Université de Montréal

L'apnée obstructive du sommeil comme facteur de risque de déclin cognitif : rôle du sexe et de l'âge

Analyse des données de la cohorte de l'Étude longitudinale canadienne sur le vieillissement

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Résumé

Trente à 50% du risque de développer une démence est attribuable à des facteurs modifiables telles l'inactivité physique, l'hypertension et la dépression. Depuis quelques années, certains auteurs considèrent que les troubles du sommeil devraient également être inclus. Notamment, l'apnée obstructive du sommeil (AOS) serait associée à un plus grand risque de déclin cognitif et de démence selon des études épidémiologiques. Toutefois, d'autres études n'ont pas observé ce lien entre l'AOS et le déclin cognitif. Notre équipe a ainsi émis l'hypothèse que certains facteurs modulent l'association entre l'AOS et le déclin cognitif, expliquant une partie de l'hétérogénéité des résultats des études précédentes.

Cette thèse vise à caractériser le rôle de l'âge, du sexe et de l'inflammation systémique dans l'association entre le risque d'AOS et la performance cognitive chez les adultes d'âge moyen et les personnes âgées. Afin d'y parvenir, nous avons utilisé le score obtenu à des variantes du questionnaire STOP afin d'établir le risque de présenter de l'AOS, une batterie de tests neuropsychologiques et le dosage de la protéine C-Réactive (CRP) dans le sang dans une grande cohorte canadienne. Ce protocole a mené à une revue narrative et à trois articles de recherche.

Le premier article a permis de brosser un portrait actuel des adultes d'âge moyen et des personnes âgées à haut risque d'AOS. Plus spécifiquement, 17,5% des participants de la cohorte (21,9% chez les hommes et 13,1% chez les femmes) ont été identifiés comme étant à haut risque d'AOS. Dans cette étude, les facteurs de risque de présenter un haut risque d'AOS étaient l'âge (55 ans et plus), le sexe masculin, la ménopause, l'obésité, les maladies cardiovasculaires, le diabète, les maladies cérébrovasculaires, les symptômes anxiodépressifs et les niveaux élevés d'inflammation systémique.

Dans le deuxième article, nous avons caractérisé les associations entre le risque d'AOS et la performance cognitive selon l'âge et le sexe. Nous avons montré que les femmes à haut risque d'AOS âgées entre 45 et 69 ans ont des performances cognitives plus faibles que celles à bas risque d'AOS, précisément dans les domaines de la mémoire épisodique et des fonctions exécutives. Nous n'avons identifié aucune association entre l'AOS et la performance cognitive

chez les hommes. De plus, nous avons observé que l'inflammation systémique médie certaines associations entre le risque d'AOS et les fonctions exécutives chez les hommes et les femmes âgées de moins de 70 ans.

Dans le troisième article, nous avons observé que l'association entre le risque d'AOS et le changement dans la performance cognitive après trois ans dépend de l'âge et du sexe. Le risque élevé d'AOS est associé à un déclin de l'attention et de la vitesse de traitement de l'information, mais à un déclin de la mémoire épisodique uniquement chez les femmes âgées de 70 ans et plus.

Cette thèse offre un éclairage nouveau quant aux facteurs pouvant moduler le lien observé entre l'AOS et la cognition dans les études épidémiologiques, ce qui pourra permettre de mieux dépister et prendre en charge les personnes apnéiques présentant un risque accru de déclin cognitif.

Mots-clés : apnée obstructive du sommeil, cognition, âge, sexe, inflammation, Étude longitudinale canadienne sur le vieillissement

Abstract

Thirty to 50% of the risk of developing dementia is attributable to modifiable factors such as physical inactivity, hypertension, and depression. In recent years, some authors have considered that sleep disorders should also be included. In particular, obstructive sleep apnea (OSA) is associated with a greater risk of cognitive decline and dementia according to epidemiological studies. However, other studies have not observed this link between OSA and cognitive decline. Our team thus hypothesized that certain factors modulate the association between OSA and cognitive decline, explaining part of the heterogeneity of the results seen in previous studies.

This thesis aims to characterize the role of age, sex, and systemic inflammation in the association between OSA risk and cognitive performance in middle-aged and older adults. To achieve this, we used the score obtained from variants of the STOP questionnaire to establish the risk of presenting with OSA, a neuropsychological battery, and measurement of C-reactive protein (CRP) in the blood in a large Canadian cohort. This protocol has led to a narrative review and three research articles.

The first article allowed to present an updated portrait of middle-aged and older adults at high-risk for OSA. Specifically, 17.5% of the cohort (21.9% in men and 13.1% in women) were identified as being at high-risk for OSA. In this study, risk factors for presenting with high-risk for OSA were age (≥ 55 years old), male sex, menopause, obesity, cardiovascular diseases, diabetes, cerebrovascular disease, anxio-depressive symptoms, and high levels of systemic inflammation.

In the second article, we characterized the associations between OSA risk and cognitive performance according to age and sex. We showed that women at high-risk for OSA aged between 45 and 69 years have lower cognitive performance than those at low-risk for OSA, specifically in the areas of episodic memory and executive functions. We did not identify any association between OSA and cognitive performance in men. Additionally, we observed that systemic inflammation mediates some associations between OSA risk and executive functions in men and women younger than 70 years.

In the third article, we observed that the association between OSA risk and change in cognitive performance after three years depends on age and sex. High-risk for OSA is associated with a decline in attention and information processing speed, but with a decline in episodic memory only in women aged 70 and older.

This thesis sheds new light on the factors that can modulate the link observed between OSA and cognition in epidemiological studies, which may allow better screening and management of apneic individuals who present an increased risk of developing cognitive decline.

Keywords: obstructive sleep apnea, cognition, age, sex, inflammation, Canadian Longitudinal Study on Aging

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Liste des sigles et abréviations

Version anglaise		Version française	
CESD-10	10-item Center for Epidemiologic Studies Depression scale	-	
AD	Alzheimer's disease	MA	Maladie d'Alzheimer
AFT	Animal Fluency Test	-	
AHI	Apnea-hypopnea index	IAH	Indice d'apnée/hypopnée
ApoE	Apolipoprotein E	-	Apolipoprotéine E
ApoE4	Apolipoprotein E4	-	Apolipoprotéine E4
BMI	Body mass index	IMC	Indice de masse corporelle
CAD	Canadian dollar	-	Dollar canadien
CIHR	Canadian Institutes of Health Research	IRSC	Instituts de recherche en santé du Canada
CLSA	Canadian Longitudinal Study on Aging	ÉLCV	Étude longitudinale canadienne sur le vieillissement
CVD	Cardiovascular disease	-	Maladie cardiovasculaire
cm	Centimeter	-	Centimètre
CRT	Choice Reaction Time	-	
COPD	Chronic obstructive pulmonary disease		Maladie pulmonaire obstructive chronique
CI	Confidence interval	-	Intervalle de confiance
CPAP	Continuous Positive Airway Pressure	-	Pression positive continue
COWAT	Controlled Oral Word Association test	-	
CRP	C-reactive protein	-	Protéine C-réactive
DXA	Dual Energy X-Ray Absorptimetry	-	Absorptiométrie à rayons X en double énergie
e.g.	Exempli gratia	-	Exemple
FDR	False-discovery rate	-	
Fig.	Figure	-	
GLM	General Linear Model	-	Modèle linéaire généralisé
hs-CRP	High-sensitivity C-reactive protein	-	

i.e.	Id est	-	C’est-à-dire
kg	Kilogram	-	Kilogramme
km	Kilometer	-	Kilomètre
MTL	Medial temporal lobe	-	Lobe temporal médian
MAT	Mental Alternation Test	-	
METS	Metabolic equivalent of task	-	Équivalent métabolique
m	Meter	-	Mètre
MCI	Mild Cognitive Impairment	TCL	Trouble cognitif léger
mg	Milligram	-	Milligramme
ms	Millisecond	-	Milliseconde
MMSE	Mini Mental State Examination	-	
Min	Minute	-	
MoCA	Montreal Cognitive Assessment	-	
N	Number of participants	-	Nombre de participants
LMM	Linear Mixed Models	-	Modèle mixte linéaire
L	Litre	-	
OSA	Obstructive sleep apnea	AOS	Apnée obstructive du sommeil
OR	Odds ratio	-	Rapport de cotes
OARS	Older Americans’ Resources and Services	-	
ODI	Oxygen desaturation index	IDO	Indice de désaturation en oxygène
PASE	Physical Activity Scale for the Elderly	-	
%BF	Percentage of body fat	-	Pourcentage de masse adipeuse
REM	Rapid-eye movement	-	
RAVLT	Rey Auditory Verbal Learning Test	-	
s/sec	Second	-	Seconde
SD	Standard deviation	-	Écart-type
SE	Standard error	-	Erreur type
K	Thousand	-	Mille
WHR	Waist-to-hip ratio	-	Rapport taille/hanche
-		FRQ	Fonds de recherche du Québec

À Marie-Anne; du beau, du vrai, du sincère

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Chapitre 1 – Introduction et contexte théorique

1.1 Position du problème

En 2022, près d'un Canadien sur cinq était âgé de 65 ans et plus (18,8%) (Statistique Canada, 2022b) et la population de personnes âgées de 85 ans et plus avait plus que doublé depuis 2001 (Statistique Canada, 2022a). Le vieillissement de la population représente un défi important pour les sociétés occidentales puisqu'il ajoute une pression sur le système de la santé et des soins et services à domicile (Statistique Canada, 2022a). Dans un contexte de rareté de main d'œuvre, il est primordial de comprendre les facteurs qui influencent les trajectoires de vieillissement afin d'éviter une surcharge du système de la santé. L'un des problèmes de santé grandissant associés au vieillissement est la démence, qui affecte près de 452 000 Canadiens de plus de 65 ans (Gouvernement du Canada, 2022). La démence désigne un ensemble de symptômes qui affectent le fonctionnement cognitif, notamment la mémoire, les capacités de planification, le langage et le jugement (Gouvernement du Canada, 2022). Entre 30 et 50% du risque de développer une démence serait attribuable à des facteurs de risque modifiables telles l'inactivité physique, l'hypertension et la dépression (Norton et al., 2014). Depuis quelques années, certains auteurs considèrent que les troubles du sommeil ou le manque de sommeil devraient être inclus parmi ces facteurs (Mander et al., 2016).

Malheureusement, une grande partie de la population ne dort pas suffisamment et/ou présente des troubles du sommeil (Gouvernement du Canada, 2019). Parmi ces troubles, l'apnée obstructive du sommeil (AOS) serait associée à un plus grand risque de déclin cognitif et de démence selon des études épidémiologiques (Blackwell et al., 2015; Chang et al., 2013; Yaffe et al., 2011). Toutefois, d'autres études n'ont pas observé ce lien entre l'AOS et le déclin cognitif (Lutsey et al., 2016, 2018; Saint Martin et al., 2015). Plus récemment, notre équipe a émis l'hypothèse que certains facteurs pouvaient moduler l'association entre l'AOS et le déclin cognitif, notamment l'âge, le sexe, l'hypertension, le diabète, le stress oxydatif, l'inflammation et l'œdème cérébral (Gosselin et al., 2019), et ainsi expliquer une partie de l'hétérogénéité des résultats des études précédentes.

Jusqu'à présent, les études portant sur l'AOS et le déclin cognitif dans de grandes cohortes ont contrôlé statistiquement pour l'effet de ces différentes variables, mais leurs rôles respectifs dans la modulation de l'association entre l'AOS et le déclin cognitif restent inconnus. L'objectif de cette thèse est de caractériser le rôle de l'âge, du sexe et de l'inflammation systémique dans l'association entre le risque d'AOS et le déclin cognitif chez les adultes d'âge moyen et les personnes âgées. Afin d'y parvenir, une grande cohorte canadienne a été étudiée. Dans ce contexte théorique, nous introduirons d'abord l'AOS (présentation clinique, diagnostic, traitement, facteurs de risque), puis, nous ferons un survol de la littérature portant sur l'association entre l'AOS et le déclin cognitif et présenterons les mécanismes pouvant expliquer ce lien. L'introduction inclut une revue narrative publiée (article 1); certains aspects de l'introduction sont moins développés, car ils se retrouvent dans cette revue narrative.

Cette thèse permettra d'explorer, pour des premières fois, les effets de l'âge, du sexe et de l'inflammation systémique sur l'association entre l'AOS et la cognition, ce qui pourrait permettre de mieux comprendre quelles caractéristiques individuelles augmentent ou réduisent le risque de déclin cognitif chez les personnes à haut risque d'AOS.

1.2 L'apnée obstructive du sommeil

1.2.1 Définition et présentation clinique

L'AOS est un trouble du sommeil caractérisé par des épisodes répétés d'obstruction partielle (hypopnées) et complète (apnées) des voies respiratoires supérieures (Kryger et al., 2011; Young et al., 2002). Pendant le sommeil, la réduction de l'activité musculaire de la langue et du palais peut mener au basculement de la langue vers l'arrière, puis à un blocage des voies respiratoires, empêchant ainsi l'air d'y circuler (Kryger et al., 2011). Le pharynx peut également s'obstruer partiellement ou complètement dû au poids exercé par le tissu adipeux accumulé autour du pharynx et au niveau du cou, particulièrement en position couchée sur le dos (Kryger et al., 2011).

Les événements respiratoires associés à l'AOS amènent un éveil cortical, une fragmentation du sommeil, une hypoxémie intermittente et un rythme sympathique augmenté, ce qui affecte la qualité du sommeil et, par le fait même, la qualité des journées (Lévy et al., 2015). Les personnes qui présentent de l'AOS peuvent rapporter de la somnolence diurne excessive, des ronflements dérangeants pour leur partenaire de lit, avoir la bouche sèche au réveil, une sensation d'étouffement durant leur sommeil et des maux de tête (Lévy et al., 2015). La somnolence diurne excessive peut être suffisamment importante pour être à la source d'accidents de travail ou de la route (Sassani et al., 2004), ce qui fait de l'AOS un enjeu de santé publique (Knauert et al., 2015). Par ailleurs, les personnes souffrant d'AOS peuvent montrer un plus haut taux d'absentéisme au travail, une humeur dépressive, des difficultés professionnelles, familiales et sociales ainsi qu'une plus faible qualité de vie (Moyer et al., 2001).

1.2.2 Diagnostic

Un diagnostic d'AOS peut être établi à la suite d'un enregistrement polysomnographique, qui inclut des signaux électroencéphalographiques, élecrooculographiques, électromyographiques, cardiaques et respiratoires, ou à l'aide d'appareils de polygraphie ambulatoires avec des mesures plus restreintes. Ces derniers ont une valeur plus limitée que la polysomnographie puisqu'ils n'impliquent généralement pas d'électroencéphalographie et ne sont pas utilisés dans des environnements contrôlés, mais ils ont l'avantage de permettre aux individus de dormir dans leur environnement habituel, reflétant mieux leurs conditions normales de sommeil (Kryger et al., 2011; Lévy et al., 2015). Des signaux pléthysmographiques obtenus via des sangles installées au niveau du thorax et de l'abdomen permettent d'observer l'effort respiratoire généralement maintenu dans l'AOS (Berry et al., 2012). Les apnées peuvent être mesurées à l'aide de ces sangles thoraciques, mais également d'une canule nasale et d'un oxymètre installé sur le doigt (Sommermeyer et al., 2012). Selon les critères mis à jour en 2012 par l'American Academy of Sleep Medicine, une apnée est identifiée lorsque survient une baisse du flot aérien de ≥ 90% pendant ≥ 10 secondes, alors qu'une hypopnée est identifiée lorsque survient une baisse du flot aérien de ≥ 30% pendant ≥ 10 secondes, accompagnée d'une désaturation en oxygène artériel de ≥ 3% ou d'un micro-éveil (Berry et al., 2012). Un indice d'apnée/hypopnée

(IAH), c'est-à-dire le nombre moyen d'apnées et d'hypopnées survenues par heure de sommeil, peut être calculé. La sévérité de l'AOS est déterminée selon les seuils suivants : légère (IAH ≥ 5 et < 15), modérée (IAH ≥ 15 et < 30) et sévère (IAH ≥ 30). D'autres variables importantes à considérer pour évaluer la sévérité de l'AOS incluent l'indice de désaturation en oxygène (IDO), la fragmentation du sommeil, et les conséquences diurnes de l'AOS. L'enregistrement polysomnographique permet de déterminer l'indice de désaturation en oxygène, qui correspond au nombre moyen d'épisodes de désaturation par heure (c'est-à-dire le nombre de baisses de saturation ≥ 4% pendant ≥ 10 secondes) (Temirbekoy et al., 2018). Les données polysomnographiques permettent également d'évaluer la fragmentation du sommeil grâce à un indice d'éveil, qui correspond au nombre d'éveils par heure (Yan et al., 2021). Finalement, en contexte clinique, le dépistage de l'AOS est basé sur les symptômes rapportés par le patient tels que la somnolence diurne, la fatigue et les symptômes anxieux et dépressifs (Saunamäki & Jehkonen, 2007).

1.2.3 Autres outils de mesure de l'AOS

Différents questionnaires permettent d'évaluer les symptômes et comorbidités de l'AOS et ainsi, permettent d'établir un risque de présenter l'AOS. Parmi ces outils, on note le questionnaire Berlin, estimant le risque de présenter de l'AOS à l'aide de dix questions appartenant à trois catégories, soit le ronflement, la fatigue ou la somnolence diurne et l'obésité ou l'hypertension, avec une sensibilité de 86%, 54% et 17%, puis une spécificité de 77%, 97% et 97% pour l'AOS légère, modérée et sévère, respectivement (Netzer et al., 1999).

Le questionnaire STOP, développé à partir du Berlin, permet d'estimer le risque de présenter de l'AOS avec l'avantage d'utiliser seulement quatre questions à répondre par oui ou non, visant quatre signes ou symptômes d'AOS formant son acronyme, soit le ronflement (*Snoring*), la fatigue (*Tiredness, fatigue or sleepiness*), l'observation d'apnées (*Observed apnea*) et l'hypertension (*high blood Pressure*) (Chung et al., 2008). Il montre une sensibilité de 66%, 74% et 80%, puis une spécificité de 60%, 53% et 49% pour l'AOS légère, modérée et sévère, respectivement (Chung et al., 2008). Une variante de ce questionnaire, le STOP-Bang, utilise quatre facteurs de risque additionnels, soit un indice de masse corporelle élevé (> 35 kg/m^2;

BMI), être âgé de plus de 50 ans (*Age*), une circonférence du cou élevée (> 40 cm; *Neck circumference*) et le sexe masculin (*Gender*) afin d'améliorer la sensibilité de l'outil (84%, 93% et 100%, pour l'AOS légère, modérée et sévère, respectivement), mais avec une moins bonne spécificité (56%, 43% et 37% pour l'AOS légère, modérée et sévère, respectivement) (Chung et al., 2008).

1.2.4 Traitement

Le traitement par pression positive continue, ou en anglais, CPAP (pour *Continuous Positive Airway Pressure*), est le traitement le plus utilisé pour l'AOS chez les adultes (Kushida et al., 2008). Cet appareil permet de garder les voies respiratoires ouvertes en créant une pression d'air positive qui voyage à travers un tube et un masque (Kryger et al., 2011). Il permet de réduire les événements respiratoires et ainsi, diminue les éveils répétés, la somnolence diurne, l'hypoxémie, la pression artérielle moyenne, les marqueurs d'inflammation, les anomalies des cellules endothéliales (Jelic & Le Jemtel, 2008) et le nombre d'événements cardiovasculaires mortels et non mortels (Marin et al., 2005). Cependant, 85% des adultes présentant de l'AOS ne sont pas diagnostiqués (Braley et al., 2018) et lorsqu'ils le sont, seulement 41% d'entre eux utilisent toujours l'appareil après un an (Lee et al., 2017). Les patients qui n'adhèrent pas au traitement rapportent qu'ils n'en voient pas le besoin, que l'appareil les incommode ou qu'il est inconfortable et qu'il est dispendieux (Lee et al., 2017).

D'autres types de traitement sont disponibles tel que l'appareil d'avancement mandibulaire, la chirurgie et la perte de poids. Les appareils d'avancement mandibulaire couvrent les dents et maintiennent la mandibule dans une position avancée, ce qui élargit les voies respiratoires supérieures et diminue leur capacité de collapsibilité (Gagnadoux et al., 2009). Les chirurgies des voies respiratoires supérieures visent à réduire le degré d'obstruction et peuvent inclure des chirurgies nasales, palatines et basées sur la langue, le retrait des amygdales chez l'enfant et, dans des cas majeurs, l'avancement maxillomandibulaire (Pavwoski & Shelgikar, 2017). Les patients apnéiques qui présentent de l'obésité peuvent bénéficier d'une perte de poids pour le traitement de l'AOS (Pavwoski & Shelgikar, 2017). Le choix du traitement dépend entre autres de l'étiologie des obstructions.

1.2.5 Épidémiologie et caractérisation de l'AOS dans les grandes cohortes

Les études épidémiologiques utilisant des questionnaires ou le diagnostic autorapporté d'AOS indiquent une prévalence variant entre 13% et 31% chez les hommes et 4% et 21% chez les femmes adultes (Appleton et al., 2018; Hiestand et al., 2006; T. Huang et al., 2018). Une étude épidémiologique américaine qui a utilisé la polysomnographie auprès de 1 520 participants âgés de 30 à 70 ans a estimé la prévalence de l'AOS modérée à sévère (IAH $\geq$ 15) à approximativement 13% chez les hommes, et 6% chez les femmes (Peppard et al., 2013). Toutefois, un effet de l'âge a été observé, avec une prévalence plus élevée dans le groupe de participants âgés de 50 à 70 ans (17% des hommes et 9% des femmes) que dans celui composé des participants âgés de 30 à 49 ans (10% des hommes et 3% des femmes; (Peppard et al., 2013)). En effet, l'âge est un facteur de risque reconnu de l'AOS (Braley et al., 2018; Zamarron et al., 1999). Une revue systématique incluant 24 études a rapporté une prévalence de l'AOS légère (IAH $\geq$ 5) entre 9% et 38% dans la population générale, et jusqu'à 84% chez les personnes âgées (Senaratna et al., 2017), alors que la prévalence de l'AOS modérée à sévère (IAH $\geq$ 15) serait entre 6% et 17% dans la population générale, atteignant 36% dans la population vieillissante. Les différences notables illustrées ci-haut en ce qui concerne la prévalence pourraient s'expliquer par la divergence des mesures et des critères utilisés dans le cadre des études épidémiologiques, les mesures subjectives menant à plus de faux positifs. De plus, des critères plus ou moins sévères sont utilisés pour déterminer la présence d'AOS à l'aide de mesures objectives utilisant la polysomnographie ou la polygraphie ambulatoire. De ce fait, certains chercheurs ont utilisé un seuil d'IAH de 5 (Foley et al., 2003; Gaeta et al., 2019; Kim et al., 2007; Kim et al., 1997; Lutsey et al., 2016; Nikodemova et al., 2013; Quan et al., 2006) pour confirmer la présence d'AOS alors que d'autres utilisent un critère plus élevé, par exemple un IAH de 15 ou plus (Blackwell et al., 2011; Cosentino et al., 2008; Dlugaj et al., 2014; Sforza et al., 2010; Spira et al., 2008; Yaffe et al., 2011). Considérant que les grandes études citées précédemment datent de quelques années et que la prévalence d'obésité augmente au fil des ans dans les pays développés, de nouvelles d'études épidémiologiques sont nécessaires afin d'avoir un portrait actuel de la prévalence de l'AOS.

1.2.6 Facteurs de risque de l'AOS

Cette section présente des facteurs de risque de l'AOS qui seront discutés de manière plus approfondie dans l'article 1 (revue narrative).

1.2.6.1 L'âge

Les personnes âgées de 65 ans et plus sont plus à risque que le reste de la population de souffrir d'AOS (Kryger et al., 2011). L'augmentation de la prévalence de l'AOS avec l'âge pourrait s'expliquer par la diminution particulièrement marquée de l'activité musculaire de la langue et du palais chez les personnes âgées lors du sommeil (Eikermann et al., 2007; Worsnop et al., 2000). La plus grande prévalence de l'AOS dans la population âgée pourrait également s'expliquer en partie par des facteurs indirects qui apparaissent en vieillissant, notamment la ménopause, l'augmentation de l'indice de masse corporelle (IMC) et de la prévalence des comorbidités de l'AOS telles que l'hypertension et les maladies cardiovasculaires (Mokhlesi et al., 2016) (ces facteurs seront décrits dans les prochaines sections).

1.2.6.2 Le sexe

Le sexe masculin serait un des principaux facteurs de risque d'AOS en raison de l'accumulation du tissu adipeux dans le haut du corps, notamment au niveau du pharynx, ce qui favorise l'effondrement et le blocage des voies respiratoires menant à l'AOS. Chez les femmes non ménopausées, ce tissu s'accumule surtout dans le bas du corps, ce qui les protègent de l'AOS jusqu'à la ménopause (Kryger et al., 2011). De plus, les hommes apnéiques rapportent plus fréquemment du ronflement, un souffle court et des apnées observées par leur partenaire de lit, tandis que les femmes apnéiques rapportent plus fréquemment des symptômes non spécifiques tels que des maux de tête, de la fatigue, de la dépression, de l'anxiété et de l'insomnie (Bonsignore et al., 2019; Lozo et al., 2017), ce qui pourrait suggérer un impact différent de l'AOS sur le fonctionnement diurne selon le sexe.

