once per month
2 less than once per week
3 on 1-2 days per week
4 on 3-5 days per week
5 daily or almost daily

2. How long time (how many minutes as an average) do you stay awake in bed before you fall asleep (after lights off)?

a. During working days: it takes about ___ minutes before I fall asleep
b. During freetime: it takes about ___ minutes

3. How often have you awakened at night during the past three months?

1 never or less than once per month 2 less than once per week
3 on 1-2 nights per week
4 on 3-5 nights per week
5 every night or almost every night

4. **If you use to wake up during night, how many times do you usually wake up during one night (during the past three months)?**

1 usually I don't wake up at night
2 once per night
3 2 times
4 3-4 times
5 at least 5 times per night

5. How often have you awakened too early in the morning without being able to fall asleep again during the past three months?

1 never or less than once per month 2 less than once per week
3 on 1-2 days per week
4 on 3-5 days per week
5 daily or almost daily

6. How well have you been sleeping during the past three months?

1 well
2 rather well
3 neither well nor badly
4 rather badly
5 badly

7. Have you used some sleeping pills (by prescription) during the past three :months?

1 never or less than once per month 2 less than once per week
3 on 1-2 days per week
4 on 3-5 days per week
5 daily or almost daily

Which sleeping pill(s) :_____

8. Do you feel excessively sleepy in the morning after awakening?

1 never or less than once per month
2 less than once per week
3 on 1-2 days per week
4 on 3-5 days per week
5 daily or almost daily

9. Do you feel excessively sleepy during daytime?

1 never or less than once per month
2 less than once per week
3 on 1-2 days per week
4 on 3-5 days per week
5 daily or almost daily

10. Have you suffered from irresistible tendency to fall asleep while at work during the past three months?

1 never or less than once per month
2 less than once per week
3 on 1-2 days per week
4 on 3-5 days per week
5 daily or almost daily

11. Have you suffered from irresistible tendency to fall asleep during free time (leisure time) during the past three months?

1 never or less than once per month
2 less than once per week
3 on 1-2 days per week
4 on 3-5 days per week
5 daily or almost daily

12. How :many hours do you usually sleep per night?

1 sleep about _____hours per night.

13. **At what time do you usually go to bed (in order to sleep)?**

a. during working week: at _____

b. during free days: at _____

14. **At what time do you usually wake up?**

a. during working week: at _____

b. during free days: at _____

15a. How often do you sleep naps at daytime?

1 never or less than once per month
2 less than once per week
3 on 1-2 days per week
4 on 3-5 days per week
5 daily or almost daily

15b. If you sleep a nap, how long do does it usually last for?

My naps usually last for about h_____min _____

16. Do you snore while sleeping (ask other people if you are not sure)?

1 never or less than once per month
2 less than once per week
3 on 1-2 nights per week
4 on 3-5 nights per week
5 every night or almost every night

17. How do you snore (ask other people about the quality of your snoring)?

1 I don't snore
2 my snoring sounds regular and it is of low voice
3 it sounds regular but rather loud
4 it sounds regular but it is very loud (other people hear my snoring in the next room)
5 I snore very loudly and intermittently (there are silent breathing pauses when snoring is not heard and at times very loud snorts with gasping)

18. Have you had breathing pauses (sleep apnea) at sleep (have other people noticed that you have pauses in respiration when you sleep)?

1 never or less than once per month
2 less than once per week
3 on 1-2 nights per week
4 on 3-5 nights per week
5 every night or almost every night

19. If you snore at least 1-2 times per week, how many years have you been snoring (ask other people if you don't know)?

I have been snoring for about _____years. I was about_____years old when I started to snore.

20. How many hours of sleep do you need per night (how many hours would you sleep if you had possibility to sleep as long as you need to)?

I need_____hours and_____min of sleep per night.

21. If you have problems with your sleep, what kind of problems do you have (describe your problems with your own words):

_____

_____

_____

_____

Markku Partinen and Thorarinn Gislason