1.2.6.3 La ménopause

La ménopause déclenche un changement dans la distribution du tissu adipeux chez les femmes, la rendant similaire aux hommes avec une accumulation dans le haut du corps et une augmentation de l'IMC, de la circonférence du cou et du ratio taille-hanche. De plus, la

ménopause aurait un impact sur les muscles dilatateurs des voies respiratoires supérieures (Jehan et al., 2015). Ces changements morphologiques augmentent leur risque de souffrir d'AOS (Heinzer et al., 2018). De ce fait, les femmes ménopausées ont une prévalence plus élevée d'AOS (21 %) que les femmes non-ménopausées (3 %) (Heinzer et al., 2018). Les femmes ménopausées n'utilisant pas de thérapie de remplacement hormonal seraient trois à quatre fois plus à risque que les femmes non ménopausées et les hommes de souffrir d'AOS, ce qui suggère un rôle protecteur de l'estrogène et de la progestérone contre l'AOS (Bixler et al., 2001; Young et al., 2002).

1.2.6.4 L'indice de masse corporelle

Le risque d'AOS augmente progressivement avec l'IMC et est encore plus fortement associé à la circonférence du cou (Young et al., 2004). L'obésité est le plus grand facteur de risque d'AOS et, fait intéressant, la relation entre l'AOS et l'obésité serait bidirectionnelle (Carter & Watenpaugh, 2008). D'une part, l'obésité augmenterait le risque d'AOS puisqu'elle est liée à plusieurs de ses comorbidités, notamment l'infarctus du myocarde, l'insuffisance cardiaque congestive, l'accident vasculaire cérébral, le diabète de type 2 et l'hypertension. D'autre part, l'AOS augmenterait le risque d'obésité en raison de l'inactivité physique découlant de la somnolence diurne qui y est associée (Carter & Watenpaugh, 2008). De plus, l'AOS, particulièrement l'hypoxémie, affecterait le contrôle de la glycémie et augmenterait les niveaux de glucose des personnes apnéiques (Framnes & Arble, 2018).

1.2.6.5 Les maladies cardiovasculaires

Des interactions complexes existent entre l'AOS et les maladies cardiovasculaires (Somers et al., 2008). La prévalence de l'AOS serait deux à trois fois plus élevée chez les personnes avec des maladies cardiovasculaires (Peppard et al., 2000) et jusqu'à 50% des personnes apnéiques montreraient des anomalies cardiaques et métaboliques (McNicholas et al., 2007). Toutefois, il est difficile d'isoler le rôle indépendant que jouent les maladies cardiovasculaires dans l'AOS en raison de la présence concomitante d'autres facteurs de risque cardiovasculaires tels que l'obésité et l'intolérance au glucose (McNicholas et al., 2007). En contrepartie, le sommeil court et de mauvaise qualité, la fragmentation du sommeil et l'hypoxémie intermittente

caractéristiques de l'AOS résulteraient en un stress oxydatif et de l'inflammation, pouvant entraîner des maladies cardiovasculaires telles que l'hypertension (Lévy et al., 2008; Ryan et al., 2005).

1.2.6.6 La morphologie crâniofaciale

Certaines caractéristiques physiologiques et crâniofaciales résultant en un rétrécissement des voies aériennes supérieures prédisposent à l'AOS, dont l'obésité, une langue épaisse, une large circonférence du cou, un goitre, une mâchoire avancée et un petit menton (Kryger et al., 2011), ce qui explique en partie les variations de prévalence de l'AOS selon l'origine ethnique (Kryger et al., 2011).

1.3 AOS, fonctionnement cognitif et risque de démence

Le lien entre l'AOS et le fonctionnement cognitif a été étudié précédemment dans de larges cohortes. Nous résumons ici les principales conclusions tirées des études transversales et longitudinales ainsi que des revues systématiques et méta-analyses. L'article 1 (revue narrative) présente cette littérature de manière plus exhaustive.

1.3.1 Aperçu des résultats des études transversales et longitudinales

Alors que la majorité des études de cohorte utilisant un devis transversal pour investiguer le lien entre l'AOS et la cognition rapportent que la présence d'AOS (auto-rapportée, évaluée par questionnaires de dépistage et par mesures ambulatoires) est associée à de plus faibles performances cognitives (Qiu et al., 2022; Shieu et al., 2022; Ward et al., 2022), d'autres ne supportent pas ces résultats (Allen et al., 2020; Sun et al., 2022). De façon similaire, plusieurs études longitudinales de cohorte montrent des associations significatives entre la présence ou la sévérité de l'AOS et un déclin cognitif dans le temps (Blackwell et al., 2015; Pase et al., 2023; Yaffe et al., 2011), bien que certaines études ne confirment pas cette association (Lutsey et al., 2016, 2018; Saint Martin et al., 2015). De manière générale, les protocoles de recherche qui incluent un diagnostic clinique (ex : trouble cognitif léger (TCL) et démence de type Alzheimer) ou des mesures de cognition globale mettent en lumière une association négative entre l'AOS et la cognition alors que ceux utilisant des tests neuropsychologiques évaluant des fonctions

cognitives plus ciblées ne semblent pas être en mesure d'en faire autant (Lutsey et al., 2016, 2018; Saint Martin et al., 2015).

Enfin, des méta-analyses et revues systématiques récentes montrent que la présence ou la sévérité de l'AOS est associée à des performances significativement plus faibles à des tests cognitifs (Bubu et al., 2020; Bucks et al., 2013; Olaithe et al., 2018) alors qu'une d'entre elles ne montre qu'un faible lien (Cross et al., 2017). Des petites études de cas contrôlées issues de cliniques de sommeil ont montré que la présence ou la sévérité de l'AOS est associée à de plus faibles performances cognitives (Kim et al., 2011; Terpening et al., 2015) alors que des études de larges cohortes issues de la communauté ne montraient aucune association significative (Blackwell et al., 2011; Lutsey et al., 2016), suggérant que la variabilité des résultats serait attribuable aux types et designs d'études ainsi qu'aux méthodes de recrutement. Lorsqu'un lien entre l'AOS et la cognition est observé, ce sont l'attention, les fonctions exécutives et la mémoire qui sont les plus souvent rapportées comme étant altérées chez les apnéiques (Bubu et al., 2020; Bucks et al., 2013; Leng et al., 2017; Olaithe et al., 2018). Par ailleurs, une méta-analyse de cinq études transversales portant sur le lien entre l'AOS et la maladie d'Alzheimer (MA) a montré que les patients Alzheimer seraient cinq fois plus à risque de souffrir d'AOS comparativement aux personnes cognitivement saines du même âge (Emamian et al., 2016).

1.3.2 Facteurs expliquant les divergences entre les études

Tel que mentionné précédemment, diverses méthodes sont utilisées afin d'évaluer la présence de l'AOS dans le cadre d'études scientifiques. La plupart des études de cohortes utilisant des questionnaires évaluant le risque d'AOS ont révélé que les participants à haut risque d'AOS avaient des performances cognitives plus faibles que ceux à bas risque (Duan et al., 2022; Shieu et al., 2022). Les études longitudinales utilisant le diagnostic auto rapporté d'AOS ont également montré que l'AOS était associée à un risque accru de TCL (Chang et al., 2013; Duan et al., 2022; Lee et al., 2019) et une apparition plus précoce de TCL ou de démence de type Alzheimer (Osorio et al., 2015). À l'inverse, parmi les études utilisant des tests objectifs tels que des enregistrements par polysomnographie, quelques-unes corroborent ces résultats (Kaur et al., 2021; Ramos et al., 2015; Ward et al., 2022; Yaffe et al., 2011), mais la plupart ont montré des

résultats limités, telles que des associations restreintes à une mesure de cognition globale (Blackwell et al., 2015) et d'attention (Saint Martin et al., 2015) en l'absence de lien avec des mesures de fonctions exécutives ou de mémoire, ou aucune preuve d'une association entre l'AOS et le fonctionnement cognitif (Allen et al., 2020; Lee et al., 2022; Lutsey et al., 2016, 2018; Parker et al., 2021; Suemoto et al., 2021). Ces résultats suggèrent que le dépistage à l'aide de questionnaires plutôt que l'inclusion des cas diagnostiqués d'AOS uniquement capture les patients particulièrement symptomatiques atteints d'AOS sévère qui pourraient être plus enclins à présenter un déclin cognitif lié à l'AOS. Bien que les évaluations objectives génèrent des informations plus détaillées et précises, les questionnaires évaluant le risque d'AOS sont moins chers et plus faciles à utiliser, représentant ainsi un outil utile pour étudier l'AOS dans de grandes cohortes.

Un deuxième facteur qui pourrait expliquer les différences entre les résultats des études est la variété des domaines cognitifs examinés. De manière générale, les études soutiennent un lien entre l'AOS et une moins bonne mémoire verbale (Addison-Brown et al., 2014; Haba-Rubio et al., 2017; Lee et al., 2022; Ramos et al., 2015; Sforza et al., 2010; Ward et al., 2022) et de moins bonnes capacités attentionnelles (Blackwell et al., 2011; Saint Martin et al., 2015). À l'inverse, les études ne supportent généralement pas un lien entre l'AOS et la mémoire tactile (Parker et al., 2021) et visuelle (Parker et al., 2021; Qiu et al., 2022; Sforza et al., 2010), les capacités visuo-spatiales (Haba-Rubio et al., 2017), le langage (Haba-Rubio et al., 2017), le raisonnement abstrait et les connaissances sémantiques (Sforza et al., 2010). Les résultats sont inconsistants en ce qui a trait à la cognition globale (lien : Blackwell et al., 2015; Spira et al., 2008; Ward et al., 2022; absence de lien : Blackwell et al., 2011; Haba-Rubio et al., 2017; Parker et al., 2021; Sforza et al., 2010), les fonctions exécutives (lien : Olaithe & Bucks, 2013; absence de lien : Blackwell et al., 2011, 2015; Lutsey et al., 2016; Parker et al., 2021; Saint Martin et al., 2015; Spira et al., 2008), la fluence verbale (lien : Addison-Brown et al., 2014; Haba-Rubio et al., 2017; Ramos et al., 2015; absence de lien : Lutsey et al., 2016; Sforza et al., 2010), et la vitesse psychomotrice/de traitement (lien : Haba-Rubio et al., 2017; Ramos et al., 2015; Ward et al., 2022; absence de lien : Lutsey et al., 2016; Parker et al., 2021; Sforza et al., 2010). Une partie

des inconsistances observées entre les études pourrait ainsi être expliquée par la variabilité dans les domaines cognitifs étudiés.

L'attention et la flexibilité mentale reposent toutes deux sur la vitesse de traitement de l'information, ce qui suggère qu'en ralentissant la vitesse de traitement, l'AOS pourrait également aggraver les performances d'attention et de flexibilité mentale. De plus, ces trois fonctions cognitives dépendent du cortex préfrontal, qui est vulnérable à l'hypoxémie et à la fragmentation du sommeil (Gosselin et al., 2019). Des déficits dans ces domaines cognitifs ont déjà été associés à l'AOS (Gagnon et al., 2014) et sont possiblement attribuables à des atteintes cérébrales induites par l'AOS, tel que décrit dans la prochaine section.

1.4 Mécanismes pouvant expliquer le lien entre l'AOS et les troubles cognitifs

1.4.1 Rôle du sommeil dans le fonctionnement cognitif

Le sommeil est essentiel au bon fonctionnement cognitif tout au long de la vie adulte (Scullin & Bliwise, 2015). La recherche montre qu'il joue un rôle important pour les capacités attentionnelles et de vigilance, les fonctions exécutives, notamment la flexibilité mentale et l'inhibition, la mémoire de travail et la mémoire à long terme (Lowe et al., 2017; Waters & Bucks, 2011).

La littérature sur le sommeil et la cognition a montré une croissance fulgurante depuis le début des années 2000 et il serait difficile de brosser un portrait exhaustif de cette littérature. Nous pouvons toutefois illustrer le rôle du sommeil dans la cognition avec quelques études marquantes. Par exemple l'étude de Walker et al. (2002) a mis en évidence le rôle actif du sommeil dans la consolidation des apprentissages moteurs. Dans cette étude, les participants devaient apprendre une tâche motrice, puis se soumettre à une évaluation de leur performance après la phase d'apprentissage. Alors qu'un groupe de participants dormait entre l'apprentissage et l'évaluation, l'autre restait éveillé. Les résultats de cette étude montrent que la performance des participants ayant dormi après l'apprentissage s'était significativement améliorée alors que ce n'était pas le cas pour les participants restés éveillés. Les résultats

montrent également une corrélation positive entre l'amélioration de la performance et le pourcentage de temps passé en stade de sommeil N2 (Walker et al., 2002). Cette étude a mis en lumière que 1) le sommeil consolide les apprentissages; 2) une période de sommeil améliore davantage la performance qu'une période d'éveil et 3) le processus de consolidation est probablement associé à une modification de l'architecture du sommeil suivant un apprentissage (Gosselin, 2020).

Feld & Diekelmann (2015) ont par la suite proposé la théorie de la consolidation active du système, selon laquelle les informations sont d'abord encodées temporairement dans les hippocampes, puis réactivées pendant le sommeil NREM, permettant une consolidation des informations à long terme dans le cortex. Cette consolidation de l'information pendant le sommeil serait associée à l'activité simultanée des ondes lentes, des fuseaux et des *sharp waves/ripples* (activité de grande amplitude associée à une oscillation à haute fréquence) (Feld & Diekelmann, 2015; Gosselin, 2020). Tononi & Cirelli (2014) ont proposé l'hypothèse d'homéostasie synaptique, selon laquelle la principale fonction du sommeil est de restaurer l'homéostasie de la synapse et, par le fait même, ses capacités à faire de nouveaux apprentissages (Gosselin, 2020). Alors que la synapse se surchargerait le jour lors des apprentissages, le sommeil, particulièrement à ondes lentes, lui permettrait de redevenir fonctionnelle et de faire de nouveaux apprentissages (Tononi & Cirelli, 2014). D'autres équipes ont également identifié des éléments du sommeil impliqués dans la consolidation de la mémoire, à savoir l'augmentation d'activité à ondes lentes (Huber et al., 2004), et dans l'encodage, à savoir la durée de sommeil (Drummond et al., 2000; Yoo et al., 2007), l'activité à ondes lentes (Tononi & Cirelli, 2014, tel que mentionné précédemment), la continuité du sommeil (Tartar et al., 2006) et la densité des fuseaux (Lafortune et al., 2014).

1.4.2 Effets de l'AOS sur la cognition des adultes

Des modèles ont été développés pour expliquer les mécanismes physiologiques pouvant expliquer un possible rôle de l'AOS sur le déclin cognitif (Gosselin et al., 2019; Polsek et al., 2018; Rosenzweig et al., 2015). Selon ces modèles, l'AOS agirait sur la santé cérébrale via la mauvaise qualité du sommeil et l'hypoxémie intermittente. Plus spécifiquement, l'AOS altère la

macroarchitecture (quantité de sommeil lent et paradoxal; Heinzer et al., 2001) et la microarchitecture (ondes lentes et fuseaux; Carvalho et al., 2014; Ju et al., 2019; Peregrim et al., 2019; Ren et al., 2020) du sommeil. Ces changements chroniques du sommeil causés par l'AOS pourraient avoir des effets délétères sur la cognition considérant les rôles essentiels que jouent la continuité du sommeil, le sommeil à ondes lentes, le sommeil paradoxal et les fuseaux de sommeil dans la neurogenèse, la plasticité cérébrale, la vigilance, ainsi que la formation et la consolidation de la mémoire (Born & Wilhelm, 2012; Cirelli, 2013). La fragmentation du sommeil et l'hypoxémie intermittente peuvent également provoquer de l'inflammation, du stress oxydatif, des dérèglements métaboliques (Polsek et al., 2018), de l'œdème cérébral et des dysfonctions endothéliales (Rosenzweig et al., 2015). Précisément, l'hypoxémie intermittente active des voies inflammatoires et favorise le dépôt d'espèces réactives de l'oxygène (Yang et al., 2022). En trop grande quantité, les espèces réactives de l'oxygène troublent les cellules et causent une diminution de la capacité antioxydante (Yang et al., 2022). Le stress oxydatif causé augmente la réponse inflammatoire, qui à son tour, renforce le stress oxydatif (Yang et al., 2022). L'accumulation de produits du stress oxydatif endommage les neurones et les voies de signalisation neuronale, ce qui peut mener à des troubles cognitifs (Yang et al., 2022).

1.4.3 Mécanismes propres aux personnes âgées et à la démence

La production et la clairance de protéines impliquées dans la MA, soit la bêta-amyloïde et la protéine tau, seraient aussi affectées par la qualité et la quantité de sommeil (Brown et al., 2016; Xie et al., 2013) ainsi que par l'AOS (Ju et al., 2019). En effet, chez des adultes sans déclin cognitif, une efficacité et un temps de sommeil réduits et une latence de sommeil augmentée seraient associés à l'accumulation de bêta-amyloïde dans le cerveau (Brown et al., 2016). L'efficacité de sommeil se définit par le rapport entre le temps de sommeil total et le temps passé au lit (Reed & Sacco, 2016). Chez la souris, la privation de sommeil est associée à une augmentation de la protéine tau, suggérant que la perturbation du sommeil pourrait aussi contribuer à la progression de la pathologie tau (Di Meco et al., 2014). Combinées aux altérations du sommeil, la formation de plaques amyloïdes et l'agrégation de protéines tau en enchevêtrements neurofibrillaires (Braak & Braak, 1991) pourraient rendre le cerveau plus vulnérable aux processus neurodégénératifs en altérant graduellement sa structure ainsi que

son fonctionnement (Sharma et al., 2018). D'ailleurs, une étude intégrant des mesures de polysomnographie, d'imagerie par résonance magnétique et de tomographie par émission de positrons a montré que les participants apnéiques avaient une charge amyloïde, un volume de matière grise, une perfusion et un métabolisme plus élevés que les participants sans AOS (André et al., 2020). D'autres études supportent également la présence d'hypertrophies de la matière grise chez les personnes apnéiques (Baril et al., 2017; Martineau-Dussault et al., 2022), qui seraient le résultat d'une neuroinflammation et d'un œdème extracellulaire (Baril et al., 2021).

Plusieurs caractéristiques individuelles sont susceptibles de rendre une personne plus vulnérable face aux conséquences de l'AOS sur la cognition. Ces caractéristiques sont présentées de façon détaillée dans l'article 1 (prochaine section).

1.5 Article 1 (revue narrative) : Obstructive Sleep Apnea and Cognitive Decline: A Review of Potential Vulnerability and Protective Factors

Afin de mieux comprendre les facteurs de protection et de vulnérabilité face aux troubles cognitifs associés à l'AOS, nous avons procédé à une revue de la littérature scientifique, ce qui a mené à l'article qui suit.

Article 1: Obstructive Sleep Apnea and Cognitive Decline: A Review of Potential Vulnerability and Protective Factors

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Contribution : Pour cet article, j'ai procédé à une revue de la littérature, rédigé et révisé de manière critique le manuscrit.

Abstract

Around 40% of dementia risk is attributable to modifiable risk factors such as physical inactivity, hypertension, diabetes and obesity. Recently, sleep disorders, including obstructive sleep apnea (OSA), have also been considered among these factors. However, despite several epidemiological studies investigating the link between OSA and cognitive decline, there is still no consensus on whether OSA increases the risk of dementia or not. Part of the heterogeneity observed in previous studies might be related to some individual characteristics that modulate the association between OSA and cognitive decline. In this narrative review, we present these individual characteristics, namely, age, sex, menopause, obesity, diabetes mellitus, hypertension, cardiovascular diseases, smoking, excessive alcohol consumption, depression, air pollution, Apolipoprotein E ε4 allele, physical activity, and cognitive reserve. To date, large cohort studies of OSA and cognitive decline tended to statistically control for the effects of these variables, but whether they interact with OSA to predict cognitive decline remains to be elucidated. Being able to better predict who is at risk of cognitive decline when they have OSA would improve clinical management and treatment decisions, particularly when patients present relatively mild OSA.

1. Introduction

More and more people are living with dementia worldwide, with no curative treatment in sight. Alzheimer's disease (AD) is by far the most common form of dementia, representing 60–70% of all dementia cases [1], and is generally preceded by a predementia stage of mild cognitive impairment (MCI). Around 40% of worldwide dementia cases are thought to be attributable to potentially modifiable risk factors, including diabetes, hypertension, obesity, physical inactivity, depression, smoking, low educational attainment, hearing impairment, low social contact, excessive alcohol consumption, and air pollution [2]. In addition, there is a growing body of evidence supporting the role of sleep disorders in the development of MCI and dementia [3–5], among which obstructive sleep apnea (OSA) could represent a modifiable risk factor of particular interest [6–9]. Therapeutic interventions targeting these modifiable risk factors may have the potential to delay dementia onset and slow its progression. Therefore, it is essential to

properly identify these modifiable risk factors, and to fully understand the mechanisms by which they may increase the risk of dementia. Moreover, it is also essential to better understand how modifiable risk and protective factors interact to increase or reduce a person's vulnerability to dementia. Better identifying individuals who could benefit from potential preventive therapies and those who should be included in clinical trials is a worldwide objective [10,11].

In this narrative review, we aim to identify individual vulnerability and protective characteristics that could have an impact on the relationship between OSA and cognitive decline, specifically MCI and AD. After defining OSA, we will present the potential mechanisms underlying the link between OSA and cognitive decline, and synthesize epidemiological studies investigating this association. We will then discuss potential vulnerability and protective characteristics that may moderate the association between OSA and cognitive decline, namely, age, sex, menopause, obesity, diabetes mellitus, hypertension, cardiovascular diseases, smoking, excessive alcohol consumption, depression, air pollution, Apolipoprotein E ε4 (ApoE4) allele, physical activity, and cognitive reserve. Understanding the roles and mechanisms of both vulnerability and protective individual characteristics could shed light on the discrepancies observed between cohort studies and eventually help individualize therapeutical intervention to prevent cognitive decline in OSA patients.

2. Definition and Prevalence of OSA

OSA is a respiratory disorder characterized by repeated episodes of partial (hypopnea) and complete (apnea) obstructions of the upper airway during sleep [12,13]. These recurrent respiratory events lead to cortical arousal and sleep fragmentation, intermittent hypoxemia, and increased sympathetic activity, affecting sleep quality and daytime functioning [14]. OSA severity is typically assessed with the apnea–hypopnea index (AHI), which is the average number of apneas and hypopneas per hour of sleep. The severity of OSA is determined according to the following thresholds: mild (AHI ≥ 5 and <15), moderate (AHI ≥ 15 and <30) or severe (AHI ≥ 30) [15]. According to a systematic review in the adult population, 9–38% of individuals present with mild OSA and 6–17% present with moderate to severe OSA [16]. In the

elderly, these estimations reach up to 84% for mild OSA and 36% for moderate to severe OSA [16]. Even more worrying, one study observed that 56% of adults aged 65 and older were at high risk of OSA, while only 8% of them had been tested for OSA and diagnosed [17]. Thus, many older adults remain undiagnosed, and therefore not treated. Furthermore, when people do get diagnosed, only about 41% remain adherent to their continuous positive airway pressure (CPAP) treatment after one year [18]. This low CPAP adherence is alarming, especially considering that this treatment could delay cognitive decline in individuals with OSA [9].

3. Potential Mechanisms Linking OSA and Cognitive Decline in Older Adults

It is well established that OSA causes sleep fragmentation and intermittent hypoxemia. More specifically, repeated micro-arousals alter both sleep macroarchitecture (time spent in stage N3 and rapid-eye movement (REM) sleep) [19] and microstructure (slow-wave and spindle characteristics) [20–23]. Considering the critical roles of sleep continuity, slow- wave sleep, REM sleep, and sleep spindles in neurogenesis, brain plasticity, alertness, and memory formation and consolidation [24,25], chronic sleep changes caused by OSA could negatively affect cognitive health [6,26,27]. REM-dependent OSA could be particularly harmful to the brain, with respiratory events occurring during this sleep stage being associated with reduced daytime regional cerebral blood flow, even in mild OSA [28]. Indeed, muscle atonia during REM sleep can increase the occurrence and the hypoxic levels of respiratory obstructive events, and thus, some individuals present respiratory events mostly in this sleep stage. Further, REM-dependent OSA is more strongly associated with excessive daytime sleepiness than NREM-OSA [29], which is in turn related to cognitive impairment [30].

Moreover, both sleep fragmentation and intermittent hypoxia interfere with brain structure and function, increasing their vulnerability to neurodegenerative diseases. Indeed, it has been suggested that a biphasic pattern of neuroimaging findings could be in play in OSA [31], with acute transitory or compensatory responses (i.e., gray matter hypertrophy, restricted white matter diffusivities) followed by evidence of cellular damage (i.e., gray matter atrophy, higher white matter hyperintensity burden, lower white matter fractional anisotropy, higher water diffusivities). In addition, OSA has been recently as- sociated with increased amyloid and tau

burden [21,32–43], two proteins involved in AD pathophysiology. Several mechanisms likely underlie these neuroimaging or pathological findings and include inflammation, oxidative stress, metabolic disturbances, cerebral edema and endothelial dysfunction [27]. Indeed, inflammation is involved in neurodegenerative processes, notably by triggering a positive feedback loop that increases amyloid beta production and oxidative stress, facilitating amyloid and tau pathology [26,44].

4. Cohort Studies Investigating the Association between OSA and Cognitive Decline in Older Adults

4.1. Cross-Sectional Studies

The majority of large cross-sectional cohort studies investigating the association be- tween OSA and cognitive impairment in middle-aged and older adults have used objective sleep measures, i.e., polysomnography or portable devices, to evaluate OSA [45–52], and one study used a questionnaire to screen for OSA [53]. While some studies have investigated cognitive performance using comprehensive neuropsychological batteries [51,53,54], others used a limited number of neuropsychological tests targeting specific cognitive functions or global functioning [45,46,49,52]. In studies showing that OSA is associated with poorer cognitive functioning, associations were found for long-term verbal memory [47], working memory [47] and global cognition [52]. The OSA severity markers or OSA-related symptoms associated with cognition were highly heterogeneous across studies, including snoring [53], self-reported apneas [53], hypoxemia [45,54] and AHI [50,51]. Other studies have not found a significant association between any OSA severity marker and cognition [46,48,49].

Despite the heterogenous results emerging from cross-sectional studies, associations between OSA and cognitive functioning seem better established in the domains of attention, memory, and processing speed, while less evidence supports an association between OSA and working memory, executive functions, language and visual abilities in middle-aged and older adults. Interestingly, in younger adults, the most affected cognitive domains in OSA are attention, episodic memory, working memory, and executive functions [14]. This suggests that while some cognitive domains appear to be affected by OSA regardless of the age (namely, memory and

attention), other cognitive domains seem less impacted by OSA with increasing age, such as executive function and working memory.

4.2. Longitudinal Studies

Longitudinal cohort studies have the advantage of quantifying cognitive decline over time. They used self-reported diagnoses (e.g., [9,55]) or in-home polysomnography or portable devices (e.g., [7,56–59]) to identify OSA cases. Furthermore, the majority of these studies used global cognitive measures or screening tools, such as the Mini-Mental State examination (MMSE; e.g., [7,59]), while a comprehensive neuropsychological battery was used in one study [58].

Among the main longitudinal cohort studies, the Study of Osteoporotic Fractures included 298 82-year-old women and found that 45% of women with OSA developed MCI or dementia at five-year follow-up, compared to 31% of women without OSA [59]. However, neither of the two neuropsychological tests used to assess global cognition and executive functions could identify impairment of specific cognitive functions related to OSA. This result was also obtained in the Atherosclerosis Risk in Communities Study that included men and women aged 45–64 years and failed to show an association between OSA and specific cognitive tests at 15-year follow-up [56], while highlighting an increased risk of dementia in individuals with severe OSA [57]. In the Osteoporotic Fractures in Men Sleep Study, including men aged 65 and older, another team showed a negative relationship between baseline nocturnal hypoxemia and global cognitive functioning after three years, while executive functions were not associated with OSA [7]. On the other hand, the Proof-SYNAPSE study used a wide selection of neuropsychological tests in men and women aged 65 years and showed only a slight decline in attention related to OSA after eight years, without any change in executive functions and memory [58].

In summary, studies using measures of global cognition and clinical diagnosis of cognitive impairment or dementia were more susceptible to highlight cognitive decline associated with OSA over time than those using comprehensive neuropsychological batteries [56–58]. This suggests that longitudinal studies are more susceptible to identify major OSA-related cognitive decline over time, but not milder cognitive decline in specific domains.

4.3. Meta-Analyses, Meta-Reviews and Systematic Reviews

Most meta-analyses and systematic reviews concluded that a significant association between OSA and cognition exists [8,60–62] and that OSA increases the risk of AD [63–65]. Interestingly, these meta-analyses and systematic reviews highlighted the fact that small cohorts and controlled case studies from sleep clinics have shown effects of OSA on cognition [66,67], while most studies of large community-based cohort studies failed to show significant associations [45,56]. Another systematic review concluded that the link between OSA and cognition is weak [68], possibly due to the age range used (50 years and over, while others included studies of participants aged 30 years and over [8,60,62]). Similarly, another systematic review showed a significant association between OSA and cognition only in adults younger than 60 years [60]. In addition to age, the variability in the strength of the association could also be due to the study types and designs, the recruitment methods and/or that only more severe OSA cases are associated with cognitive dysfunction.

5. Vulnerability Risk Factors

Not all adults with OSA are at high risk of developing MCI or dementia. Individual characteristics are likely to add to or interact with OSA severity to explain the increased risk of cognitive decline when present. Some variables are difficult to quantify, such as OSA disease duration, and will not be discussed here. Rather, we will focus on factors that should be included as moderating factors in future studies investigating the risk of cognitive decline in OSA. Of note, some studies considered potential moderating variables as confounders, such as ApoE4, sex and age. These are discussed in detail in the following subsections. Table 1 summarizes these potentially moderating factors.

5.1. Age

Age is a well-established risk factor for both OSA [17,82] and dementia [83]. The increased prevalence of OSA with age could be explained in part by indirect factors that are associated with dementia risk (e.g., increasing body mass index, menopause, increasing prevalence of health comorbidities), but also by the marked decrease in tongue and palate muscle activity during sleep in older adults [84,85]. We could therefore hypothesize that older age potentiates the negative effects of OSA on brain health, but the opposite seems to be observed. In fact, a

recent systematic review that included 68 studies showed that young and middle-aged adults (30 to 60 years old) suffering from OSA had impairments in attention, executive functions and memory, while apneic adults aged 60 and over had cognitive functioning comparable to non-apneic people of the same age [60]. It is possible that other conditions occurring mainly with advancing age, such as cardiovascular diseases, hypertension and neurodegenerative diseases, could significantly influence cognitive functioning in the elderly, and therefore hide or blur the association between apnea and cognition. This could explain the weaker association between OSA and cognition; however, this hypothesis remains to be tested.

Table 1. Individual characteristics that could interact with OSA severity to predict risk of cognitive decline

Evidence Availability	**Individual Characteristics**	**Individuals with OSA Potentially at Increased Risk of Cognitive Decline**	**Studies Supporting the Potential Role**
A few studies have tested these variables	Sex	Women	[52,69–71]
	ApoE4	*ApoE4* carriers	[47,52,72,73]
Almost no studies have tested these variables	Menopause	Postmenopausal women	[74]
	Smoking	Smokers	[75]
	Cognitive reserve	Individuals with a low cognitive reserve	[76]
Heterogeneous results or not tested	Age	Young and middle-aged adults	[60]
	Obesity	Obese individuals	[26,77]
	Diabetes mellitus	Diabetic individuals	No evidence found
	Hypertension	Individuals with hypertension	[78,79]
	Cardiovascular diseases	Individuals with cardiovascular diseases	No evidence found
	Excessive alcohol consumption	Individuals having moderate to high alcohol consumption	No evidence found

	Depression	Individual with depression	[80]
	Physical activity	Inactive individuals	[81]
	Air pollution	Individuals exposed to high levels of air pollution	No evidence found

5.2. Sex and Menopause

The prevalence of dementia is higher in women by 19–29% in many parts of the world, including Europe, Latin America, Australia, and areas outside of the Pacific region of Asia [86], and women represent approximately two-thirds of AD dementia cases in the United States [87]. In addition to women's longer life expectancies as compared to men's, this disparity could be due to the different effects of some risk factors in men and women, with some being more common (e.g., lower access to education) and having a stronger impact in women than in men (e.g., ApoE4 genotype), and others being specific to women (e.g., menopause) [87].

With respect to OSA, men, as compared to women, tend to accumulate more fatty tissue in the upper body, especially in the pharynx, which promotes airway collapse and blockage leading to OSA [12]. Accordingly, epidemiological studies using polysomnography, questionnaires or self-reported OSA diagnoses found a prevalence ranging from 13% to 31% in men and 4% to 21% in women [88–93]. Moreover, men and women with OSA seem to experience different symptoms. Men report snoring, shortness of breath and apnea observed by the bed partner, while women report non-specific symptoms such as headaches, fatigue, depression, anxiety and insomnia [94,95], suggesting a sex-specific impact of OSA on diurnal functioning. Of note, these sex differences might reflect an assessment bias. In fact, since initial research was mainly conducted in men, their symptoms appear to be more typical, while women's symptoms might be as frequent, but have received less attention. Furthermore, women might experience similar symptoms as men, but these symptoms might be less frequently reported by their bed partners.

Few studies have examined sex differences in the association between OSA and cognition. Among them, two Taiwanese studies found an interaction effect between sex and sleep disturbances on cognition [71,96]. Chiu et al. [96] showed that men reporting difficulty

breathing during sleep, habitual snoring, and prolonged sleep duration (>8.5 h) were at higher risk of cognitive impairment, whereas in women, only prolonged sleep duration was associated with cognitive impairment. However, Chang et al. [71] showed that women with OSA, but not men, were more likely to develop dementia. Similarly, the Hispanic Community Health Study showed no association between OSA and cognition in men, while a high AHI in women was associated with a marked decrease in cognitive performance in all three cognitive domains assessed (executive function, memory and information processing speed) [69]. Age stratified analyses indicated that this sex effect was specific to the 45–54 age group, which corresponds to the age of perimenopause in most women. In older women (65–74 years), only an association between OSA and information processing speed was observed. Interestingly, cross-sectional studies of cohorts including only women showed significant associations between OSA and poorer cognition [52,70], while cohorts including only men showed no such association [45,49]. Neuroimaging studies from one group included between 10 and 16 women with OSA and highlighted OSA and sex interactions, where only women showed white matter alterations [97], cortical thinning [98] and unilateral volume changes in the hippocampus [99].

Physiological mechanisms that could explain women's vulnerability are still not clear, but the inflammatory response to OSA is among those suspected. An interesting study of apneic adults without known comorbidities showed an increase in inflammatory biomarkers and cardiovascular risk markers (e.g., C-reactive protein, fibrinogen and elevated erythrocyte sedimentation rate) particularly in women, even though apneic men showed higher levels of uric acid, a marker of hypoxia [100]. With equivalent AHI, women have higher levels of fibrinogen and C-reactive protein compared to men [101].

Menopause is another factor that could explain women's vulnerability to OSA. Importantly, menopause is accompanied by decreased metabolic activity and increased amyloid burden, characteristics of an AD endophenotype [102]. In fact, a three-year longitudinal study observed postmenopausal women and showed a higher rate of amyloid deposition compared to pre-menopausal women and men, and a higher rate of hippocampal volume loss compared to pre- and perimenopausal women and men [103]. AD pathology appears years to decades prior to

clinically detectable symptoms, corresponding to the age of perimenopause in most women [102]. Menopause transition could thus increase the risk of AD in women.

Menopause is characterized by estrogen and progesterone depletion, which triggers an adipose tissue distribution change, making this distribution similar to what is observed in men [13]. Postmenopausal women have more adipose accumulation in the upper body and increased body mass index (BMI), neck circumference, and waist-to-hip ratio, all increasing their risk of OSA [104]. Indeed, postmenopausal women not using hormone replacement therapy are three to four times more likely than non-menopausal women to suffer from OSA, suggesting a protective role for estrogen and progesterone against OSA [13,105].

Postmenopausal women at high risk of OSA, as assessed by the Berlin Questionnaire [106], reported more subjective cognitive impairment than those at low risk of OSA [74]. An interesting review about ovarian hormones, sleep, and cognition suggests that the loss of ovarian hormones following menopause could increase the development of sleep disorders, and thus could precipitate cognitive decline and dementia in women [107]. More precisely, increases in sleep disorders could enhance inflammation, leading to neurodegeneration and cognitive decline. Thus, menopause could accelerate OSA-related cognitive decline. Although limited data are available, a recent meta-analysis showed that hormone replacement therapy improves cognitive function in women with AD [108]. Since hormone replacement therapy improves sleep in some, but not all studies [107], its potential to reduce OSA-related vulnerability to cognitive decline needs to be investigated.

5.3. Obesity

Results from a 36-year longitudinal study showed that middle-aged adults with a combination of obesity and high abdominal circumference have a 3.6-fold increase in dementia risk, even after controlling for diabetes and other vascular comorbidities [109]. This increased risk can be explained by the fact that adipocytes secrete pro-inflammatory cytokines that alter synaptic and neuronal plasticity, which in turn contributes to neurodegenerative processes [110]. Furthermore, obesity-related inflammation leads to oxidative stress, which also plays a role in neurodegenerative processes [111].

The risk of OSA increases progressively with BMI and is even more strongly associated with neck circumference [112]. Obesity is the strongest risk factor for OSA and its relationship with OSA might be bidirectional [113]. While obesity is linked to several co-morbidities exacerbated by OSA, such as myocardial infarction, congestive heart failure, stroke, type 2 diabetes and hypertension, OSA is thought to increase the risk of obesity due to the physical inactivity associated with daytime sleepiness [113].

Considering obesity's possible contribution to neurodegenerative processes and its strong link to OSA, Polsek et al. [26] suggested that co-morbid obesity could promote AD progression in individuals with OSA. Yet, most studies investigating the link between OSA and cognitive decline have statistically controlled for obesity but have not stratified their analyses according to obesity. Interestingly, one recent study found that obese OSA patients have reduced performance in working memory and psychomotor vigilance compared to non-obese OSA patients [77]. More studies are therefore needed to verify if overweight or obese adults are particularly vulnerable to cognitive alterations linked to OSA.

5.4. Diabetes Mellitus

A pooled meta-analysis of 2.3 million individuals with type 2 diabetes showed that diabetes is associated with a 1.6-fold increase in dementia risk [114]. In addition to a possible increase in amyloid and tau burden in diabetic patients [115,116], non-AD mechanisms could also link type 2 diabetes to neurodegeneration, as a result of insulin resistance disturbing cerebral insulin pathways, vascular endothelial dysfunction leading to hypoxic neuronal injury and inflammation disrupting the blood–brain barrier [117].

Up to 30% of patients with OSA suffer from type 2 diabetes [118], and up to 86% of obese patients with type 2 diabetes suffer from OSA [119]. The link between OSA and diabetes is believed to be bidirectional but has not yet been fully elucidated. On the one hand, the autonomic dysfunction characteristic of diabetes could lead to respiratory instabilities, increasing the risk of OSA [120]. On the other hand, intermittent hypoxemia, sleep fragmentation and reduced time spent in N3 and REM sleep in OSA may increase the risk of

developing alterations in glucose metabolism such as insulin resistance, glucose intolerance and type 2 diabetes [120–123].

Regarding the interaction between diabetes and OSA, a study of adults (mean age = 55 years) with prediabetes or type 2 diabetes found no association between OSA and cognitive performance [124]. It is important to mention that most participants (43%) had only mild OSA in that study. Thus, more studies are needed to verify if cognitive impairment and decline are particularly important in diabetic individuals with mild, moderate or severe OSA.

5.5. Hypertension

Results from the Framingham Offspring cohort study showed that midlife systolic hypertension and the persistence of systolic hypertension into later life were associated with a 1.6 to 2-fold increase in dementia risk at 18-year follow-up [125]. Various pathways could link hypertension to dementia, including small vessel disease, large artery atherosclerosis, and hypertension-related cardiac dysfunction, which predispose to cerebral hypoperfusion [125].

An estimated 50% of patients with hypertension present with OSA [126]. Conversely, individuals with OSA have an extra 1.8-fold risk of resistant hypertension compared to those without OSA [127]. The link between OSA and hypertension could be explained by anatomical changes resulting from hypoxia. In fact, intermittent hypoxia triggers an intense cardiovascular response, leading to sympathetic overactivity, which in turn contributes to hypertension [128]. It is therefore possible that intermittent hypoxemia and sleep fragmentation accentuate the effects of hypertension on cognitive decline, while hypertension may in turn potentiate the effects of OSA on the risk of dementia by increasing oxidative stress and inflammatory response [78]. Moreover, a study of men and women aged 60 years and older showed working memory impairment related to OSA and hypertension [79].

5.6. Cardiovascular Diseases

Dementia and cardiovascular diseases share common risk factors that could lead to cognitive decline, such as diabetes mellitus, smoking, and hypertension [129]. Moreover, studies have also linked dementia to specific cardiovascular diseases, such as coronary heart disease, atrial

fibrillation and heart failure [129]. While it is not yet established if cardiovascular diseases per se increase the risk of dementia or if it is due to shared risk factors, cardiovascular diseases could contribute directly to cognitive decline through cerebral hypoperfusion, hypoxia, embolisms, and infarcts [129]. Moreover, one study showed that genetic predisposition to coronary artery disease increases dementia risk three years after a cardiovascular disease diagnosis [130].

It is difficult to isolate the independent role that cardiovascular diseases may play in OSA because of the concomitant presence of other cardiovascular risk factors such as obesity and glucose intolerance [131]. However, the prevalence of OSA is estimated to be two to three times higher in people with cardiovascular diseases [132], and up to 50% of apneic patients show cardiac and metabolic abnormalities [131]. Fragmented sleep and recurrent cycles of decreased oxygen levels and reoxygenation associated with OSA lead to oxidative stress and inflammation, which damage blood vessel walls and increase hypertension [133,134]. Considering the cascade of deleterious consequences produced by both OSA and cardiovascular diseases, it is likely that treating OSA could help mitigate their negative impacts on brain health.

5.7. Smoking

It is highly recognized that smoking increases the risk of cognitive decline and dementia [2,135]. A multi-ethnic cohort study including adults aged 50–60 years indicates that smoking more than two packs of cigarettes daily doubles the risk of dementia at 23-year follow-up [136]. In addition, a Chinese study conducted with current, past and non- smokers aged 20–60 years who reported snoring or daytime drowsiness showed that the coexistence of OSA and chronic smoking results in more pronounced cognitive impairment than smoking alone [75]. Specifically, inhaling cigarette smoke increases oxidative stress and systemic inflammation, phenomena also observed in OSA [75]. Thus, the concomitant presence of smoking and OSA could precipitate cognitive decline.

5.8. Excessive Alcohol Consumption

A scoping review of 28 systematic reviews revealed that excessive alcohol consumption is linked to an increased dementia risk, while low to moderate drinking is associated with a decreased

risk [137]. Alcohol could lead to brain damage directly, through its neurotoxic effect on brain structure and function [137]. In fact, chronic alcohol abuse could lead to loss of white matter, with astrocytes, oligodendrocytes, and synaptic terminals being particularly vulnerable to the toxic effects of alcohol [138]. Moreover, heavy alcohol consumption can cause high blood pressure, ischemic heart disease, cardiomyopathy, atrial fibrillation, and strokes, which are in turn associated with increased risk of vascular dementia [137,139]. Low to moderate alcohol consumption is associated with lower odds for dementia than abstainers; while this link is not yet well understood, the inclusion of former drinkers who might have already suffered from alcohol-related consequences in the group of abstainers could explain part of the results [140].

Due to its relaxing properties, alcohol increases upper airway collapsibility and could thus represent a risk factor for the occurrence of apneas when it is ingested before bed- time [141–143]. Results from systematic reviews and meta-analysis revealed that alcohol consumption is associated with a 25% increased risk of OSA [143], an increase in AHI of 2.33 to 3.98 events per hour, and a 0.60% to 2.72% decrease in lowest oxygen saturation [142,144]. Furthermore, results from the Wisconsin Sleep Cohort Study showed that alcohol's negative impact on OSA may not be restricted to its consumption near bedtime, but to its habitual consumption [141]. In fact, for each increase of one self-reported drink per day, men had 25% greater odds of OSA, while women's alcohol consumption was not associated with OSA [141]. However, no study has investigated the presence of cognitive dysfunction in OSA adults having moderate to high alcohol consumption. Thus, alcohol could represent a modifiable risk factor for dementia when consumed in excess and could also predispose to OSA even in a lower dosage.

5.9. Depression

Cohort studies and meta-analyses suggest that a history of depression is associated with an increased dementia risk, with depressive symptoms independently associated with cognitive decline [2,145]. However, it is not well established whether depression increases the risk of dementia or is an early marker of brain changes associated with dementia [2,135].

A systematic review and meta-analysis indicates that OSA is linked to depression, with longitudinal studies being more susceptible to highlight cognitive decline associated with OSA

than cross-sectional studies [146]. In fact, two longitudinal studies suggested that OSA is an independent risk factor for depression, with participants with OSA being about twice as likely to be depressed as those without OSA [147,148]. According to a model developed by Kerner and Roose [80], cerebral hypoperfusion, endothelial dysfunction and neuroinflammation due to OSA could initiate or amplify the development of cerebral small vessel disease and blood–brain barrier dysfunction, resulting in white matter lesions, gray matter loss, white matter fiber tract abnormalities, neuronal damage, synaptic plasticity and neurodegenerative processes, in turn leading to depressive symptoms and cognitive impairment [80]. One study found that depressive symptoms observed in OSA patients were associated with accentuated excessive daytime sleepiness [149]. Whether depression in OSA patients is a daytime consequence of OSA, an early marker of neurodegeneration, or a risk factor that interacts with OSA to hasten cognitive decline is a highly relevant clinical question.

5.10. Air Pollution

Air pollution is a recognized risk factor for dementia [2,150,151]. A systematic review of longitudinal studies suggested that exposure to particulate matter, nitrogen dioxide and carbon monoxide increases dementia risk [151]. It has been hypothesized that the mechanisms underlying the effects of air pollution on brain health could include inflammation, microglial activation, reactive oxygen species, and the production and deposition of amyloid-beta peptides [150].

Although it is well known that air pollution has deleterious effects on respiratory health, its relationship with OSA remains unclear [152]. A recent systematic review including five cross-sectional studies of adults objectively assessed for OSA suggested a relationship between air pollution exposure and increased risk of OSA, with variability attributed to seasons, temperatures and geographic locations [152].

Furthermore, air pollution and OSA share common potential pathways to health conditions and cognitive decline such as hypertension, insulin resistance, oxidative stress, inflammation and endothelial dysfunction [151]. Laratta et al. [153] suggested an interaction of OSA and air pollution on systemic inflammation. In fact, this team observed increased levels of inflammation

with high particulate matter exposure in individuals with suspected OSA, and with black carbon exposure in patients with moderate to severe OSA [153]. Considering the potential deleterious effects of both inflammation and health conditions on the brain, it is likely that OSA and exposure to air pollution have a joint negative effect on cognitive health. Moreover, air pollution and OSA could increase dementia risk through an indirect pathway related to metabolic dysfunctions such as diabetes [154], hyperglycemia and low high-density lipoprotein cholesterol [155]. Future studies should verify if exposure to air pollution makes patients particularly vulnerable to cognitive alterations linked to OSA.

5.11. ApoE4

ApoE is a protein involved in cholesterol transport, growth and repair of the nervous system during development or after injury, synaptic and dendritic remodeling, and the scavenging of amyloid [156–158]. Carriers of the ApoE4 allele have decreased expression of the ApoE protein, and thus, its beneficial role in the central nervous system is reduced.

The ApoE4 allele remains, to this day, the strongest genetic risk factor for sporadic AD [156,159]. Most studies have shown an association between ApoE4 allele carrier status and poor performance in various cognitive domains in elderly people without dementia [160–162]. Even with the increased prevalence of OSA in older individuals, these studies did not take into account the presence or absence of OSA in their analyses. How- ever, the presence of ApoE4 alone is not sufficient to cause cognitive decline and is thought to be a susceptibility factor that interacts with other genetic and environmental influences to increase the risk of cognitive decline [162,163]; one of these factors could be OSA.

While one study showed that ApoE4 was associated with an increased risk of moderate to severe OSA and higher AHI [164], others did not show this link [165–167]. A few studies have shown that in apneic patients aged 30 or over, the presence of the ApoE4 allele is associated with more cognitive impairment as compared to non-carriers [47,52,72,73]. These results could be explained by the vulnerability of ApoE4 carriers to central nervous system injuries of various origins, such as the oxidative stress associated with OSA [72,73]. Whether cognitive impairment in ApoE4 carriers with OSA progresses to dementia is a question that must be investigated.

6. Protective Factors

6.1. Physical Activity

Physical inactivity is the most significant modifiable risk factor for AD in the United States, Europe and England, where approximately one-third of the adult population is physically inactive (i.e., less than 20 min of vigorous activity during three or more days or less than 30 min of moderate activity during five or more days per week) [168]. Results from randomized controlled trials in healthy inactive older adults show that low-intensity exercise programs improve cognitive functioning and decrease the risk of cognitive de- cline [135]. Physical activity promotes brain plasticity and neurogenesis as well as vascular health by reducing blood pressure, lipids, obesity, and markers of inflammation [169]. In addition, physical activity is associated with lower levels of AD pathology such as tau and beta-amyloid [170].

A systematic review of physical activity and OSA suggests that apneic patients often display low levels of physical activity, possibly due to the fatigue and daytime sleepiness characteristics of OSA [81]. Conversely, exercise training programs of at least a three-week duration are associated with a decrease in AHI and symptoms of drowsiness despite no change in BMI [81]. This decrease in OSA symptomatology may be due to increased upper airway dilator strength and fatigue resistance, decreased nasal resistance, and increased respiratory stability during deep sleep [171]. Physical activity could therefore improve OSA symptoms and cognitive performance, and possibly delay OSA-related cognitive impairment, but this needs to be tested.

6.2. Cognitive Reserve

The level of education, intelligence and main occupation are markers of the cognitive reserve, which makes it possible to withstand a deterioration of cerebral structures and to preserve cognitive and behavioral functions at an optimal level when a neurodegenerative process sets in [172]. Worldwide, low levels of education are believed to be the most important modifiable risk factor for AD [168].

With respect to OSA, higher intelligence is thought to have a protective effect against OSA-related cognitive decline, possibly due to the associated cognitive reserve, and may compensate

for the hypoxic brain damage or daytime sleepiness associated with OSA [76]. In fact, one study showed similar levels of attention in highly intelligent participants with and without OSA, while in those with normal intelligence, apneic patients had reduced attention compared to the control group [76]. Since cognitive reserve is a well-established protective factor of dementia, future studies will need to determine whether cognitive reserve can delay, or even prevent, cognitive decline in apneic patients.

7. Clinical Impact and Future Directions

Clinicians often face a dilemma as to whether they should treat patients with mild OSA or those with low diurnal symptoms. When they prescribe OSA treatment, patients may refuse it or may fail to use it on an on-going basis. With the recent findings on OSA and the risk of cognitive decline, clinicians and patients should now take into account the risk of developing dementia if OSA remains untreated. Identifying vulnerability and protective characteristics in OSA and their impact on cognitive decline has the potential to guide clinicians in treatment decisions, for example, through the use of decision trees or software/web applications based on machine learning and available for clinicians. Patients presenting with OSA and multiple vulnerability factors for cognitive decline could thus be offered treatment even if they only have mild OSA. To improve the management of OSA in this at-risk population, systematic screening for OSA could be implemented in memory clinics and cardiology/cardiovascular hospital units.

Furthermore, studies investigating the link between OSA and cognitive decline often do not characterize participants with respect to underlying pathology. Since AD pathology is present during a long silent phase, it is possibly present in some participants and left undetected by cognitive screening. Since the influence of risk and protective factors possibly differs according to the presence or absence of AD pathology, future studies should quantify participants' AD pathology. Finally, patients with multiple sleep disorders (i.e., those with OSA combined with insomnia, REM sleep behavior disorder, circadian misalignment) may be at higher risk of cognitive decline and dementia. The effects of having multiple sleep disorders should be investigated in future studies, rather than excluding patients based on comorbid sleep disorders.

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1.6 Lacunes dans la littérature actuelle

Tel que décrit précédemment, des divergences importantes existent entre les études qui ont investigué le lien entre l'AOS et les troubles ou le déclin cognitif. Ces divergences pourraient être expliquées par des facteurs modérateurs qui protégeraient ou rendraient plus vulnérable le patient apnéique face aux troubles cognitifs. En effet, il est possible que l'AOS seule n'altère pas le fonctionnement cérébral de manière suffisamment importante pour mener à des troubles cognitifs observables, mais que la présence concomitante d'autres facteurs précipite un déclin cognitif. Également, il est possible que l'AOS ne joue qu'un rôle indirect et que des variables médiatrices expliquent majoritairement les associations entre l'AOS et la cognition. À ce jour, nous avons très peu d'information sur ces facteurs possiblement modérateurs ou médiateurs.

D'abord, il est essentiel d'obtenir une estimation à jour la prévalence d'AOS et de déterminer les caractéristiques individuelles mettant à risque les individus de présenter de l'AOS dans la population canadienne d'adultes d'âge moyen et âgés. Une telle investigation dans un large échantillon représentatif de la population est nécessaire afin d'améliorer le dépistage et la prévention de l'AOS. De plus, elle permettrait d'identifier les facteurs possiblement modérateurs ou médiateurs du lien entre l'AOS et les troubles cognitifs qui devraient faire l'objet d'études futures.

Ensuite, il est primordial de comprendre si le lien entre l'AOS et le fonctionnement cognitif est différent selon l'âge et le sexe. De manière générale, les études passées n'ont pas pris en compte ces caractéristiques individuelles dans l'étude du lien entre l'AOS et le fonctionnement cognitif. Mieux comprendre le rôle de ces différentes variables individuelles a le potentiel de guider les cliniciens dans leur décision de traitement. En effet, les cliniciens sont souvent confrontés à un dilemme quant au traitement de patients avec une AOS légère ou présentant peu de symptômes diurnes. Des patients qui présentent des facteurs de vulnérabilité pourraient se voir offrir un traitement, même s'ils ne présentent que de l'AOS légère.

Finalement, il est nécessaire d'investiguer le rôle de l'inflammation systémique et de la ménopause dans l'association entre l'AOS et la cognition. Comprendre si ces variables constituent des mécanismes qui modèrent ou médient le lien entre l'AOS et la performance

cognitive pourrait permettre de mieux cibler les personnes apnéiques les plus susceptibles de présenter des troubles cognitifs liés à l'AOS et de les prendre en charge en priorité.

1.7 Objectifs et hypothèses de la thèse

L'objectif général de cette thèse était de caractériser le rôle de variables individuelles dans le risque de présenter de l'AOS ainsi que des possibles troubles cognitifs associés à l'AOS. Plus spécifiquement, cette thèse visait à caractériser l'association entre l'AOS ainsi que l'âge, le sexe et l'inflammation systémique pour expliquer les performances cognitives de façon transversale et longitudinale. Pour atteindre ces objectifs, nous avons eu recours à la cohorte nationale de l'Étude longitudinale canadienne sur le vieillissement, constituée de 30 097 personnes âgées et d'âge moyen testées au temps de base et lors d'un suivi après trois ans. Cette thèse a mené à trois articles scientifiques originaux :

1.7.1 Article 2

L'article 2 avait pour objectif d'estimer la prévalence canadienne de l'AOS chez les hommes et les femmes âgés de 45 ans et plus à partir d'un score de risque d'AOS. Nous avions aussi pour objectif d'identifier les associations entre un haut risque d'AOS et des comorbidités liées à l'AOS, la ménopause et des marqueurs d'inflammation systémique. Cette étude populationnelle est la plus vaste au Canada à ce jour (N= 27,210 participants).

1.7.2 Article 3

L'objectif de l'article 3 était de caractériser les associations entre le risque d'AOS et la performance cognitive selon l'âge et le sexe. L'objectif secondaire était d'investiguer si le niveau d'inflammation systémique médiait cette association. Nous avons émis l'hypothèse que l'association entre le risque d'AOS et les basses performances cognitives serait plus forte chez les plus jeunes participants (adultes d'âge moyen), et particulièrement chez les femmes et les personnes ayant des hauts niveaux d'inflammation systémique.

1.7.3 Article 4

L'article 4 avait pour objectif de déterminer l'association entre le risque d'AOS et le changement dans la performance cognitive après trois ans selon l'âge et le sexe. Nous avons émis l'hypothèse que les participants ayant un haut risque d'AOS présenteraient un déclin cognitif plus abrupte que ceux à bas risque d'AOS après trois ans, principalement dans les domaines de la mémoire verbale et de l'attention. De plus, nous nous attendions à ce que les femmes d'âge moyen à haut risque d'AOS montrent un déclin cognitif plus abrupte que les femmes plus âgées et les hommes de tous âges.

Chapitre 2 – Méthodologie et résultats

2.1 Article 2

Article 2 : A portrait of obstructive sleep apnea risk factors in 27,210 middle-aged and older adults in the Canadian Longitudinal Study on Aging

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*Ces autrices ont contribué de manière équivalente à cet article.

Contribution : Pour cet article, j'ai procédé à une revue de la littérature, interprété les résultats d'analyse, rédigé et révisé de manière critique le manuscrit.

Abstract

Determining the prevalence and characteristics of individuals susceptible to present with obstructive sleep apnea (OSA) is essential for developing targeted and efficient prevention and screening strategies. We included 27,210 participants aged ≥45 years old (50.3% women) from the Canadian Longitudinal Study on Aging. Using the STOP questionnaire combined to the percentage of body fat (%BF), we estimated the prevalence of individuals at high-risk for OSA in a sex and age-specific manner, and tested the relation with comorbidities, menopause and systemic inflammation. The prevalence was 17.5%, and was lower in women (13.1%) than in men (21.9%). A high level of high- sensitivity C-reactive protein was the strongest factor associated with OSA risk and this association was 1.3–2.3 times higher in women than in men. OSA risk increased with age, cardiovascular diseases, diabetes mellitus, anxio-depressive symptoms, asthma and arthritis. In women, post-menopausal status was associated with a high OSA risk. Nearly 1 adult out of 5 older than 45 is at risk for OSA in Canada. Comorbidities, menopause and systemic inflammation, more than age, explain increased OSA prevalence. Considering this high prevalence and associations with medical and mental comorbidities, health care practitioners should incorporate systematic OSA screening in their clinical procedures.

Introduction

Obstructive sleep apnea (OSA) represents a major public health issue. In fact, nearly one billion adults aged 30–69 years suffer from OSA worldwide[1]. Moreover, as there is a graded increase in OSA prevalence with increasing body mass index (BMI)[2], it will likely continue increasing with time due to the epidemic of obesity. The association between OSA and medical and mood conditions such as diabetes, hypertension, coronary artery disease, myocardial infarction, congestive heart failure, stroke, and depression[3–5] is also worrying since a bidirectional relationship is suspected[6–9]. Unfortunately, OSA remains largely under-diagnosed and under-treated[10–13]. The main obstacles are that patients often do not recognize the symptoms, most health professionals do not routinely screen for OSA, and patients find difficult to adhere to continuous positive airway pressure (CPAP) treatment[14].

Determining the prevalence and characteristics of individuals susceptible to present with OSA in representative population samples is essential for developing more targeted and efficient prevention and systematic screening strategies. This is particularly true for late middle-aged and older adults who are more susceptible to present OSA compared to young adults[15]. Moreover, considering that previous work reported sex differences in how OSA is associated with medical conditions and blood markers (e.g.: apneic women showing higher inflammation levels and being more susceptible to obesity than men)[16,17], studies now have to include sex differences in their analyses[18] (Supplementary information).

Investigating OSA prevalence in large cohorts is challenging, as using objective measures of OSA (i.e., polysomnography) is generally limited to smaller samples. To our knowledge, four regional studies used random sampling and polysomnographic recordings to estimate OSA prevalence and assess its association with risk factors and symptoms in adults aged 18–85 in the past 15 years[16,19–21]. Prevalence of mild OSA, defined by an apnea–hypopnea index (AHI) of ≥ 5 but < 15, ranged between 47 and 84% in men, and 25 and 61% in women, while that of moderate-to-severe OSA (AHI ≥ 15) varied between 19 and 50% in men and 8 and 23% in women[16,19,20]. The large variations observed in OSA prevalence were due to its strong positive associations with age and BMI, metabolic comorbidities and menopause[16,19,20]. Other large cohort studies[22,23] used self-reported diagnosis of OSA obtained through surveys, which probably captures more symptomatic or severe cases, as shown by the drastically lower prevalence that was reported (13–14% in men and 4–6% in women). These results confirm that using self-reported diagnosis, especially in people with mild OSA who are possibly unaware of their condition, leads to an underestimation of OSA prevalence[10,24].

Another approach to estimate OSA prevalence in large cohorts is using validated screening tools[25–27]. The STOP is based on the Berlin questionnaire and was validated in sleep clinics, surgical and general populations[28,29]. It assesses the self-reported presence of four typical signs and symptoms of OSA, namely Snoring; daytime Tiredness; Observed apnea; and high blood Pressure, which form the STOP acronym. The STOP-Bang is an alternative scoring algorithm that includes four demographic variables: BMI (B), age (a), neck circumference (n) and sex (g)[28].

Recent systematic reviews reported that a STOP-Bang score of 3 or more has a sensitivity ranging between 88%[30] and 94%[31] for detecting moderate-to-severe OSA, but has a much lower specificity (24–42%[30,31]). The STOP / STOP-Bang thus represent useful tools to identify individuals at risk of having a severe form of OSA that should undergo objective polysomnographic testing in clinical settings[31], as well as to estimate the prevalence of adults susceptible to present OSA (referred as being "at high-risk for OSA" in this article) in large cohorts.

The primary objective of this study was to estimate the sex-specific prevalence of OSA in the national population-based cohort of the Canadian Longitudinal Study on Aging (CLSA) that includes adults aged ≥ 45 years old. We used the STOP questionnaire combined to the percentage of body fat (%BF), an objective measure of obesity that reliably estimates the prevalence of obesity in the CLSA[32], and accounted for the "B" item of the "Bang". Sex-specific analyses were stratified according to age, as well as menopausal status for women. A second objective was to identify the sex-specific associations of OSA-related comorbidities and levels of systemic inflammation with high-risk for OSA while controlling for recognized socio-demographic and lifestyle-related confounding variables. Our study represents the largest population-based study (N = 27,210 participants) using validated screening questions to estimate sex-specific OSA prevalence, while focusing on adults aged 45–85 who may differ from younger adults in terms of OSA prevalence and determinants.

Material and methods

Study design and participants

The CLSA is a national prospective longitudinal study, which includes a total of 51,338 Canadian women and men aged 45–85 years old at the time of recruitment. Participants were separated in two distinct cohorts (comprehensive, N=30,097; tracking, N=21,241) and will be followed until 2033 or death. The CLSA comprehensive cohort recruitment and baseline data collection started in mid-2012 and ended in mid-2015. The design, sampling and source population have been described in detail previously[33]. Our study used the baseline cross-sectional data included in the comprehensive cohort comprising questions pertaining to sleep.

The 30,097 participants of the comprehensive cohort were fluent in English or French, followed in person and living within 25–50 km of one of 11 CLSA data collection sites located in seven Canadian provinces. As evaluated by CLSA's trained interviewers, participants were free of identifiable signs of cognitive impairment that would prevent them from giving their informed consent and understanding the assessments and tasks. Participants provided information through a computer-assisted interview on aspects relevant to health and aging, and through physical examination, questionnaires, neuropsychological assessment, and biological sample collection during home and site visits. Data pertaining to sleep was collected during home visits.

The CLSA is overseen by a collaborative Research Ethics Board forum chaired at McMaster University, and our own study was approved by the Centre intégré universitaire de santé et services sociaux du Nord-de-l'Ile-de- Montréal Research Ethics Board (REB 2018–1584). This research has been performed in accordance with the Declaration of Helsinki. Informed consent was obtained from all participants included in the CLSA.

Measures

Obstructive sleep apnea. We estimated the prevalence of adults susceptible to present OSA using four questions forming the STOP score[28] combined to the whole body fat percentage with sex-specific cutoffs[34], resulting in what we refer to as the STOP-Obesity score. For the "B" item, we used the %BF instead of the BMI since the latter underestimates the prevalence of obesity in the CLSA[32]. Neck circumference, one of the 8 questions in the STOP-Bang, is not available in the CLSA cohort, which is why we only used the STOP portion of the questionnaire along with an obesity measure. However, we performed our analyses considering age and sex ("a" and "g" in the acronym, see below).

Snoring was assessed by the yes/no question "Do you snore loudly? By 'loudly' I mean louder than talking or loud enough to be heard through closed doors". Observed apnea was assessed by the yes/no question "Has anyone ever observed you stop breathing in your sleep?". With respect to high blood pressure, participants were asked the yes/no question "Has a doctor ever told you that you have high blood pressure or hypertension?". Answers were double-checked with information pertaining to the current intake of hypertensive medication. A score of one

was given for each of these questions answered with a “yes”. Daytime tiredness/sleepiness was assessed by the interviewer asking “Over the last month, how often do you find it difficult to stay awake during your normal waking hours when you want to?”, with suggested response categories being “Never”, “Less than once per week”, “Once or twice a week”, “3–5 times per week” or “6–7 times per week”. Participants reporting difficulty staying awake ≥ 3 times per week were considered as experiencing significant daytime sleepiness and were given a score of one. The %BF was measured using a Hologic Discovery A Dual Energy X-Ray Absorptimetry (DXA) machine[35]. Women with a %BF > 35% and men with a %BF > 25% were considered obese, and were given one point for the obesity criterion. The maximum score on the STOP is 4, and participants scoring ≥ 2 are considered at high-risk of having OSA[28]. Our adapted STOP-Obesity score could reach a maximum value of 5 instead of 4, and we considered participants scoring ≥ 3 to be at high-risk for having OSA. We established this cutoff based on recent meta-analyses and studies reporting a high sensitivity for a STOP-Bang score ≥ 3 in patients with mild, moderate and severe OSA[30,31,36,37]. As the CLSA does not include specific questions pertaining to a prior diagnosis of OSA, the terminology “being at high-risk for OSA” refers to the odds of presenting with OSA at the time of testing. It possibly includes individuals who already have OSA and does not exclusively refer to the probability of developing it in the future.

Clinical, sociodemographic and lifestyle variables

Clinical, lifestyle and sociodemographic variables related to OSA were selected based on the literature[19,20,23,27,38], clinical relevance, and availability in the CLSA cohort. Details on the lifestyle and sociodemographic variables are provided in the Supplementary material.

Clinical variables included systemic inflammation, assessed using the level of high-sensitivity C-reactive protein (hs-CRP), and categorized as normal (< 1 mg/L), mild (1–3 mg/L), moderate (3–10 mg/L) and high (> 10 mg/L)[39]. Chronic health conditions diagnosed by a health professional which were expected to, or have already lasted, 6 months or more were considered. This information was reported by the participants, who were asked to answer yes or no to questions about each chronic condition’s diagnosis; all questions systematically started by, “Has a doctor ever told you that you have [chronic medical condition]?”. The chronic medical conditions

included were cardiovascular diseases (myocardial infarction, angina pectoris, and/or congestive heart failure), cerebrovascular diseases (stroke and/or transient ischemic attacks), diabetes mellitus, hypothyroidism, arthritis, osteoporosis, memory problems, dementia, anxiety, Parkinson's disease, chronic obstructive pulmonary disease (COPD) and asthma. The 10-item Center for Epidemiologic Studies Depression scale (CESD-10) was used to assess the presence of depression, where a participant scoring ≥ 10 was considered having depression[40]. Participants who reported having anxiety and/or who scored ≥ 10 on the CESD-10 were considered having an anxious-depressive disorder. Menopausal status was also recorded; women who answered "yes" to "Have you gone through menopause, meaning that your menstrual periods stopped for at least one year and did not restart?" were considered post-menopausal. The others were considered non-menopausal and included pre- and peri-menopausal women.

Statistical analyses

Descriptive and regression analyses considered the CLSA inflation and analytic weights, respectively, accounting for the age-stratified sampling strategy and an individual's probability of inclusion in the CLSA (influenced by unequal sampling probabilities across sampling units and response rates)[41].

Categorical variables were presented using crude frequencies and weighted proportions. Using chi-square tests, we compared i) the proportion of women and men presenting the individual items of the STOP-Obesity screening tool; ii) the sex-specific estimates of the prevalence of high-risk for OSA between age categories (45–49; 50–54; 55–59; 60–64; 65–69; 70–74; 75–79; ≥ 80); and iii) the estimates of the prevalence of high-risk for OSA between non- and post-menopausal women within age categories. Estimates of the number of middle-aged and older Canadian individuals at high-risk for OSA were calculated using the population of women and men aged ≥ 45 years obtained from the 2016 Canadian Census, multiplied by the sex- and age-specific high-risk for OSA prevalence obtained in the CLSA cohort.

The independent association between high-risk for having OSA and OSA-related comorbidities, level of inflammation, as well as menopausal status for women were tested with multivariate

logistic regressions, adjusted for the socio-demographic (age, marital status, ethnicity, income, education level, working status) and lifestyle-related determinants (smoking, alcohol consumption, level of physical activity, sleep duration, sleep quality). Odds ratios > 1 implied that participants presenting a specific comorbidity or a higher-than-normal level of inflammation > 1 mg/L were more likely to be at high-risk for OSA than those who did not present these characteristics.

To better understand whether the sex- and age-specific variations observed in OSA risk can be associated with OSA-related comorbidities and systemic inflammation, we performed sensitivity analyses with the whole cohort (i.e., regardless of OSA risk) using chi-square tests to evaluate: (i) the sex- and age-specific prevalence of comorbidities, and (ii) the sex- and age-specific prevalence of moderate and high levels of systemic inflammation. Moreover, high levels of hs-CRP are known to be associated with obesity[42], which is a component of our STOP-Obesity score. In order to verify if systemic inflammation was associated with OSA risk independent of obesity, we performed additional sex-specific linear regressions between hs-CRP and each STOP-Obesity item (i.e., snoring; tiredness, sleepiness, fatigue; observed apneas; high blood pressure; obesity) while controlling for all the other items. Results from the sensitivity analyses are presented in the Supplementary material.

Analyses used all participants for whom the variables of interest were available, for women and men, separately. We did not impute missing data. Statistical analyses were performed using IBM SPSS Statistics version 25.0 (Chicago, IL, USA).

Ethics declaration

The CLSA is overseen by a collaborative Research Ethics Board forum chaired at McMaster University, and our own study was approved by the Centre intégré universitaire de santé et services sociaux du Nord-de-l'Ile-de-Montréal Research Ethics Board (REB 2018–1584).

Consent to participate

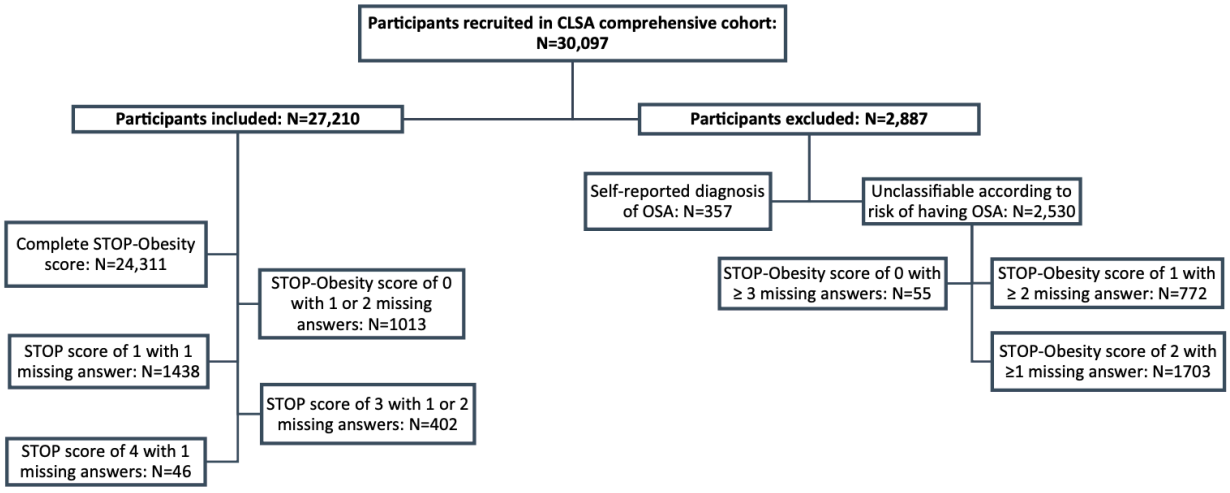
Informed consent was obtained from all participants included in the CLSA.

Results

Population

Of the initial 30,097 participants, we included 27,210 of them (13,799 women and 13,411 men; 59.2 ± 9.8 years old) that we could classify at low- or high-risk for OSA based on their score on the STOP-Obesity (< 3 vs ≥ 3). Of those 27,210 participants, 24,311 answered the four STOP items and had their %BF information available. We classified an additional 2,899 participants although they had one or more missing information on the STOP-Obesity score (Fig. 1). We excluded 2,887 participants, either because they reported having a diagnosis of OSA and no information was available on whether or not they were treated for OSA (N = 357), or because they were impossible to classify according to their risk of having OSA (N = 2,530). Excluded participants were slightly older, and more likely to be women compared to those included in the analyses.

Figure 1. Flowchart describing the inclusion and exclusion of participants for analyses based on the surrogate STOP score



Prevalence of adults at high-risk for OSA in the CLSA cohort

Based on a STOP-Obesity score ≥ 3, we classified 17.5% of participants (95%CI: 17.0–18.0%) as being at high-risk for OSA, with a prevalence of 21.9% in men (95%CI: 21.2–22.6%) and 13.1% in women (95%CI: 12.5–13.7%). Table 1 presents sex-specific proportions of participants at low- and high-risk for OSA in each age and menopausal category. Participants at high-risk for OSA were more likely to be 55 years old or more, while women at high-risk for OSA were post-menopausal in a greater proportion than those at low-risk for OSA. Supplementary Table S1 presents detailed socio-demographic, clinical and lifestyle characteristics of women and men at low- and high-risk for OSA. Table 2 presents sex-specific prevalence of each risk factor included in the STOP-Obesity score. Compared to men, women at high-risk for OSA showed a lower prevalence of snoring, observed apneas, and obesity; however, women reported more daytime sleepiness and high blood pressure than men.

Prevalence by age categories

Figure 2 shows the age-specific prevalence of OSA in women and men. High-risk for OSA was 1.2 to 2.0 times more prevalent in men than in women, independent of age. In women, the prevalence of high-risk for OSA increased with age following a quasi-linear trend. In men, this prevalence rather showed an inverted U-shape with a plateau between 55 and 74 years.

Prevalence by menopausal status

The prevalence of high-risk for OSA varied with menopausal status: 7% (95% CI: 6–8%) of non- and 14% (95% CI: 13–15%) of post-menopausal women were at high-risk for OSA. In non-menopausal women, there was an abrupt increase in women aged 55–59 years while in post-menopausal women, OSA risk was relatively stable between 45 and 59 years old, before tending to increase at ages 60 and more (see Fig. 3).

Table 1. Crude number and weighted proportion of women and men in each age and menopausal category, based to their risk of having OSA (low-risk vs high-risk)

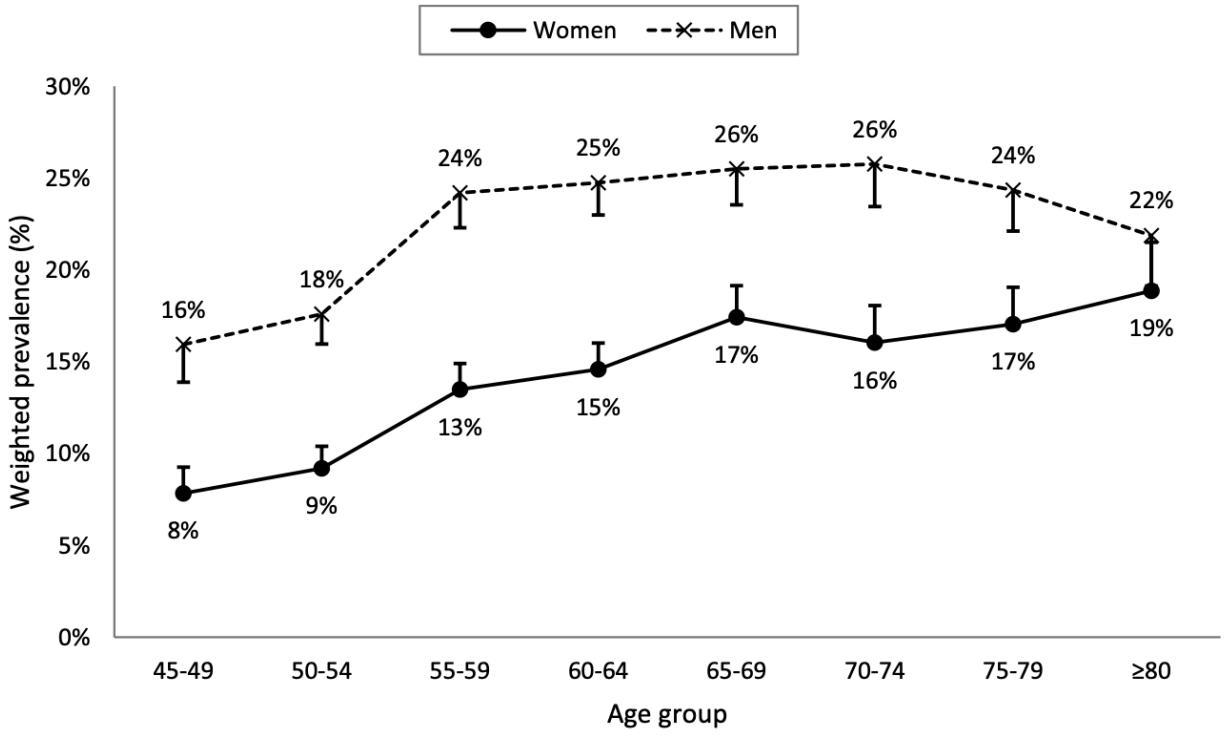
		Women				Men			
		Low-risk		High-risk		Low-risk		High-risk	
		N	(%)	N	(%)	N	(%)	N	(%)
Total *N*		11,790	··	2009	··	10,313	··	3098	··
Age (years)	45-49	1286	(16.3)	121	(9.4)	1045	(17.0)	205	(12.0)
	50-54	2048	(26.9)	230	(18.6)	1743	(30.1)	399	(23.9)
	55-59	1965	(14.5)	338	(15.5)	1493	(13.0)	494	(15.4)
	60-64	1974	(15.0)	374	(17.5)	1777	(15.5)	717	(19.0)
	65-69	1593	(10.3)	356	(14.9)	1418	(8.7)	509	(11.1)
	70-74	1078	(6.7)	217	(8.7)	1050	(6.2)	355	(8.0)
	75-79	1138	(6.4)	223	(9.0)	1115	(5.8)	318	(6.9)
	≥80	708	(4.0)	150	(6.4)	672	(3.7)	201	(3.8)
Post-menopausal status		7790	(68.7)	1343	(82.3)	··	··	··	··

Low-risk for OSA corresponds to a STOP-Obesity score < 3; High-risk for OSA corresponds to a STOP-Obesity score ≥ 3. Abbreviations: N number of participants, OSA obstructive sleep apnea.

Table 2. Prevalence (95% CI) of individual STOP-Obesity variables in women and men at low- and high-risk for OSA

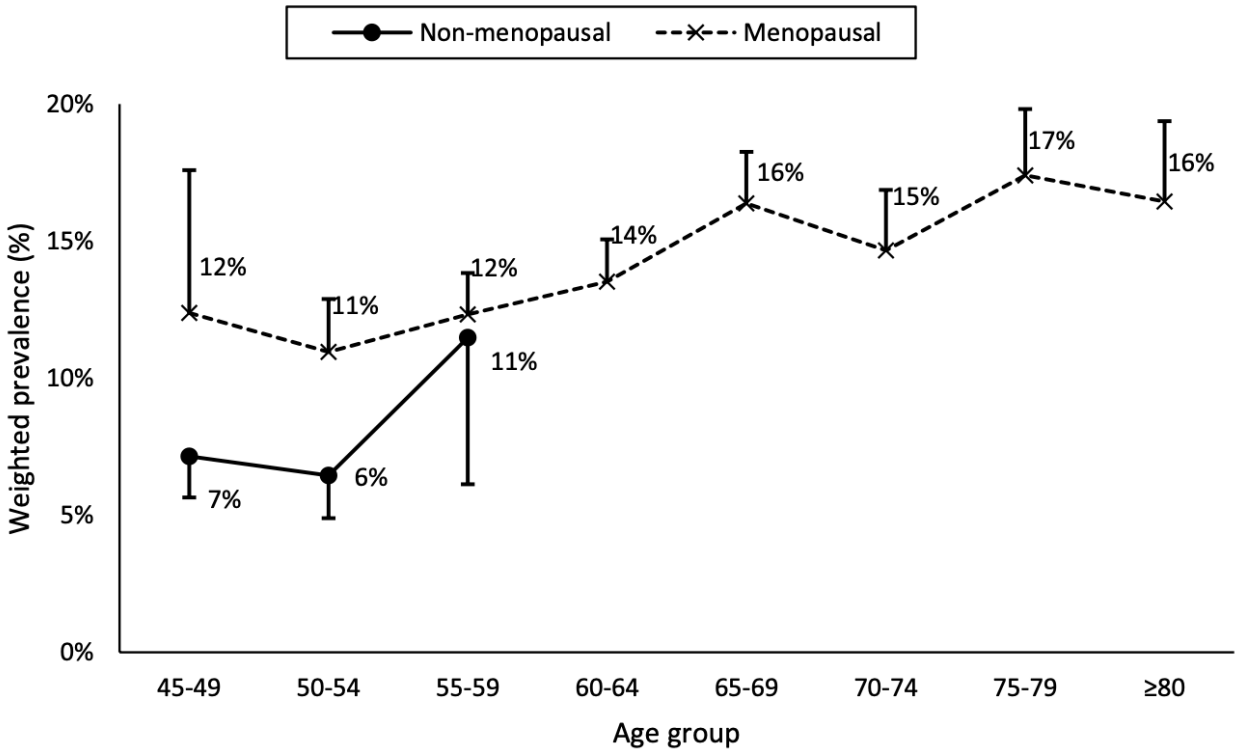
	Women		Men	
	Low-risk (N=11,790)	High-risk (N = 2009)	Low-risk (N=10,313)	High-risk (N = 3098)
S – Snoring	11.4 (10.2-12.6)	74.7 (73.1-76.3)	21.9 (20.7-23.1)	80.2 (79.0-81.4)
T – Tiredness, sleepiness or fatigue	4.0 (2.9-5.1)	33.8 (31.1-36.5)	4.3 (3.2-5.4)	25.3 (22.8-27.8)
O – Observed apnea	2.8 (1.8-3.8)	46.0 (43.1-48.9)	7.9 (6.9-8.9)	62.7 (59.8-64.6)
P – High blood pressure	20.9 (19.7-22.1)	78.0 (76.8-79.2)	21.2 (20.1-22.3)	71.9 (70.7-73.1)
Obesity – % body fat	68.5 (67.6-69.4)	98.0 (97.7 – 98.3)	59.9 (58.9-60.9)	95.8 (95.4 – 96.2)

Figure 2. Prevalence of participants at high-risk for OSA by age group in women (solid curve) and men (dashed curve)



Error bars represent the 95% confidence interval.

Figure 3. Prevalence of non-menopausal (solid curve) and post-menopausal (dashed curve) women at high- risk for OSA by age



Error bars represent the 95% confidence interval.

Extrapolation to the Canadian population

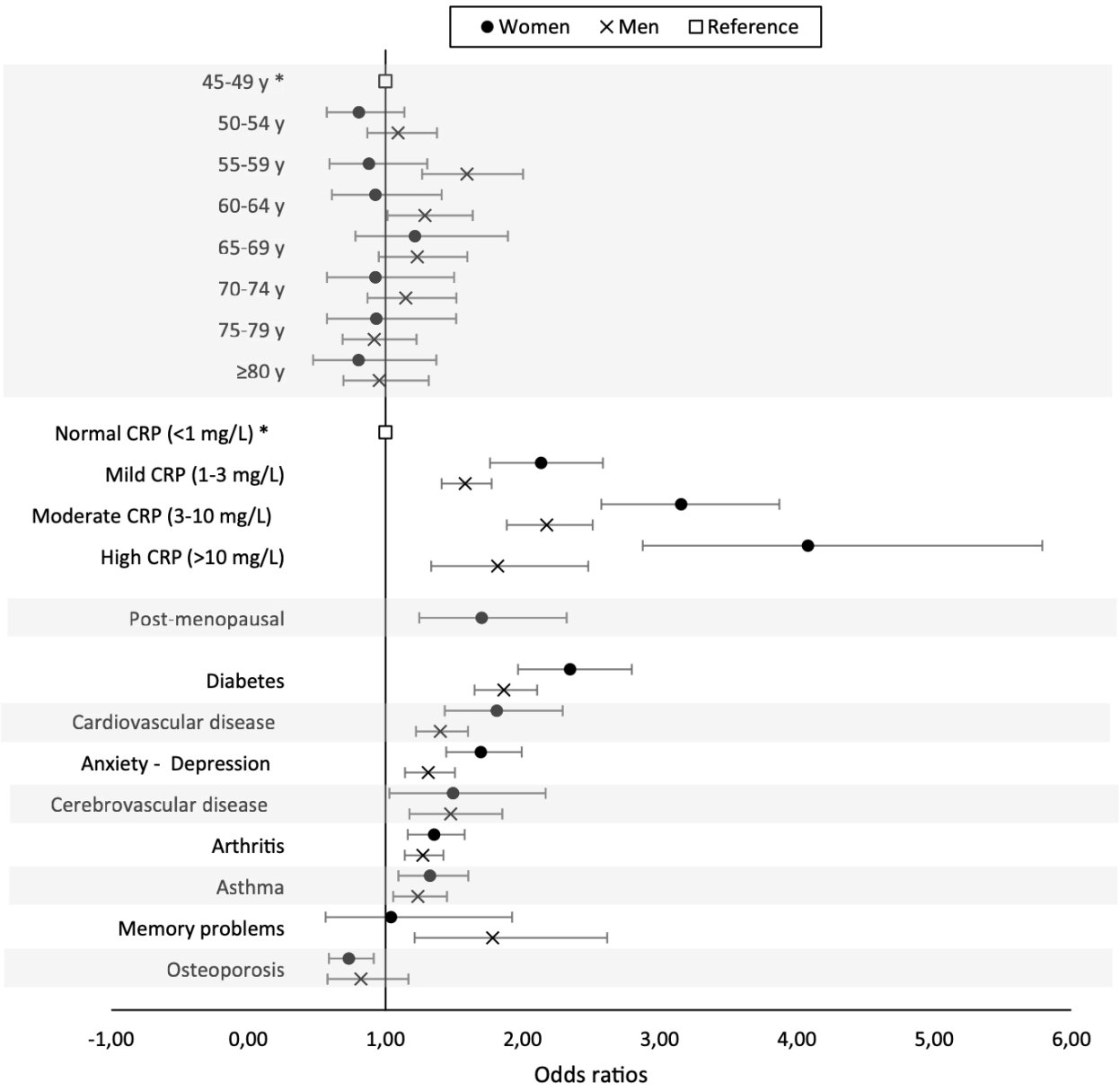
According to the 2016 Canadian Census, approximately five million men and 5.1 million women are aged 45–64 years old in Canada, and 2.9 million men and 3.4 million women are aged ≥ 65. Based on the CLSA cohort average age-specific prevalence of 11.6% in women and 21.4% in men aged 45–64, and 17.8% and 25.0% in older women and men, this corresponds to 1.2 and 1.8 million Canadian women and men, respectively, being at high-risk for OSA.

Association of clinical and subjective sleep variables with high-risk for OSA

Figure 4 illustrates the sex-specific association between individual comorbidities, level of inflammation and menopause (in women) and OSA risk, when adjusted for socio-demographic

and lifestyle determinants. Since age is considered as an important risk factor for OSA[15], we included it in Fig. 4. For clarity purposes, determinants without a significant association with OSA risk (i.e., COPD, hypothyroidism, dementia and Parkinson's disease) are not shown in Fig. 4 but are presented in the Supplementary Table S2. A level of hs-CRP ≥ 1 mg/L was the strongest independent factor associated with a high OSA risk. The association between systemic inflammation and OSA risk was 1.3 to 2.3 times stronger in women than in men. In fact, in women, the odds ratios increased with higher levels of inflammation, ranging from 2.1 (mild inflammation, hs-CRP between 1 and 3 mg/L) to 4.1 (high inflammation, hs-CRP ≥ 10 mg/L), while in men, they were similar for all hs-CRP levels (1.6, 2.2 and 1.8 for mild, moderate and high inflammation, respectively). Moreover, women and men with diabetes, cardio- and cerebrovascular comorbidities, anxio-depressive symptoms, arthritis and asthma were more likely to be considered at high-risk for OSA. Only in men were memory problems associated with high-risk for OSA, while osteoporosis was associated with lower risk for OSA only in women. Being post-menopausal was also strongly associated with high-risk for OSA.

Figure 4. Adjusted odds ratios for high-risk for OSA in women (black circles) and men (grey x-marks) of age, level of systemic inflammation, OSA-related comorbidities and menopausal status with a statistically significant association with risk for OSA



White squares represent the reference categories. Bars represent the 95% confidence intervals. Hypothyroidism, chronic obstructive pulmonary disease, dementia, and Parkinson's disease were included in the models but are not shown since they were not associated with high-risk for OSA.

Discussion

Our population-based study indicated that 13.1% of Canadian women (or 1.2 million) and 21.9% of Canadian men (or 1.8 million) aged ≥ 45 are at high-risk for presenting OSA and that this risk is 1.2- to twofold higher for middle-aged and older men than women. Cardiovascular diseases, diabetes mellitus, anxio-depressive symptoms, asthma, arthritis and high levels of hs-CRP conferred a greater risk for OSA. The association between systemic inflammation and OSA risk was stronger in women than men. Age alone was not associated with a higher risk for OSA, but comorbidities that typically become more prevalent with aging, as well as menopause in women, showed strong, independent associations with OSA risk. This is the largest population-based study to determine how OSA risk factors vary by sex.

The OSA prevalence estimated in this study is in the range reported in previous non-Canadian studies using screening questionnaires in younger and smaller cohorts (15–31%)[25–27]. However, our estimation is higher than in studies based on self-reported OSA diagnosis (4–14%)*22,23*, supporting the idea that OSA is often undiagnosed. The present estimated OSA prevalence was, however, lower than that observed using polysomnographic recordings in the same age range (19–36% in women, 35–85% in men)[19,20], suggesting that STOP questions might only capture moderate-to-severe OSA.

Both OSA expression and prevalence are sex-specific: women and men typically report different symptoms, and prevalence is higher in men than in women. We and others found that women with OSA or at high-risk for OSA are less likely to report snoring and witnessed apneas than men18,[43–45], either because they are embarrassed[45], or are not notified by a bed partner if they choke or stop breathing. Given that our stereotype of OSA symptoms is based on those reported by men, physicians need to consider women's atypical symptoms in order to successfully diagnose OSA in women. Our study highlights the need to adapt the concept of "typical" OSA symptoms in order to screen OSA efficiently in women and men. Accordingly, because of the alternative symptoms associated with OSA in women, the sensitivity of OSA screening questions / tools may not be optimal, resulting in an underestimation of the OSA

prevalence in women[46]. For example, since the symptoms presented in the STOP-Bang are based on men's, low scores on the STOP-Bang could, in fact, predict severe forms of OSA in women (sensitivity of 80% in women AHI > 30[47]). Developing and validating OSA screening questionnaires in older women is necessary to ensure a valid epidemiologic portrait of OSA prevalence is large cohort studies.

In women, although the estimated OSA prevalence increases with age, age per se was not independently associated with an increased OSA risk. In the CLSA and other cohorts[19,23,48–51], menopause was more strongly associated with OSA than age. However, in women aged 55–59 years from our sample, prevalence of OSA risk was similar in non-menopausal and menopausal women. This reflects the continuous nature of the menopausal process, which makes it difficult to classify women in two categories. As such, the lack of difference between the two groups in this age-range might be attributable to the fact that several non-menopausal women were possibly in perimenopause. This lack of difference could also be linked to the prevalence of obesity measured by the %BF and reaching its plateau at age 60, when all women are post-menopausal. Interestingly, studies[48,52,53] showed that morphological changes in post-menopausal women like increased waist and neck circumferences could account for their increased OSA risk.

Menopause-associated hormonal decreases might also affect OSA risk, where drops in progesterone and 17-ß-estradiol could act on the upper airway dilator muscles and affect ventilation control, airway collapsibility and respiratory drive[23,52,54–56]. Other studies showed that surgical menopause before 50 years old is independently associated with higher OSA prevalence[49] due to the abrupt post-surgical changes in ovarian hormone levels. OSA risk also tends to be lower in women taking hormone therapy following oophorectomy[49]. A modulating role of ovarian hormones on OSA risk, combined with its effect on morphological changes, is thus possible.

The steep increase in prevalence of high-risk for OSA in men over 55 years is likely related to the concomitant abrupt increased prevalence of diabetes, cardio- and cerebrovascular diseases, arthritis, as well as obesity between 50 and 59 years old. In both women and men, the

relationship between obesity and OSA is believed to be bidirectional[2,57]. While obesity is linked to several comorbid conditions aggravated by OSA (e.g., metabolic and cardiovascular diseases) with possible additive effects[16], OSA could lead to weight gain and obesity by affecting energy metabolism and provoking physical inactivity[2].

While the risk was similar in men for mild, moderate and high levels of systemic inflammation, increasing levels of inflammation in women conferred a greater OSA risk. Our results build on those reported in a pooled sample of the Nurses' Health Study, the Nurses' Health Study II, the Health Professionals Follow-up Study and the Multi-Ethnic Study of Atherosclerosis, in which high CRP levels were associated with increased OSA risk[58]. While inflammation could result from comorbidities and obesity, a recent systematic review and meta-analysis showed increased CRP levels in non-smoking OSA patients without other medical conditions compared to controls[59]. Moreover, results from our sensitivity analyses showed that systemic inflammation was independently associated with STOP-Obesity items other than obesity, especially in women. These results suggest that OSA risk is likely associated with systemic inflammation and that this association is independent of obesity[23,46,48,50,60–62].

Our results confirm that the prevalence of OSA-associated comorbidities is sex- and age-specific. With the exception of cardiovascular diseases, all comorbidities were more prevalent in women than men at high-risk for OSA, and increased with age in both sexes. Their increased prevalence with age could account for the non-linear association between age and high-risk for OSA, suggesting that the strength of the relationship between OSA risk and comorbidities would become more important than age as individuals acquire years. These results are consistent with our regression models, where age was not independently associated with high-risk for OSA in either women or men aged ≥ 65.

Complex bidirectional, causal relationships may link OSA to several comorbidities[16,63–67] and cardio- and cerebrovascular diseases[64,68]. Recent bidirectional models proposed that sympathetic excitation associated with cardiovascular diseases[69], diabetes[63], and stroke[67] exacerbates OSA, while OSA-induced hypoxia and sleep fragmentation generate sympathetic activation and inflammation leading to metabolic, cardio- and cerebrovascular diseases[69,70].

Since OSA and chronic medical conditions also share common risk factors such as obesity, age and physical inactivity[3,67], isolating the independent impact of each comorbidity on the presence of OSA is complicated. The association of each comorbidity with OSA is also likely amplified by the coexistence of different chronic conditions and / or obesity. In fact, the Nagahama study showed the concomitant presence of hypertension, diabetes or metabolic syndrome with obesity additively increased the prevalence of moderate- to-severe OSA[16].

Considering that most studies controlled for sex without exploring sex differences, our findings that risk factors differentially affect women and men should motivate further investigations of their reciprocity with OSA in both sexes.

The biggest strength of this study is its large sample size, and thus its power allowing the evaluation of sex- specific relationship between several comorbidities and risk factors, and OSA prevalence. The CLSA cohort was sampled to include a proportion of women and men representative of the actual Canadian population, allowing for the generalization of the prevalence of sex-specific risk factors to the Canadian population. It also enabled a precise evaluation of the prevalence of typical and atypical OSA symptoms, especially in women because their symptoms are not often standard and are underrepresented in the OSA literature. Our findings will increase awareness of the high prevalence of individuals at risk for OSA and its different clinical presentation in women, leading to the development of sex-specific prevention and treatment strategies.

A first limitation of this study pertains to the generalizability of our results to participants from other ethnicities, since more than 90% of the participants of our cohort were Caucasian. The CLSA did not over-sample ethnic and aboriginal populations to make the cohort representative of the Canadian population with respect to ethnic/cultural background[33]. Since the underlying pathogenesis for OSA risk could differ by ethnicity, our results might not be representative of non-Caucasian Canadians. Second, another limitation is the cross-sectional analyses which do not allow the determination of causal relationships between risk factors and OSA prevalence. It might also have introduced a non-response bias, since participants unclassified according to OSA risk were older, were more overweight / obese, and more often, women. Third, since neck

circumference was not collected in the CLSA cohort, we used the STOP-Obesity to conduct sex-specific analyses instead of the STOP-Bang, which has better predictive values[28,29]. Since neck circumference is a predictor as important as age[71], prevalence of high-risk for OSA was likely underestimated. Fourth, the CLSA neither asked participants whether they were diagnosed with OSA by a clinician, nor did it collect information about the use of continuous positive airway pressure (CPAP) therapy, which is the most common treatment for OSA. Some participants with OSA might have been misclassified as being at low-risk for OSA after reporting an absence of symptoms assessed by the STOP-Obesity because symptoms were reduced or eliminated by CPAP treatment. Fifth, we estimated prevalence based on the presence of self-reported OSA symptoms and lacked any objective recordings, such as in-laboratory polysomnography or home sleep apnea testing. However, we based our STOP-Obesity cutoff score on recent meta-analyses and studies comparing polysomnography data to STOP-Bang scores ≥ 3[30,31,36,37]. In fact, using this score to detect moderate-to-severe OSA with a cutoff of 3 showed a sensitivity between 88%[30] and 94%[31] with a negative predictive value of 93%[30]. Using this same cutoff on the STOP-Obesity (score range: 0 to 5) makes it more severe than on the STOP-Bang (score range: 0 to 8), and has the advantage of reducing the number of false negatives. Sixth, using the STOP-Obesity questionnaire dichotomizes participants as being at low- or high-risk for OSA, which does not account for all possible ranges of OSA.

Conclusion

This Canadian population-based study offers an updated portrait of middle-aged and older adults at high- risk for OSA. It confirms that being ≥ 55 years old, a male or a post-menopausal woman, overweight or obese, with cardiovascular diseases, diabetes, cerebrovascular disease, anxio-depressive symptoms and higher levels of inflammation are associated with a higher risk for OSA. Given the aging of the population, and increasing prevalence of obesity and chronic health conditions, OSA prevalence will likely continue increasing. An important barrier to OSA diagnosis and treatment is that patients often do not recognize the symptoms, while health professionals do not routinely screen for OSA and sleep issues. It is essential to raise awareness in the general public on the determinants associated with OSA and the impact of OSA for

women and men, and to incorporate OSA screening among standard clinical procedures. The CLSA cohort will be followed each 3 years for the next 20 years, allowing a continuing investigation of the temporal relationship between OSA and reported comorbid diseases and symptoms in middle-aged and older adults.

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Author contributions

C.T., J.L., G.M., M.B., and N.G. analyzed the data, interpreted the results, and wrote the manuscript. All authors critically reviewed the manuscript for intellectual content and data interpretation. N.G. supervised the study. Cynthia Thompson and Julie Legault contributed equally to the work and are thus co-first authors.

Competing interests

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corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Supplementary material

Supplementary methods

Participants in the CLSA comprehensive cohort were sampled using provincial healthcare registration databases (N = 4,129; 14%) or telephone random digit dialing (N = 25,968; 86%), and divided among seven participating provinces to ensure more precise estimates of various parameters within each national region. The response rate (contact rate * cooperation rate) was 9% for the healthcare registries sampling and 10% for the telephone random digit dialing sampling. Sampling was stratified by sex, age (45-54; 55-64; 65-74 and 75-85) and distance from the data collection sites. The CLSA cohort is representative of the eligible Canadian population and generalizable on many key variables, although the cohort was more educated, had a higher household income, a greater proportion of Canadian-born participants and a better self-reported appreciation of general health[1]. Also, the CLSA comprehensive cohort was recruited from urban regions located 25-50 km from the data collection sites, which limits the generalizability of our findings to populations living in more rural areas.

Sociodemographic and lifestyle-related control variables included age, sex, marital status, ethnicity, income, level of education, working status, smoking, alcohol consumption and level of physical activity, and are detailed in the supplementary material. Marital status was dichotomized as either “living with a spouse” or not, the latter including single, divorced and widowed participants. Ethnicity was dichotomized as “Caucasian” and “Non-Caucasian” based on the self-reported racial / cultural background. Income was stratified as <$20K, $20K-49,9K, $50K-99,9K, $100K-149,9K, >$150K CAD. Four categories were used for education level: less than secondary graduation; secondary graduation without post-secondary education; some post-secondary education; post-secondary education degree / diploma. Information related to working status was stratified as active worker, partly retired, or not working (completely retired / unemployed / housewives).

Lifestyle-related variables pertained to modifiable behaviors and included self-reported smoking, alcohol consumption, level of physical activity, hours of sleep per night and general sleep quality. Three categories were used for smoking status: current smoker, past smoker or

never smoker. Alcohol use was stratified based on the long-term health risk determined by the Canadian Guidelines for Low-Risk Drinking[2]: high-risk, >10 drinks for women and >15 drinks for men weekly; low-risk, 1-10 drinks for women and 1-15 drinks for men weekly; and no drinking. Physical activity was quantified using the Physical Activity Scale for the Elderly (PASE) questionnaire[3] which gives a global score in METS (metabolic equivalent of task) representing the individuals' daily energy expenditure, and quintile cut-off values specific for women and men were used. Self-reported sleep duration and quality duration were also considered. Participants who reported sleeping between 6 and 8 hours per night were considered "normal" sleepers, while those sleeping less than 6 hours or more than 8 hours per night were considered "short" and "long" sleepers, respectively. General sleep quality was assessed by the interviewer asking the multiple-choice question "How satisfied of dissatisfied are you with your current sleep pattern?", with suggested response categories being "Very satisfied", "Satisfied", "Neutral", "Dissatisfied" and "Very dissatisfied". Participants who answered being dissatisfied or very dissatisfied were considered having unsatisfactory sleep quality while the others were considered having satisfactory sleep.

Supplementary results

Supplementary table S1 shows detailed socio-demographic, clinical and lifestyle characteristics of women and men at low- and high-risk of OSA.

Supplementary table S2 presents the weighted prevalence odds ratios with 95% confidence intervals for high-risk of having OSA in women and men participants for all clinical variables included in the regression models.

Sensitivity analyses of OSA-related medical comorbidities and level of inflammation with respect to age

Because age was not independently associated with high-risk of OSA, we investigated how OSA-related medical comorbidities varied with age in women and men (Supplementary figure S1). Regardless of OSA risk, in both women and men, prevalence of cardiovascular and cerebrovascular comorbidities increased exponentially with age, while the increases in diabetes

and arthritis followed a logarithmic trend. Memory problems were more prevalent with increasing age, with an abrupt increase in men aged 70 years old and more. Osteoporosis was also more prevalent with age, especially in women as compared to men. The prevalence of depression-anxiety disorders decreased at ages 65 and over in both women and men, and the prevalence of asthma also decreased with age. The prevalence of moderate to high systemic inflammation (≥3 mg/L) also increased with age in both women and men. All changes reported from the sensitivity analyses were significant ($p<0.001$).

Sensitivity analyses to verify the association between systemic inflammation and OSA risk, independently of obesity

We conducted sex-specific linear regressions to test the independent association of each STOP-Obesity item with blood hs-CRP level (Supplementary table S3). The results showed that in women, the presence of snoring, tiredness and/or fatigue, observed apneas, high blood pressure and obesity were all significantly associated with higher hs-CRP levels. In men, observed apneas, high blood pressure and obesity were associated with hs-CRP levels, but not snoring nor tiredness.

Supplementary table S1: Crude number and weighted proportion of women and men presenting each socio-demographic, clinical and lifestyle determinant, based to their risk of having OSA (low vs high)

		Women				Men			
		Low-risk		High-risk		Low-risk		High-risk	
		N	(%)	N	(%)	N	(%)	N	(%)
Total N		11,790	-----	2009	-----	10,313	-----	3098	-----
Marital status	Living with a spouse	7493	73.2	1093	62.6	8127	82.9	2512	84.4
Ethnicity	Caucasian	10,843	91.7	1772	88.2	9376	90.4	2827	90.6
Education	No secondary degree	576	4.5	180	9.0	425	3.5	192	5.3
	Secondary degree	1155	9.5	251	12.7	192	7.4	274	8.4
	No post-secondary degree	832	6.5	202	9.3	698	6.1	250	6.7
	Post-secondary degree	9216	79.5	1373	69.0	8340	83.0	2378	79.6
Working status	Working	5408	56.3	745	44.2	4841	62.7	1258	54.1
	Partly retired	1091	8.6	169	8.8	1305	10.1	447	12.3
	Retired/ Unemployed	5232	35.2	1082	47.0	4153	27.2	1390	33.6
Income	<$20,000	614	5.4	122	6.3	512	5.0	168	6.6
	$20-50,000	2486	22.5	453	23.4	2175	22.3	620	21.7
	$50-100,000	3885	35.2	620	32.9	3429	35.7	1041	34.2
	$100-150,000	2136	19.1	358	19.2	1901	19.9	579	20.4
	>$150,000	358	17.7	341	18.2	1638	17.0	459	17.0
Smoking status	No smoker	6176	53.0	905	44.7	4824	50.5	1128	39.5
	Past smoker	4711	38.9	913	45.4	4533	39.7	1166	50.3
	Current smoker	903	8.1	191	9.6	955	9.8	307	10.2
Alcohol	No drinker	2475	21.5	578	31.9	1475	14.4	553	18.2
	Low-risk drinker	6537	68.0	882	58.1	6474	72.8	1733	67.7
	High-risk drinker	1089	10.6	154	10.0	1163	12.8	394	14.2
Sleep duration	Short (<6h)	1503	12.1	441	21.6	1028	10.3	493	16.2
	Normal (6-8h)	9586	81.9	1405	70.3	8812	67.7	2447	79.6
	Long (>8h)	676	6.0	150	8.1	457	3.9	148	4.2
Sleep quality	Satisfactory	8624	73.0	1217	59.5	8273	79.5	2187	69.8
Level of	Normal (<1	4222	42.7	313	18.5	4492	50.3	879	33.4

inflammation (hs-CRP)	mg/L)								
	Mild (1-3 mg/L)	3842	35.3	683	38.5	3446	35.8	1216	41.5
	Moderate (3-10 mg/L)	2135	19.3	638	35.3	1279	11.7	632	22.1
	High (>10 mg/L)	320	2.7	149	7.8	223	2.2	94	3.0
Comorbidities	Diabetes	1386	10.6	642	30.4	1580	12.9	969	27.2
	Cardiovascular	908	6.4	346	15.6	1491	11.2	728	19.6
	Cerebrovascular	365	2.4	141	6.4	400	2.7	214	5.2
	Anxiety / Depression	2620	22.1	767	39.5	1442	14.4	692	23.1
	Memory problems	152	1.2	49	2.9	136	1.2	81	2.9
	COPD	615	4.3	217	10.7	416	3.3	224	5.8
	Asthma	1670	14.2	456	23.0	1052	10.8	392	13.9
	Arthritis	4474	32.8	1079	51.2	2668	21.9	1095	31.7
	Hypothyroidism	2193	17.7	485	24.3	595	5.2	222	7.1
	Dementia	19	0.2	7	0.3	24	0.1	8	0.3
	Osteoporosis	1764	12.2	297	13.9	241	1.8	77	2.2
	Parkinson's disease	39	0.3	6	0.2	57	0.5	14	0.3
PASE score	Quintile 1	2440	18.0	652	30.3	2319	17.8	904	25.1
	Quintile 2	2542	19.6	476	22.6	2384	19.8	724	20.9
	Quintile 3	2406	20.1	354	18.7	2143	20.3	630	20.8
	Quintile 4	2197	21.0	271	14.3	1803	20.9	462	17.8
	Quintile 5	2126	21.4	232	14.1	1570	21.3	353	15.4

Notes: Low-risk of OSA corresponds to a STOP-Obesity score <3; High-risk of OSA corresponds to a STOP-Obesity score ≥3. Low-risk drinker: 1-10 drinks for women and 1-15 drinks for men, weekly. High-risk drinker: >10 drinks for women and >15 drinks for men, weekly. PASE quintiles use sex-specific cutoff values.

Abbreviations: OSA: Obstructive sleep apnea; COPD: Chronic obstructive pulmonary disease; PASE: Physical activity scale for the elderly; hs-CRP: high-sensitivity C-reactive protein.

Supplementary table S2: Sex-specific weighted prevalence odds ratios with 95% confidence intervals for high-risk of having OSA in relation to age, menopausal status, comorbidities and level of systemic inflammation (hs-CRP)

Factor		Women		Men	
		Beta	OR (95%CI)	Beta	OR (95%CI)
Age	45-49 *	Reference category		Reference category	
	50-54	0.81	0.57 – 1.14	1.09	0.87 – 1.38
	55-59	0.88	0.59 – 1.31	1.59	1.27 – 2.00
	60-64	0.93	0.61 – 1.41	1.29	1.01 – 1.64
	65-69	1.22	0.78 – 1.89	1.23	0.95 – 1.60
	70-74	0.93	0.57 – 1.50	1.15	0.87 – 1.52
	75-79	0.93	0.57 – 1.52	0.92	0.69 – 1.23
	≥80	0.80	0.47 – 1.37	0.96	0.69 – 1.32
Level of inflammation (hs-CRP)	Normal (<1 mg/L) *	Reference category		Reference category	
	Mild (1-3 mg/L)	2.13	1.76 – 2.59	1.58	1.41 – 1.77
	Moderate (3-10 mg/L)	3.16	2.57 – 3.87	2.18	1.88 – 2.51
	High (>10 mg/L)	4.08	2.88 – 5.79	1.82	1.82 – 2.48
Post-menopausal		1.70	1.25 – 2.32	-----	-----
Comorbidities	Diabetes	2.35	1.97 – 2.80	1.86	1.65 – 2.11
	Cardiovascular	1.81	1.43 – 2.29	1.40	1.22 – 1.60
	Anxiety- Depression	1.70	1.44 – 1.99	1.31	1.14 – 1.51
	Cerebrovascular	1.49	1.03 – 2.17	1.48	1.18 – 1.85
	Arthritis	1.35	1.16 – 1.58	1.27	1.14 – 1.42
	Asthma	1.33	1.09 – 1.60	1.24	1.06 – 1.45
	Memory problems	1.04	0.56 – 1.92	1.78	1.21 – 2.62
	Osteoporosis	0.73	0.59 – 0.91	0.82	0.58 – 1.18
	Hypothyroidism	1.17	0.98 – 1.39	1.00	0.81 – 1.23
	Dementia	0.77	0.17 – 3.47	0.59	0.18 – 1.96
	COPD	1.13	0.85 – 1.51	1.09	0.86 – 1.37
	Parkinson’s disease	1.65	0.51 – 5.33	0.69	0.32 – 1.46

Notes: Asterisks indicate the reference categories.

Abbreviations: OSA: obstructive sleep apnea; hs-CRP: high sensitivity C-reactive protein; OR: odds ratio.

Supplementary table S3: Sex-specific, weighted multiple linear regressions testing the association of signs and symptoms used in the STOP-Obesity score to estimate risk of OSA, and blood hs-CRP

		Beta (95% CI)	SE	t	p
Women	Snoring [S]	0.63 (0.42 – 0.85)	0.11	5.78	<0.001
	Tiredness, sleepiness, fatigue [T]	0.54 (0.22 – 0.86)	0.16	3.31	0.001
	Observed apneas [O]	1.08 (0.78 – 1.39)	0.16	6.92	<0.001
	High blood pressure [P]	0.67 (0.48 – 0.86)	0.10	6.97	<0.001
	% body fat >35% [Obesity]	1.50 (1.31 – 1.70)	0.10	15.04	<0.001
Men	Snoring [S]	-0.05 (-0.21 – 0.12)	0.09	-0.54	0.591
	Tiredness, sleepiness, fatigue [T]	0.12 (-0.16 – 0.40)	0.14	0.82	0.410
	Observed apneas [O]	0.32 (0.12 – 0.51)	0.10	3.13	0.002
	High blood pressure [P]	0.48 (0.32 – 0.65)	0.09	5.67	<0.001
	% body fat >25% [Obesity]	0.88 (0.71 – 1.06)	0.09	10.04	<0.001

Abbreviations: OSA: obstructive sleep apnea; hs-CRP: high sensitivity C-reactive protein; CI: confidence interval; SE: standard error.

SUPPLEMENTARY FIGURE CAPTION

Figure S1: Prevalence of A) diabetes; B) cardiovascular diseases; C) anxiety-depression; D) cerebrovascular diseases; E) arthritis; F) asthma; G) memory problems; H) osteoporosis; and I) moderate to high levels of inflammation in women (dark curve) and men (light curve) according to the age group. Data represent prevalence obtained in all women and men, regardless of their risk of having OSA.

2.2 Article 3

Article 3: Association between risk of obstructive sleep apnea, inflammation and cognition after 45 years old in the Canadian Longitudinal Study on Aging

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*Ces autrices ont contribué de manière équivalente à cet article.

Contribution : Pour cet article, j'ai procédé à une revue de la littérature, interprété les résultats d'analyse, rédigé et révisé de manière critique le manuscrit.

Abstract

Background: The association between obstructive sleep apnea and cognitive functioning is not yet fully understood and could be influenced by factors such as sex, age and systemic inflammation. We determined the sex- and age-specific association between obstructive sleep apnea risk and cognitive performance, and the influence of systemic inflammation on this association.

Methods: We included 25,899 participants from the Canadian Longitudinal Study of Aging comprehensive cohort, aged 45-85 years (51% women). We conducted sex- and age-specific (45-59; 60-69; ≥70) general linear models between obstructive sleep apnea risk and cognitive scores, and tested the moderating and mediating effects of high-sensitivity C-reactive protein levels. Obstructive sleep apnea risk was estimated by combining the STOP and whole-body fat percentage. Cognitive tests assessed episodic verbal memory, executive functions and psychomotor speed. Levels of high-sensitivity C- reactive protein were obtained through blood samples.

Results: Higher obstructive sleep apnea risk was associated with poorer episodic memory in women aged 45e59 years, and poorer executive function ($p < 0.05$ on multiple tests) in women aged 45e59 and 60e69 years. No such association was found in men. High-sensitivity C-reactive protein levels mediated some associations between obstructive sleep apnea risk and executive function in women and men aged <70 years.

Conclusions: Being at high-risk for obstructive sleep apnea is associated with poorer cognition in women aged <70 years. These associations were partly mediated by systemic inflammation. These results underscore the importance of obstructive sleep apnea diagnosis, treatment and appropriate follow-up, particularly in middle-aged women who might already show signs of early cognitive impairments.

1. Introduction

Obstructive sleep apnea (OSA) is characterized by repeated complete or partial upper airway obstructions, resulting in sleep fragmentation and intermittent hypoxemia.[1] The prevalence of

OSA, when defined with an apnea-hypopnea index ≥15, ranges from 6-17% in the general adult population, and can reach up to 49% in adults aged 40-85 years.[2] However, OSA is underdiagnosed, with only 3% of adults reporting a formal diagnosis[3] while a quarter are at risk[4] according to a Canadian study. OSA-related sleep fragmentation and intermittent hypoxemia induce oxidative stress, neuroinflammation and edema, which could interfere with brain plasticity and neurogenesis, and affect brain structure (e.g. the prefrontal and parietal cortex, the hippocampus) and function (episodic memory, attention and executive functions).[5] Consequently, efforts were recently made to verify whether OSA is linked to abnormal cognitive decline in large cohorts of late middle-aged and older adults. Yet, results are not clear: an association between OSA and cognition was observed in several studies, but not in others.[6] These heterogeneous results could be explained by moderating factors that increase or decrease the deleterious impact of OSA on cognition.[7] These factors include, among others, age, sex and systemic inflammation that may interact with OSA to alter cognitive function. As such, a study of 8,059 adults aged 45-74 years showed a stronger association between OSA and brain health in women compared to men, particularly in those aged 45-54 years.[8] Furthermore, a recent study of 291 participants suggested that having high levels of systemic inflammation increases the predictive value of poorer nighttime sleep quality on dementia risk.[9] Characterizing vulnerability and protective factors could improve the identification of OSA patients at high-risk of cognitive dysfunction.

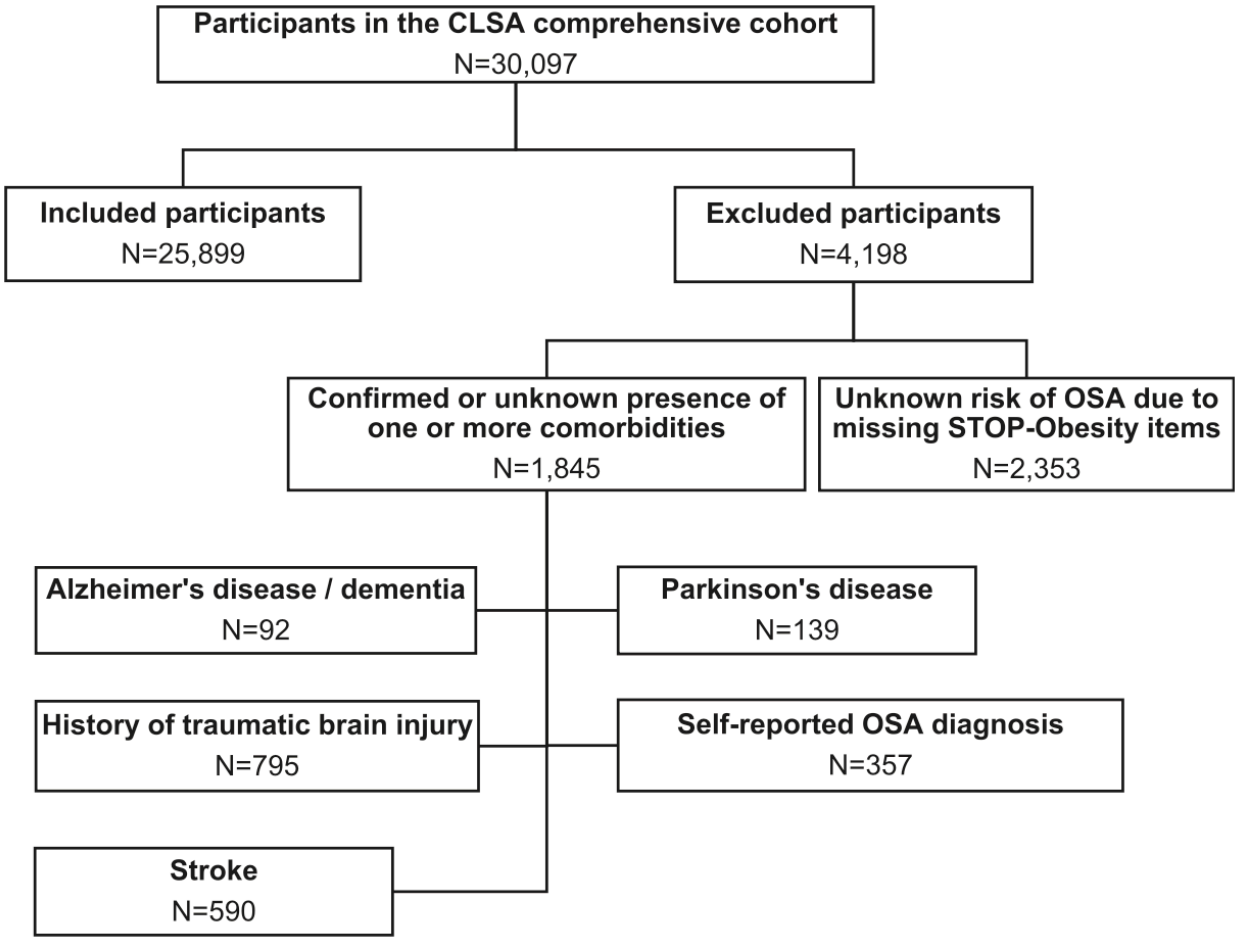
The present study aimed at determining the age and sex-specific independent relationship between OSA risk, as determined by the STOP score[10] combined with the whole-body fat percentage measured with the Hologic Discovery A Dual Energy X-Ray Absorptiometry (DXA), and cognitive performance in a cohort of adults aged 45-85 years old (N=25,899) from the Canadian Longitudinal Study on Aging (CLSA). We also investigated whether the level of systemic inflammation mediates this relationship. We hypothesized that a stronger association between higher OSA risk and poorer cognitive performance will be observed in younger (e.g., middle-aged) participants, specifically women, and in individuals with higher levels of inflammation.

2. Material and methods

2.1 Study design and participants

The CLSA is a national population-based, prospective study on healthy aging.[11] Participants were aged 45-85 years, fluent in English or French, living within 25 km of a data collection site and able to give their informed consent and understand the instructions. They were recruited using provincial healthcare registration databases (N=4,129; 9% response rate) or telephone random digit dialling (N=25,968; 10% response rate). This study used baseline data collected between 2011 and 2015 from 30,097 participants who answered questionnaires during computer-assisted interviews, and underwent physical examinations including Hologic Discovery A Dual Energy X-Ray Absorptiometry (DXA), neuropsychological assessments and blood collection. Participants with dementia, neurologic condition or traumatic brain injury with loss of consciousness $\geq$20 minutes, or reporting sleep apnea were excluded (Figure 1).

Figure 1: Flowchart describing the inclusion and exclusion of participants for analyses based on the STOP-Obesity score



The CLSA is overseen by a collaborative Research Ethics Board forum chaired at McMaster University. Participation in the CLSA cohort is voluntary and all individuals provided written informed consent. Our study was approved by the Research Ethics Board of the Centre intégré universitaire de santé et services sociaux du Nord-de-l'Île-de-Montréal (REB 2018-1584). We used the STROBE cross-sectional reporting guidelines (von Elm et al., n.d.).

2.2 Measures

2.2.1 Classification for OSA risk

Four questions assessed the self-reported presence of OSA risk factors. Yes/no questions assessed **S**noring, **O**bserved apneas and high blood **P**ressure (confirmed with current intake of hypertensive medication). Daytime **T**iredness, sleepiness or fatigue was considered present if experienced ≥3 times per week. This forms the STOP score, which has a sensitivity of 79.5% and specificity of 48.6% in detecting severe OSA when participants scoring ≥2 were considered at high-risk for OSA.[10] Adding age, sex, body mass index (BMI) and neck circumference (unavailable in the CLSA) to the STOP score increases its sensitivity to 100% in detecting severe OSA.[10] Rather than including age and sex, we stratified our analyses for age and sex. Since BMI underestimates the prevalence of obesity as compared to body fat percentage (%BF) in the CLSA,[13] and DXA-measured variables are associated with worse OSA indices in women and men,[14] we added the %BF derived from DXA to the STOP score.[15] Women with a %BF>35% and men with a %BF>25% were considered obese[16] and given an additional point. By adding an obesity measure, our STOP-Obesity score had a maximum value of 5. According to recent systematic reviews, a STOP-Bang score of 3 or more has a sensitivity between 88%[17] and 94%[18] for detecting moderate-to-severe OSA, and a negative predictive value reaching 93%[17]. As a proxy for the threshold of 3 of the full STOP-Bang score[10], participants scoring ≥3 were considered at high-risk for OSA. Participants with missing STOP items or unavailable %BF were excluded (Figure 1).

2.2.2 Cognitive performance assessment

The neuropsychological tests administered in a standardized order by CLSA trained interviewers assessed three domains: verbal memory (Rey Auditory Verbal Learning Test (RAVLT)), executive functions (Animal Fluency test, Mental Alternation test, Stroop test (Victoria version) and Controlled Oral Word Association test) and psychomotor speed (Choice reaction time; see Table 1 for details).[26]

Tableau 1. Description of neuropsychological testing battery

Cognitive domains	Cognitive functions	Tests	Tasks	Outcomes
Verbal memory	Memory, learning and retention	Rey Auditory Verbal Learning Test (RAVLT), immediate and 5-min delayed recall[20]	Recall as many words from a 15 common noun list heard five consecutive times (one word per second). The number of words remembered in the first immediate recall trial (RAVLT immediate recall) and at 5-min delayed recall trial (RAVLT 5-min recall) were reported.	Number of words
Executive functions	Semantic word fluency	Animal Fluency test (AFT)[21]	Give as many animal names as possible over a 60-s trial	Number of words
	Mental flexibility and processing speed	Mental Alternation test (MAT)[22]	Give as many alternations of matched pairs of numbers and letters over a 30-s trial	Number of correct matched pairs
	Mental speed and control, inhibition, attention	Stroop test Victoria version[23,24]	Condition 1: name the color of dots printed on a card Condition 2: name the color of the words printed on a card Condition 3: name the color of the ink in which a color word is printed on a card	Time in seconds for conditions 1, 2 and 3
			Interference index i) Low: time for condition 2 / time for condition 1 ii) High: time for condition 3 / time for condition 1	Absolute score
	Phonemic word fluency	Controlled Oral Word Association test (COWAT)[25]	Give as many words beginning with a specific letter (F-, A-, S-) during three 60-s trials (one trial per letter)	Total number of words
Psychomotor speed	Psychomotor speed	Choice reaction time (CRT)[26]	Touch an interactive computer screen as quickly as possible at	Mean latency over

			the place a target appears in one of the two blank boxes presented.	60 trials, in milliseconds

2.2.3 Sociodemographic, lifestyle-related and medical comorbidities

Covariables were selected based on the literature, clinical relevance, and availability in the CLSA (see supplementary material). Sociodemographic variables included age, marital status, ethnicity, income, education and working status. Lifestyle-related variables included smoking, alcohol consumption, physical activity, self-reported average hours of sleep per night and general sleep quality. Clinical variables included chronic health conditions diagnosed by a health professional which were expected to, or have already lasted, ≥6 months, and were self-reported: cardiovascular diseases, diabetes mellitus, chronic obstructive pulmonary disease, asthma and anxious-depressive symptoms. Depressive symptoms were also assessed using the 10-item Center for Epidemiologic Studies Depression scale (CESD-10, score ≥10) screening tool.[27] The concentration of high-sensitivity C-reactive protein (hs-CRP)[28,29] was categorized as normal (<1 mg/L), mild (1-3 mg/L), moderate (3-10 mg/L) and high (>10 mg/L).[30,31] We also add functional status assessed using the Older Americans' Resources and Services multidimensional functional assessment questionnaire,[32] health perception and menopausal status (non- or post-menopausal).

2.3 Analysis

We weighted the descriptive analyses using the inflation weights, and the General Linear Model (GLM), moderation and mediation analyses using the analytic weights provided by CLSA[33] to account for possible biases due to the age-stratified sampling strategy, as well as unequal selection and non-response probability.

Sex-specific, age-stratified (middle-aged, 45-59; younger-old, 60-69; older-old, ≥70)[34] univariate associations of OSA risk and sociodemographic, lifestyle-related and clinical variables were tested using chi-square tests (categorical variables) and Student's t-tests (continuous variables). Age groups were determined based on the literature.[34]

Sex-specific, age-stratified associations between OSA risk and scores on neuropsychological tests were assessed using GLM. Model 1 accounted for socio-demographic variables; lifestyle-related variables were added in Model 2; and clinical variable were added to Model 3 (fully adjusted). Results for all models are presented in eTable 3. We confirmed lack of multicollinearity between covariables using pairwise Pearson's correlations.

We used Hayes' SPSS Process macro version 3.4 to conduct sex-specific, age-stratified moderation (Figure 2) and mediation (Figure 3) analyses, adjusted all variables previously entered in the GLM. To test the moderating effect of hs-CRP levels on the relationship between OSA risk and cognitive scores, we used Process macro model 1 multiple regression with mean centering. Simple mediation analyses using Process macro model 4 returned the unstandardized regression coefficients between the model's variables, representing the total (c) and direct effects (a, b, c'). Mediation results were interpreted if the unstandardized regression coefficients associated with paths "c", "a" and "b" were statistically significant (see Supplementary materials).

The effect of OSA risk on the level of hs-CRP as a mediator is illustrated as path "a", the effect of hs-CRP as a mediator on cognitive performance is path "b". Path "a" multiplied by path "b" represents the indirect effect of hs-CRP on cognitive outcomes. Path "c" is the total effect of risk of OSA on cognitive performance, and corresponds to the sum of the direct (path " c' ") and indirect (path "a" * path "b") effects.

Sensitivity analyses are described below, but globally assessed whether i) using the validated STOP score alone or combined with other measures of obesity (waist-to-hip ratio;[35] BMI≥30 kg/m;[36] BMI≥35 kg/m;[10] fat mass index),[37] ii) including participants with a self-reported OSA diagnosis; iii) not controlling for sleep quality/duration, health perception and functional status modified the associations between OSA risk and cognition. We also verified whether performances on neuropsychological tests were different between non- and post-menopausal women and tested whether menopausal status and education moderated the relationship between OSA risk and cognition.

Analyses used all participants for whom the variables of interest were available, without imputing missing data. Statistical analyses were performed using IBM SPSS Statistics version 25.0 (Chicago, IL, USA). The level of significance was set at $p<0.05$, after family-wise false-discovery rate (FDR) correction.

Figure 2 : Conceptual representation of the simple moderation model using the level of hs-CRP

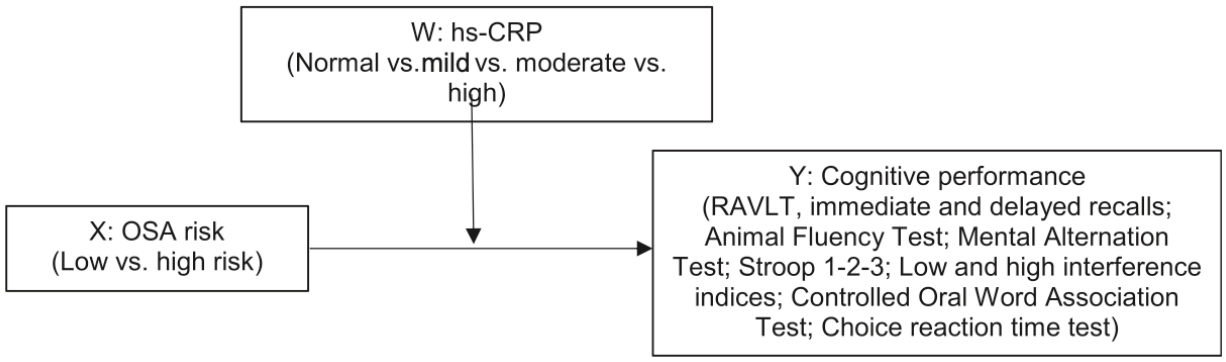
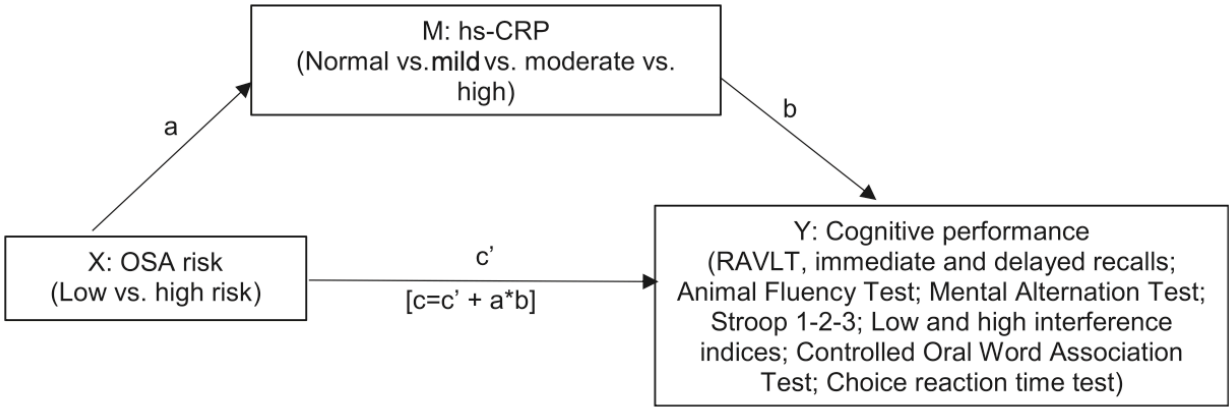


Figure 3 : Conceptual representation of the simple mediation model using the level of hs-CRP



3. Results

We included 25, 899 participants in our analyses (see eTable 1). Table 2 presents the characteristics and phenotype of OSA symptoms and risk factors of women and men stratified by age. eTable 2 presents the sex- and age-specific socio-demographic, lifestyle-related and clinical characteristics that were adjusted for in the statistical analyses.

3.1. Age-stratified differences in cognitive performance based on OSA risk and sex

When adjusting for socio-demographic, lifestyle-related and clinical variables, women aged 45e59 at high-risk for OSA had poorer performances on the Rey Auditory Verbal Learning Test (RAVLT) immediate and 5-min recalls, Animal Fluency test, Mental Alternation test, Stroop 2 and 3, and Stroop low and high- interference index compared to those at low-risk for OSA. In women aged 60e69 at high-risk for OSA, poorer performances on the Mental Alternation Test, Stroop 2 and Stroop low-interference index were also observed compared to those at low-risk for OSA (Table 3). In women aged ≥70 years old and men of all ages, no association was found between OSA risk and cognitive performance.

Table 2. Description of the sample according to the age group and risk for OSA

		Middle-aged: 45-59 years old			Younger-old: 60-69 years old			Older-old: 70-85 years old		
		Low-risk	High-risk	p	Low-risk	High-risk	p	Low-risk	High-risk	p
WOMEN	**Group size,** N (%)	5174 (90.3)	653 (9.7)	------	3454 (84.8)	685 (15.2)	------	2775 (83.1)	555 (16.9)	------
	Snoring [S], N (%)	639 (12.6)	507 (80.8)	<0.001	370 (11.3)	515 (77.8)	<0.001	180 (6.8)	326 (61.1)	<0.001
	Daytime tiredness, sleepiness or fatigue [T], N (%)	202 (4.0)	218 (31.7)	<0.001	123 (3.3)	186 (28.1)	<0.001	120 (5.0)	221 (45.2)	<0.001
	Observed apneas [O], N (%)	154 (3.0)	316 (50.0)	<0.001	79 (2.5)	311 (48.7)	<0.001	54 (1.9)	180 (33.1)	<0.001
	High blood pressure [P], N (%)	691 (12.5)	457 (69.9)	<0.001	917 (26.3)	551 (79.0)	<0.001	1122 (40.8)	501 (90.7)	<0.001
	Percentage body fat > 35% [Obesity], N (%)	3219 (61.2)	627 (98.5)	<0.001	2615 (79.0)	656 (97.2)	<0.001	2040 (78.9)	540 (99.0)	<0.001
	Age, years (mean ± SD)	52.0 ± 3.8	52.8 ± 3.9	<0.001	64.0 ± 2.7	64.2 ± 2.7	<0.001	76.0 ± 4.2	76.4 ± 4.3	<0.001
	Post-menopausal, N (%)	2585 (48.2)	367 (61.3)	<0.001	2859 (100.0)	519 (100.0)	>0.99	2087 (100.0)	381 (100.0)	>0.99
	Education									
	No secondary degree, N (%)	106 (2.0)	21 (3.2)		138 (4.6)	58 (9.7)		303 (12.6)	92 (19.2)	
	Secondary degree, N (%)	398 (7.7)	77 (12.1)	<0.001	363 (11.0)	84 (13.1)	<0.001	356 (13.1)	76 (13.6)	<0.001
	No post-secondary degree, N (%)	300 (5.5)	58 (8.0)		262 (7.4)	72 (10.3)		242 (8.7)	56 (9.5)	
	Post-secondary degree, N (%)	4367 (84.8)	497 (76.8)		2687 (76.9)	468 (67.0)		1870 (65.6)	331 (57.8)	
	C-reactive protein									

	levels									
	Normal, (<1 mg/L), N (%)	2147 (47.9)	110 (19.7)		1173 (38.0)	92 (16.6)		782 (32.7)	96 (19.7)	
	Mild, (1-3 mg/L), N (%)	1552 (32.7)	191 (34.2)	<0.001	1190 (37.8)	233 (39.0)	<0.001	980 (40.6)	218 (45.7)	<0.001
	Moderate, (≥3 mg/L), N (%)	803 (16.7)	222 (38.0)		663 (21.6)	221 (35.0)		588 (23.7)	152 (29.4)	
	High, (≥10 mg/L), N (%)	133 (2.7)	52 (8.1)		91 (2.5)	61 (9.4)		78 (3.0)	26 (5.2)	
MEN	**Group size,** N (%)	4102 (81.5)	1034 (18.5)	------	3014 (75.2)	1056 (24.8)	------	2616 (76.2)	781 (23.8)	------
	Snoring [S], N (%)	980 (25.7)	865 (85.7)	<0.001	539 (18.8)	805 (79.7)	<0.001	296 (11.9)	502 (65.8)	<0.001
	Daytime tiredness, sleepiness or fatigue [T], N (%)	165 (4.0)	215 (20.4)	<0.001	119 (4.1)	232 (23.2)	<0.001	115 (5.3)	254 (37.2)	<0.001
	Observed apneas [O], N (%)	337 (8.8)	685 (68.0)	<0.001	19388 (7.1)	636 (62.2)	<0.001	154 (6.1)	394 (50.2)	<0.001
	High blood pressure [P], N (%)	611 (13.8)	677 (64.4)	<0.001	825 (26.6)	823 (75.8)	<0.001	1016 (39.0)	652 (84.6)	<0.001
	Percentage body fat > 25% [Obesity], N (%)	2260 (54.2)	979 (95.2)	<0.001	1918 (64.5)	1009 (97.0)	<0.001	1911 (74.8)	748 (97.0)	<0.001
	Age, years (mean ± SD)	51.8 ± 3.7	52.5 ± 3.8	<0.001	63.7 ± 2.8	63.9 ± 2.8	<0.001	76.1 ± 4.3	75.6 ± 4.1	<0.001
	Education									
	No secondary degree, N (%)	85 (2.1)	34 (2.9)		95 (3.1)	62 (5.0)		203 (8.1)	75 (10.9)	
	Secondary degree, N (%)	280 (6.8)	90 (8.3)	<0.001	240 (8.0)	90 (8.2)	<0.001	252 (9.0)	70 (8.0)	<0.001
	No post-secondary degree,	239 (5.6)	75 (6.0)		223 (7.2)	87 (7.8)		194 (6.7)	67 (6.6)	

	N (%)									
	Post-secondary degree, N (%)	3498 (85.6)	835 (82.8)		2451 (81.7)	815 (79.0)		1952 (76.2)	567 (74.6)	
	C-reactive protein levels									
	Normal, (<1 mg/L), N (%)	1972 (54.2)	306 (35.5)		1312 (47.4)	282 (32.2)		976 (40.9)	226 (31.3)	
	Mild, (1-3 mg/L), N (%)	1298 (33.8)	393 (40.5)	<0.001	1025 (38.4)	429 (41.4)	<0.001	950 (40.2)	306 (43.2)	<0.001
	Moderate, (≥3 mg/L), N (%)	428 (10.4)	217 (21.5)		374 (12.0)	206 (22.4)		386 (15.4)	154 (22.5)	
	High, (≥10 mg/L), N (%)	66 (1.7)	27 (2.6)		60 (2.2)	37 (4.0)		76 (3.5)	25 (3.1)	

N are crude numbers, proportions are weighted to account for the sampling strategy.

SD: standard deviation

Table 3. Scores on the neuropsychological tests according to risk of having OSA

	Neuropsychological test	Middle-aged: 45-59 years old		Younger-old: 60-69 years old		Older-old: 70-85 years old	
		Low risk	High risk	Low risk	High risk	Low risk	High risk
WOMEN	**Group size,** N (%)	5174 (90.3)	653 (9.7)	3454 (84.8)	685 (15.2)	2775 (83.1)	555 (16.9)
	RAVLT Immediate recall						
	Adjusted model	6.91 (6.85 – 6.96)	6.68 (6.50– 6.85)	6.44 (6.36 – 6.52)	6.45 (6.24 – 6.66)	5.51 (5.42 – 5.60)	5.55 (5.32 – 5.79)
	Δ	-0.23 (-0.42 – -0.04)*		0.01 (-0.24 – 0.22)		0.04 (-0.21 – 0.30)	
	RAVLT 5-min recall						
	Adjusted model	5.40 (5.34 – 5.46)	5.15 (4.95 – 5.35)	4.71 (4.62 – 4.80)	4.52 (4.27 – 4.76)	3.65 (3.54 – 3.76)	3.68 (3.41 – 3.94)
	Δ	-0.25 (-0.47 - -0.03)*		-0.19 (-0.46 – 0.07)		0.03 (-0.26 – 0.31)	
	Animal Fluency test						
	Adjusted model	23.07 (22.90 – 23.24)	22.40 (21.86 – 22.95)	21.11 (20.86 – 21.36)	20.79 (20.16 – 21.41)	18.22 (17.94 – 18.50)	17.88 (17.18 – 18.58)
	Δ	-0.67 (-1.25 - -0.09)*		-0.32 (-1.01 – 0.36)		-0.34 (-1.10 – 0.41)	
	Mental Alternation test						
	Adjusted model	28.76 (28.53 – 28.99)	27.84 (27.08 – 28.59)	26.69 (26.33 – 27.05)	25.48 (24.57 – 26.40)	23.42 (22.98 – 23.86)	22.64 (21.52 – 23.75)
	Δ	-0.92 (-1.72 - -0.12)*		-1.21 (-2.20 - -0.21)*		-0.78 (-2.00 – 0.43)	
	Stroop 1						
	Adjusted model	11.22 (11.16 – 11.29)	11.21 (11.00 – 11.43)	12.17 (12.05 – 12.28)	12.21 (11.92 – 12.49)	13.39 (13.21 – 13.56)	13.56 (13.13 – 13.99)
	Δ	-0.01 (-0.24 – 0.22)		0.04 (-0.27 – 0.35)		0.18 (-0.29 – 0.64)	
	Stroop 2						
	Adjusted model	13.73 (13.65 – 13.81)	14.09 (13.81 – 14.36)	15.57 (15.42 – 15.73)	16.16 (15.76 – 16.56)	18.18 (17.94 – 18.43)	18.90 (18.29 – 19.51)
	Δ	0.36 (0.07 – 0.64)*		0.59 (0.15 – 1.02)*		0.72 (0.06 – 1.38)	

	Stroop 3						
	Adjusted model	21.55 (21.39 – 21.71)	22.33 (21.81 – 22.86)	26.04 (25.36 – 26.72)	26.12 (24.40 – 27.84)	30.91 (30.36-31.46)	31.43 (30.05 – 32.82)
	Δ	0.78 (0.24 – 1.33)*		0.08 (-1.80 – 1.95)		0.53 (-0.98 – 2.03)	
	Stroop low-interference index						
	Adjusted model	1.24 (1.23 – 1.24)	1.27 (1.25 – 1.29)	1.30 (1.28 – 1.31)	1.34 (1.31 – 1.36)	1.38 (1.37 – 1.40)	1.42 (1.38 – 1.45)
	Δ	0.04 (0.01 – 0.06)*		0.04 (0.01 – 0.07)*		0.03 (-0.01 – 0.08)	
	Stroop high-interference index						
	Adjusted model	1.95 (1.94 – 1.96)	2.02 (1.98 – 2.07)	2.16 (2.12 – 2.21)	2.16 (2.05 – 2.28)	2.34 (2.31 – 2.38)	2.36 (2.27 – 2.45)
	Δ	0.08 (0.03 – 0.12)*		0.00 (-0.12 – 0.12)		0.02 (-0.08 – 0.12)	
	COWAT						
	Adjusted model	42.99 (42.64 – 43.34)	41.99 (40.83 – 43.15)	41.15 (40.58 – 41.72)	40.00 (38.55 – 41.46)	38.59 (37.91 – 39.26)	39.09 (37.37 – 40.81)
	Δ	-1.00 (-2.23 – 0.23)		-1.15 (-2.73 – 0.44)		0.50 (-1.36 – 2.37)	
	Choice Reaction Time Test						
	Adjusted model	776.4 (771.3 – 781.5)	773.9 (757.2 – 790.5)	866.5 (853.0 – 880.0)	857.4 (823.1 – 891.7)	974.3 (95412 – 994.5)	935.2 (884.4 – 986.1)
	Δ	-2.5 (-20.1 – 15.1)		-9.1 (-46.5 – 28.2)		-39.1 (-94.3 – 16.2)	
MEN	**Group size,** N (%)	4102 (81.5)	1034 (18.5)	3014 (75.2)	1056 (24.8)	2616 (76.2)	781 (23.8)
	RAVLT Immediate recall						
	Adjusted model	6.12 (6.07 – 6.18)	6.16 (6.05 – 6.27)	5.65 (5.57 – 5.72)	5.62 (5.48 – 5.76)	4.60 (4.51 – 4.68)	4.58 (4.42 – 4.75)
	Δ	0.04 (-0.09 – 0.16)		-0.03 (-0.19 – 0.13)		-0.02 (-0.21 – 0.17)	
	RAVLT 5-min recall						
	Adjusted model	4.38 (4.32 –	4.37 (4.24 –	3.71 (3.62 – 3.79)	3.70 (3.55 –	2.64 (2.54 –	2.76 (2.59 –

		4.44)	4.49)		3.85)	2.73)	2.95)
	Δ	-0.01 (-0.15 – 0.13)		-0.01 (-0.18 – 0.17)		0.13 (-0.07 – 0.34)	
	Animal Fluency test						
	Adjusted model	23.37 (23.20 – 23.54)	23.18 (22.81 – 23.55)	21.74 (21.48 – 22.00)	21.76 (21.29 – 22.23)	18.68 (18.38 – 18.98)	18.27 (17.71 – 18.83)
	Δ	-0.19 (-0.60 – 0.23)		0.02 (-0.53 – 0.56)		-0.41 (-1.05 – 0.23)	
	Mental Alternation test						
	Adjusted model	30.10 (29.84 – 30.35)	30.42 (29.88 – 30.96)	28.25 (27.86 – 28.63)	27.93 (27.24 – 28.62)	25.14 (24.64 – 25.65)	24.31 (23.37 – 25.24)
	Δ	0.33 (-0.27 – 0.93)		-0.32 (-1.12 – 0.49)		-0.84 (-1.91 – 0.24)	
	Stroop 1						
	Adjusted model	11.55 (11.48 – 11.62)	11.48 (11.32 – 11.63)	12.58 (12.45 – 12.70)	12.49 (12.27 – 12.71)	14.13 (13.95 – 14.31)	14.29 (13.95 – 14.62)
	Δ	-0.07 (-0.24 – 0.10)		-0.09 (-0.35 – 0.17)		0.16 (-0.23 – 0.54)	
	Stroop 2						
	Adjusted model	14.10 (14.013.99 – 14.19)	14.01 (13.80 – 14.21)	15.93 (15.77 – 16.09)	16.17 (15.88 – 16.46)	19.02 (18.75 – 19.30)	19.53 (19.03 – 20.04)
	Δ	-0.09 (-0.32 – 0.13)		0.24 (-0.10 – 0.58)		0.51 (-0.07 – 1.09)	
	Stroop 3						
	Adjusted model	22.34 (22.14 – 22.53)	22.57 (22.15 – 22.99)	26.25 (25.91 – 26.59)	26.79 (26.18 – 27.40)	32.12 (31.54 – 32.69)	33.68 (32.62 – 34.75)
	Δ	0.23 (-0.24 – 0.70)		0.54 (-0.18 – 1.25)		1.57 (0.34 – 2.79)	
	Stroop low-interference index						
	Adjusted model	1.23 (1.23 – 1.24)	1.23 (1.22 – 1.24)	1.28 (1.27 – 1.29)	1.31 (1.29 – 1.33)	1.36 (1.35 – 1.38)	1.39 (1.36 – 1.42)
	Δ	0.00 (-0.02 – 0.01)		0.03 (0.00 – 0.05)		0.03 (0.00 – 0.07)	
	Stroop high-interference index						

	Adjusted model	1.96 (1.95 – 1.98)	1.99 (1.96 – 2.02)	2.12 (2.10 – 2.15)	2.17 (2.12 – 2.21)	2.30 (2.27 – 2.34)	2.40 (2.33 – 2.47)
	Δ	0.03 (-0.01 – 0.07)		0.04 (-0.01 – 0.10)		0.10 (0.02 – 0.18)	
	COWAT						
	Adjusted model	40.81 (40.45 – 41.17)	40.86 (40.09 – 41.63)	39.46 (38.89 – 40.03)	39.10 (38.08 – 40.11)	36.26 (35.54 – 36.99)	34.88 (33.54 – 36.21)
	Δ	0.05 (-0.81 – 0.91)		-0.36 (-1.55 – 0.83)		-1.39 (-2.92 – 0.14)	
	Choice Reaction Time Test						
	Adjusted model	750.4 (745.3 – 755.6)	748.2 (737.2 – 759.3)	835.5 (825.0 – 845.9)	850.7 (832.1 – 869.4)	913.9 (899.6 – 928.1)	917.1 (890.7 – 943.4)
	Δ	-2.2 (-14.5 – 10.1)		15.3 (-6.5 – 37.1)		3.2 (-27.0 – 33.4)	

RAVLT: Rey auditory verbal learning test; COWAT: Controlled oral word association test; Δ: score of participants at high-risk of OSA minus score of participants at low-risk of OSA

Adjusted models include socio-demographic (age, education, income, working status, marital status, ethnicity), lifestyle (smoking, alcohol, physical activity, sleep quality, sleep duration) and clinical (cardiovascular disease, diabetes, chronic obstructive pulmonary disease, anxiety-depression, asthma, functional status, general health perception, menopausal status for women, levels of C-reactive protein concentration) covariables.

All results are presented as adjusted means with 95% confidence intervals.

All p-values were FDR-adjusted for multiple comparisons

*: FDR-adjusted p-value is significant (<0.05)

3.2. Role of hs-CRP in the association between OSA risk and cognition

In women aged 60-69, the relationship between the Controlled Oral Word Association test (COWAT) score and OSA risk was moderated by inflammation, where higher hs-CRP levels enhanced the association between OSA risk and poorer cognition (Table 4). In men aged 45-59, similar moderating effects were found for the RAVLT 5-min recall.

Table 4. Level of hs-CRP as the moderator of the OSA risk and cognitive performance relationship

Sex	Age	Cognition	β (95% CI)	p-values
Women	**45-59**	----------	----------	----------
	60-69	**COWAT**		
		Interaction		
		Risk OSA * hs-CRP	-1.66 (-3.15 - -0.17)	0.029
		Conditional effects		
		One SD below mean	0.94 (-1.27 – 3.15)	0.403
		At the mean	-0.47 (-1.88 – 0.94)	0.512
		One SD above mean	-1.89 (-3.41 – -0.37)	0.015
	70-85	----------	----------	----------
Men	**45-59**	**RAVLT 5-min recall**		
		Interaction		
		Risk OSA * hs-CRP	0.20 (0.00 – 0.39)	0.046
		Conditional effects		
		One SD below mean	-0.20 (-0.43 – 0.04)	0.097
		At the mean	-0.06 (-0.23 – 0.10)	0.454
		One SD above mean	0.09 (-0.11 – 0.29)	0.381
	60-69	----------	----------	----------
	70-85	----------	----------	----------

The conditional effects of risk of OSA on cognitive performance with levels of hs-CRP as a moderator are presented for the significant moderation analyses. All moderation analyses were adjusted for socio-demographic (education, income, working status, marital status, ethnicity), lifestyle-related (smoking, alcohol, physical activity, sleep quality, sleep duration) and clinical (cardiovascular diseases, diabetes, chronic obstructive pulmonary disease, anxiety - depression, asthma, functional status, general health perception, menopausal status in women) covariables. p-values were corrected using family-wise FDR-correction.

OSA: Obstructive sleep apnea; hs-CRP: high-sensitivity C-reactive protein; CI: confidence interval; RAVLT: Rey auditory verbal learning test; COWAT: Controlled oral word association test; SD: standard deviation.

The mediation analyses (Table 5) showed that the proportion of the total effect of OSA risk on cognition explained by the levels of hs-CRP in women aged 45-59 was 22% for the Animal Fluency test score, 16% for the Stroop 3 score and 28% for the COWAT score. In women aged 60-69, levels of hs-CRP explained 15% of the total effect of OSA risk on the Stroop 2 score. In men aged 60-69, levels of hs-CRP explained 8% of the total effect of OSA risk on the Stroop 3 score, and 11% on the low- and high-interference indices. These mediation effects were all significant.

Table 5. Level of hs-CRP as the mediator of the relationship between OSA risk and cognitive performance

Sex	Age	Cognition	Total effect [c] (95% CI)	Direct effect [c'] (95% CI)	Indirect effect [a*b] (95% CI)	% mediation [a*b/c]	p
Women	45-59	AFT	-0.81 (-1.45 - -0.17)	-0.63 (-1.29 – 0.02)	-0.18 (-0.30 - -0.06)	21.8	0.006
		Stroop 3	0.69 (0.07 – 1.31)	0.58 (-0.05 – 1.21)	0.11 (0.00 – 0.23)	16.3	0.035
		COWAT	-1.49 (-2.87 - -0.12)	-1.08 (-2.47 – 0.31)	-0.42 (-0.67 - -0.17)	27.9	0.003
	60-69	Stroop 2	0.65 (0.30 – 1.01)	0.55 (0.19 – 0.91)	0.10 (0.04 – 0.17)	15.0	0.002
	70-85	----------	----------	----------	----------	----------	-------
Men	45-59	----------	----------	----------	----------	----------	-------
	60-69	Stroop 3	0.96 (0.28 – 1.62)	0.88 (0.20 – 1.55)	0.08 (0.01 – 0.16)	8.1	0.039
		Low-interference index	0.025 (0.005 – 0.044)	0.022 (0.002 – 0.042)	0.003 (0.001 – 0.005)	10.9	0.019
		High-interference index	0.061 (0.012 – 0.110)	0.054 (0.005 – 0.103)	0.007 (0.002 – 0.014)	11.4	0.014
	70-85	----------	----------	----------	----------	----------	-------

Only significant mediation analyses are presented. All mediation analyses were adjusted for socio-demographic (age, education, income, working status, marital status, ethnicity), lifestyle-related (smoking, alcohol, physical activity, sleep quality, sleep duration) and clinical (cardiovascular diseases, diabetes, chronic obstructive pulmonary disease, anxiety - depression, asthma, functional status, general health perception, menopausal status in women) covariables. When assumptions were met, results from the mediation analyses were reported as the indirect effect (a*b) and the percentage of the association between OSA risk and cognition mediated by hs-CRP (a*b/c). The indirect effect (a*b) was significant if the lower and upper CI values did not include 0. Family-wise FDR corrections were applied to the p-values of the Sobel tests for the indirect effects of significant mediation analyses.

OSA: obstructive sleep apnea; hs-CRP: high-sensitivity C-reactive protein; AFT: Animal fluency test; COWAT: Controlled oral word association test; CI: Confidence interval.

3.3. Sensitivity analyses

Using the STOP alone or in combination with other obesity measures (see Methods), including participants reporting an OSA diagnosis, and not controlling for sleep quality/duration, health perception and functional status yielded results similar to those reported above. Menopausal status and education did not moderate the association between OSA risk and cognition, but non- menopausal women performed better than post-menopausal women on four cognitive tests (see Supplemental material for details).

4. Discussion

In the present study of 25,899 Canadian participants, women aged 45-69 years at high-risk for OSA, defined by a score combining the STOP and whole-body fat percentage of 3 or more, had poorer episodic verbal memory, attention and executive functions than those at low-risk for OSA. These associations were not observed in women aged ≥70 or in men. In addition to the moderating role of age and sex, we found that systemic inflammation measured with hs-CRP moderated some associations between OSA risk and attention and episodic memory. Moreover, systemic inflammation mediated several associations particularly in women and for attention and executive function; more specifically, high systemic inflammation explained part of the significant associations between risk of OSA and cognition. This study identifies individual characteristics putting adults at higher risk of presenting OSA-related cognitive problems, and reiterates the importance of making additional efforts to screen, diagnose and treat OSA in middle-aged women.

While differences in cognitive performance between middle-aged women at low- and high-risk for OSA were statistically significant, they did not seem clinically significant. Since neurodegeneration presents as a continuum, it would not be surprising that OSA-associated brain changes are observed before the development of cognitive deficits.[38] An absence of

clinically significant cognitive impairment should therefore not be confused with an absence of brain alterations. It is thus also possible that men of all ages and women aged 70 or more, despite not showing changes in cognitive functioning, would still be in a neurodegenerative process involving OSA-associated brain changes similar to those found in AD. Thus, the OSA-related cognitive impairment highlighted in this large representative sample of the Canadian population should be considered by public health stakeholders to orient a preventive approach to cognitive health at the population level.

It is recognized that individual characteristics (e.g., age, sex, comorbidities) may influence the risk of developing cognitive dysfunction in the presence of OSA.[7] Obtained from a large sample tested with a comprehensive neuropsychological battery, our results confirm previous findings obtained in smaller cohorts that OSA and its association with cognitive changes is stronger in younger (<60 years old) women compared to older women and men. For example, in the Hispanic Community Health Study (8,059 participants) only women with OSA aged 45-54 showed impaired episodic memory and executive functions.[8] Other studies showed more cognitive impairment in older[39] and middle-aged women[40] with or at risk for OSA compared to women without or at low-risk for OSA. While we can speculate that older adults are particularly vulnerable to the effects of OSA on cognition, the literature[7] and the present study suggest otherwise: the greatest OSA-related cognitive differences between groups were observed in middle-aged women. While OSA in older adults may correlate with cognitive decline, this association may be obscured by conditions prevalent in older adults (e.g.: cardiovascular diseases, hypertension and neurodegenerative diseases) that are recognized independent risk factors for cognitive impairment and dementia, and to the fact that the elderly are less sensitive to sleep deprivation.[41]

Our results emphasize that the presence of systemic inflammation should be considered when assessing the risk of cognitive dysfunction in apneic patients. In fact, we found that systemic inflammation interacts wih OSA to explain a significant proportion of the effect of OSA risk on cognition in women and men, especially with respect to performance in executive functions. This supports a recent study from the Framingham cohort showing that higher baseline CRP

levels interacted with fragmented sleep to predict a higher dementia risk 13 years later.[9] While associations between sleep fragmentation and memory deficits, and between hypoxemia and executive functions deficits have been suggested,[6] our results indicate that systemic inflammation could be related to executive functions deficits, with memory deficits being due to the disruption of sleep dependent memory consolidation processes. Moreover, proinflammatory cytokines crossing the blood-brain barrier could result in cellular changes, apoptosis, and gray matter atrophy,[42] and exacerbate amyloid and tau pathologies.[43] Interestingly, with equivalent OSA severity, women show higher levels of fibrinogen and C-reactive protein than men,[44] suggesting their inflammatory response to OSA could explain the development of cognitive impairment. Menopause, partly through an increase in systemic inflammation, could also precipitate cognitive decline.[45] In the present study, menopausal status had no effect on the association between OSA risk and cognition, possibly because we only had access to self-reported menopausal status, and not to the objective sex hormone profile, which is particularly informative in perimenopause.

The main strength of this study is the use of a comprehensive neuropsychological assessment in the largest cohort used to date to investigate cognitive performance in relation to OSA. However, the study has limitations. First, we lacked objective measures of sleep. Nevertheless, combining the STOP and a measure of obesity has a good sensitivity and negative predictive value, and could thus be easily translated to a clinical setting. The STOP, however, uses typically male symptoms, which could limit its ability to identify women at high-risk for OSA. Second, the use of only one inflammatory marker limits our understanding of its significance and future studies should integrate multiple inflammatory markers to have a better portrait of the physiological mechanisms involved.

4.1 Conclusions

This study reinforces the idea that OSA should be considered as an early modifiable factor of cognitive decline, particularly in women younger than 70. With follow-up assessments conducted every 3 years for the next 20 years, the CLSA cohort offers a unique opportunity to track sex- and age-specific cognitive changes with respect to OSA risk. Futures studies should

investigate the role played by OSA-related medical comorbidities and systemic inflammation on neurodegenerative processes, which are likely sex-dependent and could modify the relationship between OSA and cognitive decline at older ages. Determining the factors that enhance the impact of OSA on cognitive function may aid clinical decision-making and potential treatment.[46] While OSA-associated brain changes can be present before the development of cognitive deficits,[38] it is crucial to screen middle-aged and older individuals for cognitive impairment[47] and OSA and to recommend therapy in order to stave off cognitive impairment.

Disclaimer

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Conflict of interest

Authors have no competing interests to declare.

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: https://doi.org/10.1016/j.sleep.2022.02.006.

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Supplementary data

Supplemental methods

Measures

Specific questions used to obtain the STOP component of the adapted STOP-Obesity score and classify participants according to their OSA risk

i) Snoring: "Do you snore loudly? By 'loudly' I mean louder than talking or loud enough to be heard through closed doors", with possible answers being yes or no.

ii) Daytime Tiredness/sleepiness or fatigue: "Over the last month, how often do you find it difficult to stay awake during your normal waking hours when you want to?", with suggested response categories being "Never", "Less than once per week", "Once or twice a week", "3-5 times per week" or "6-7 times per week". Participants reporting difficulty staying awake ≥3 times per week were considered as experiencing significant daytime sleepiness.

iii) Observed apneas: "Has anyone ever observed you stop breathing in your sleep?", with possible answers being yes or no.

iv) High blood Pressure: "Has a doctor ever told you that you have high blood pressure or hypertension?", with possible answers being yes or no. Answers to this question were double-checked with information pertaining to the current intake of hypertensive medication.

Categorization of sociodemographic variables

Marital status was dichotomized as either "living with a spouse" or not, the latter including single, divorced and widowed participants.

Ethnicity was dichotomized as "Caucasian" and "Non-Caucasian", the latter including Black, Korean, Filipino, Japanese, Chinese, South Asian, Southeast Asian, West Asian, Arab, Latin American, multiple ethnicities and others.

Income was stratified as <20,000$, 20,000-49,999$, 50,000-99,999$, 100,000-149,999$, >150,000$.

Education level was stratified as “less than secondary graduation”, “secondary graduation without post-secondary education”, “some post-secondary education”, “post-secondary education degree / diploma”.

Working status was stratified as “active worker”, “partly retired”, or “not working”, the latter including participants completely retired and unemployed.

Categorization of lifestyle-related variables

Smoking status was stratified as “current smoker”, “former smoker” or “never smoker”.

Alcohol use was stratified based on the long-term health risk determined by the Canadian Guidelines for Low-Risk Drinking as “high-risk drinking” (>10 drinks for women and >15 drinks for men, weekly), “low-risk drinking” (1-10 drinks for women and 1-15 drinks for men, weekly) and “no drinking”.[1]

Physical activity was quantified using the Physical Activity Scale for the Elderly (PASE) questionnaire[2] which gives a global score in METS (metabolic equivalent of task) representing the individuals’ daily energy expenditure. Quintile cutoff values specific for men and women were used.

Average hours of sleep per night were self-reported. Participants were classified as “normal” sleepers if they reported sleeping between 6 and 8 hours per night, “short” sleepers if they reported <6 hours of sleep per night, and “long” sleepers if they reported >8 hours of sleep per night.[3]

General sleep quality was assessed by the question “How satisfied of dissatisfied are you with your current sleep pattern?”, with suggested response categories being “Very satisfied”, “Satisfied”, “Neutral”, “Dissatisfied” and “Very dissatisfied”. Participants who answered being dissatisfied or very dissatisfied with their sleep were considered having unsatisfactory sleep.

Clinical variables

For each chronic health condition, i.e. cardiovascular diseases (myocardial infarction, angina pectoris, and/or congestive heart failure), diabetes mellitus, anxiety, chronic obstructive pulmonary disease and asthma, participants were asked yes/no questions that all started by, "Has a doctor ever told you that you have [a chronic medical condition]?".

Depression was assessed using the 10-item Center for Epidemiologic Studies Depression scale (CESD-10) screening tool,[4] which contains 10 questions about feelings such as depression, loneliness, hopefulness for the future, and restless sleep. Participants with a score ≥10 were considered as presenting significant depressive symptoms. Participants reporting having anxiety and/or scoring ≥10 on the CESD-10 were considered as having anxiety-depression disorder.

Functional status was assessed using the Older Americans' Resources and Services (OARS) multidimensional functional assessment questionnaires, where participants are questioned on their ability to perform 7 basic and 7 instrumental activities of daily living, including meal preparation.[5] Participants were classified as either having no functional impairment or having some functional impairment.

Self-reported general health perception was assessed by the question "In general, would you say your health is excellent, very good, good, fair or poor", where participants answering "fair" or "poor" were considered perceiving their health as poor.

Menopausal status was assessed by the question "Have you gone through menopause, meaning that your menstrual periods stopped for at least one year and did not restart?", where women who answered "yes" were considered post-menopausal and those who answered "no" were considered non-menopausal.

Specifications on the moderation and mediation analyses

Simple moderation analyses using model 1 multiple regression with mean centering were used to test the moderating effect of hs-CRP levels (moderator W) on the relationship between OSA risk (independent variable X) and the scores on each cognitive test (dependent variables Y). The first step of the multiple regression analyses calculated the independent effects of X and W on Y, and the interaction term X*W was added at the second step. Outputs were the conditional effects of X on Y, at three levels of W (mean; mean – 1 SD; mean + 1 SD). When significant, interaction results were reported as the beta coefficient (95% CI).

Mediation analyses using model 4 from Process macro were computed, returning the unstandardized regression coefficients between the model's variables that represent the total (c) and direct effects (a, b, c'). The direct effect of OSA risk (X) on level of hs-CRP as a mediator (M) is referred to as path "a", the direct effect of hs-CRP as a mediator (M) on cognitive performance (Y) is referred to as path "b". Path "a" multiplied by path "b" represents the indirect effect of hs-CRP (M) on cognitive outcomes (Y), i.e. the change in cognitive performance explained by the level of hs-CRP. Path "c" is the total effect of risk of OSA (X) on cognitive performance (Y), and corresponds to the sum of the direct effect of OSA risk on cognitive performance (path "c' ") and indirect effects (path "a" multiplied by path "b"). Results from the mediation analyses were interpreted if the unstandardized regression coefficients associated with paths "c", "a" and "b" were statistically significant. Of note, none of the unstandardized regression coefficients associated with paths "c", "a" and "b" were statistically significant in women aged ≥70 and men, so the mediation analyses were not interpreted.

The indirect effect (a*b), quantifying the mediating effect of hs-CRP, was significant if the lower and upper CI values did not include 0. For significant mediation analyses, the percentage of the association between OSA risk and cognition explained by hs-CRP and corresponding to the ratio between the indirect effect and the total effect (a*b/c) was also reported.

Supplemental results

Sex- and age-specific differences in OSA risk

Figure 1 presents the participant flowchart. We included 25,899 participants (13,296 women and 12,603 men, aged 59.1±9.8 years old). Of these, 4,764 had a STOP-Obesity score ≥3 and were classified at high-risk for having OSA, representing 16.6% (15.5 – 17.7%) of the cohort. The proportion of women at high-risk for OSA was 12.4% (10.9 – 13.9 %) and increased from 9.7% (7.4 – 12.0%) to 15.2% (12.6 – 17.8%) and 16.9% (13.8 – 20%) for women aged 45-59, 60-69 and ≥70, respectively. The proportion of men at high-risk for OSA was 20.9% (19.4 – 22.4%), varying from 18.5% (16.1 – 20.9%) to 24.8% (22.2 – 27%) and 23.8% (20.8 – 26.%) for ages 45-59, 60-69 and ≥70, respectively. Sex-specific, age-stratified characteristics and risk factors of the study population are presented in Supplemental eTable 2.

Supplemental sensitivity analyses

Use of validated STOP score alone and combined to other obesity measures

Using the fully adjusted GLM models described in the main article, we tested whether classifying participants for their risk for OSA using the STOP score alone, or in combination with different measures of obesity, affected the relationship between OSA risk and cognition. We tested the following obesity measures: i) waist-to-hip ratio (WHR); WHR cutoff value for obesity was >0.9 for women and >0.85 for men;[6] ii) BMI with a cutoff value for obesity >30 kg/m2;[7] iii) BMI with a cutoff value for obesity >35 kg/m2;[8] iv) fat mass index, with cutoff values for obesity >11.8 kg/m2 for women and >8.3 kg/m2 for men.[9] Participants scoring ≥2 for the STOP score alone,[8] or ≥3 for the STOP score combined to any measure of obesity[10] were considered at high-risk for OSA. Using the STOP alone or with any obesity measure yielded similar results as using the STOP combined to the %BF. In all cases, women aged 45-59 at high-risk for OSA performed significantly worse than those at low-risk on 4 to 7 tests assessing episodic memory and executive functioning, while women aged 60-69 and ≥70 at high-risk for OSA had poorer performances than those at low-risk on 1 to 3 tests. In men of all ages, there were no

associations between being at risk for OSA and cognition, regardless of whether the STOP was used alone or combined with an obesity measure.

Inclusion of participants with a diagnosis of OSA

Our main results were obtained from a sample of 25,899 participants of the CLSA comprehensive cohort that excluded participants having a diagnosis of OSA given by a health professional (N=357). Those participants were excluded mainly because no information was provided on whether they used some treatment for OSA, such as Continuous Positive Airway Pressure (CPAP) therapy, that could have a beneficial impact on cognition.[11] In order to assess the robustness of the results obtained from the General Linear Models (GLM) testing the sex- and age-specific association of OSA risk and the scores on the neuropsychological tests, we performed the fully adjusted GLM, controlling for all socio-demographic, lifestyle-related and clinical variables, on our sample in which we included the participants who reported a diagnosis of OSA. A false-discovery rate (FDR) correction was applied to account for multiple comparisons. Results were consistent with those obtained when they were excluded. Specifically, while being at high-risk for OSA did not have a significant effect on the RAVLT immediate recall score anymore (p=0.054) in women aged 45-59 at high-risk for OSA, scores remained significantly worse than those obtained by women at low-risk on the Animal Fluency Test (23.1 [22.9-23.2] vs 22.4 [21.9-23.0], p=0.037), Mental Alternation Test (28.7 [28.5-29.0] vs 27.8 [27.1-28.6]. p=0.036), Stroop 2 (13.7 [13.6-13.8] vs 14.1 [13.8-14.4], p=0.025), Stroop 3 (21.5 [21.4-21.7] vs 22.4 [21.8-22.9], p=0.006), Stroop low- (1.24 [1.23-1.24] vs 1.27 [1.25-1.29], p=0.004) and high-interference (1.95 [1.94-1.96] vs 2.02 [1.98-2.07], p=0.004) index. Women at high-risk for OSA aged 60-69 also had a worse performance than those at low-risk on the Mental Alternation Test (26.7 [26.3-27.0] vs 25.5 [24.7-26.4], p=0.041), Stroop 2 (15.6 [15.4-15.7] vs 16.1 [15.7-16.5], p=0.024) and Stroop low-interference index (1.30 [1.28-1.31] vs 1.34 [1.31-1.36], p=0.012). In men of all ages, high-risk for OSA was not associated with cognitive performance in the fully adjusted analyses.

Moderating effect of sex and age on the association of OSA risk and cognitive performance

In order to verify if sex moderated the association between OSA risk and cognition in each age group, age-specific simple moderation analyses following the procedure described above were performed (W: sex; X: OSA risk; Y: scores on each neuropsychological test). Sex moderated the association between OSA risk and the scores obtained on the Mental Alternation test, , the Stroop 2 and the Stroop low-interference index in participants aged 45-59 years. In participants aged ≥70, sex only moderated the relationship between OSA risk and the Stroop 2 score. In all cases, women at high-risk for OSA performed worse than those at low-risk, while there were no differences in men. Sex had no moderating effect on the relationship between OSA risk and cognition in participants aged 60-69.

We also performed sex-specific simple moderation analyses to test the moderating effect of age on the association between OSA risk and cognition (W: age group; X: OSA risk; Y: score on each neuropsychological test). No moderating effect of age was obtained in women nor in men.

Association of menopausal status with cognitive performance

In order to test if menopausal status (non- vs post-menopausal) had an effect on cognitive performance in our cohort and thus, could interact with OSA risk to explain the differences observed strictly in women aged 45-59, we compared the scores on all neuropsychological tests based on menopausal status using the unadjusted and fully adjusted GLM, the latter controlling for age as a continuous variable, as well as the socio-demographic, lifestyle-related and clinical variables. A FDR correction was applied to account for multiple comparisons. We also performed simple moderation analyses to evaluate if menopausal status moderated the relationship between OSA risk and cognitive function. Results from the GLM showed that non-menopausal women performed significantly better than post-menopausal women on the Mental Alternation Test (29.0 [28.7-29.4] vs 28.3 [28.0-28.7], p=0.029), Stroop 2 (13.6 [13.5-13.7] vs 13.9 [13.8-14.1], p=0.003), and COWAT (43.5 [43.0-44.0] vs 42.3 [41.7-42.8], p=0.009) tests, even in the fully adjusted models. However, the moderation analyses showed that menopausal status did not have a moderating effect on the association between OSA risk and any cognitive test. This suggests that being post-menopausal has a limited impact on the association between OSA risk and cognitive function in middle-aged women.

Moderating effect of education on the association of OSA risk and cognitive performance

A high level of education is recognized to have a protective effect against cognitive impairment and dementia.12,13 To ensure that the impact of OSA risk on cognition (or its lack thereof) was not moderated by the education level, sex- and age-specific simple moderation analyses, following the procedure described above, were performed (W: education level; X: OSA risk; Y: scores on each neuropsychological test). Education level was found to moderate the association between OSA risk and cognitive performance for the Stroop high-interference index in women aged 45-59, the Stroop low-interference index in women aged ≥70, the Stroop 1 in men aged 45-59 and the COWAT in men aged 60-69. Lower levels of education enhanced the association between OSA risk and poorer performance on the Stroop low-interference index in women aged ≥70. In the other three cases, although the interaction was significant, there were no significant effect of OSA risk on the neuropsychological tests at specific values of the education level (mean; mean – 1 SD; mean + 1 SD).

eTable 1 : Characteristics of included and excluded participants

OSA and cognition in the CLSA	**Total cohort**	**Participants included (A)**	**Participants excluded**		**P <0.05**
			Comorbidities and incomplete STOP-Obesity (B)	**Incomplete STOP-Obesity only (C)**	
Total N	30,097	25,899	4,198	2,353	----------
Snoring [S], N (%) *Missing values*	7,282 (24.7) *3,937 (11.1)*	6,524 (25.3) *1,634 (5.5)*	758 (20.8) *2,303 (50.4)*	187 (10.5) *2,033 (83.3)*	A vs B,C
Tiredness, sleepiness, fatigue [T], N (%) *Missing values*	2,666 (8.6) *61 (0.2)*	2,170 (8.0) *29 (0.1)*	496 (12.8) *32 (0.7)*	229 (10.9) *26 (1.1)*	A vs B,C
Observed apneas [O], N (%) *Missing values*	4,245 (14.1) *1,899 (5.7)*	3,493 (13.3) *447 (1.8)*	752 (19.6) *1,452 (33.7)*	197 (9.3) *1,303 (57.1)*	A vs B,C
High blood pressure [P], N (%) *Missing values*	11,101 (31.8) *179 (0.5)*	8,843 (29.4) *90 (0.3)*	2,258 (48.4) *89 (1.9)*	1,354 (52.7) *75 (3.1)*	A vs B,C
Body fat >35% (women) or >25% (men) [Obesity], N (%) *Missing values*	21,814 (68.5) *1,310 (4.5)*	18,522 (67.5) *873 (3.5)*	3,292 (75.5) *437 (10.9)*	1,915 (79.6) *328 (15.6)*	A vs B
Women, N (%) *Missing values*	15,320 (50.4) *0 (0)*	13,296 (50.9) *0 (0)*	2,024 (46.7) *0 (0)*	1,332 (55.7) *0 (0)*	A vs B,C
Age, mean (SD) *Missing values*	59.5 (10.0) *0*	59.1 (9.8) *0*	62.4 (10.7) *0*	59.4 (10.1) *0*	A vs B
Living with a spouse, N (%) *Missing values*	20,651 (75.8) *8 (0.0)*	18,365 (77.7) *6 (0.0)*	2,286 (62.6) *2 (0.0)*	1,094 (54.7) *1 (0.0)*	A vs B,C
Caucasian, N (%) *Missing values*	27,412 (89.9) *259 (0.8)*	23,623 (90.1) *226 (0.8)*	3,789 (88.7) *33 (0.7)*	2,109 (87.5) *19 (0.6)*	A vs B
Post-menopausal, N (%) *Missing values*	10,158 (30.5) *2,708 (7.5)*	8,798 (30.5) *2,234 (7.3)*	1,360 (30.3) *474 (9.5)*	903 (37.0) *307 (10.9)*	A vs B,C
Education No secondary degree, N (%)	1,643 (4.8)	1,272 (4.3)	371 (8.6)	232 (9.7)	A vs B,C

Secondary degree, N (%)	2,839 (9.9)	2,376 (8.7)	463 (10.6)	281 (11.4)	
No post-secondary degree, N (%)	2,238 (6.7)	1,875 (6.5)	363 (7.8)	216 (8.9)	
Post-secondary degree, N (%)	23,327 (79.4)	20,338 (80.3)	2,989 (72.7)	1,619 (69.8)	
Missing values	*50 (0.1)*	*38 (0.1)*	*12 (0.3)*	*5 (0.2)*	
Income					A vs B,C
<20,000$, N (%)	1,567 (5.0)	1,364 (5.2)	203 (4.2)	124 (4.7)	
20-50,000$, N (%)	6,360 (21.0)	5,456 (20.9)	904 (21.6)	507 (21.9)	
50-100,000$, N (%)	9,906 (32.9)	8,544 (32.9)	1,362 (33.0)	754 (33.3)	
100-150,000$, N (%)	5,524 (18.3)	4,715 (18.2)	809 (19.3)	455 (18.6)	
>150,000$, N (%)	4,799 (16.2)	4,143 (16.2)	656 (15.8)	366 (15.6)	
Missing values	*1,941 (6.6)*	*1,677 (6.6)*	*264 (6.2)*	*147 (5.9)*	
Working status					A vs B,C
Retired/Unemployed, N (%)	13,372 (33.4)	11,132 (32.0)	2,240 (42.7)	1,256 (43.6)	
Partly retired, N (%)	3,310 (9.5)	2,871 (9.5)	439 (9.6)	243 (9.5)	
Worker, N (%)	13,305 (56.7)	11,814 (58.1)	1,491 (46.8)	835 (46.0)	
Missing values	*110 (0.4)*	*82 (0.3)*	*28 (0.8)*	*19 (0.9)*	
Smoking status					A vs B,C
No smoker, N (%)	14,242 (49.5)	12,501 (50.4)	1,741 (42.7)	977 (42.1)	
Past smoker, N (%)	13,144 (41.1)	11,200 (40.7)	1,944 (44.3)	1,072 (43.5)	
Current smoker, N (%)	2,710 (9.4)	2,198 (8.9)	512 (13.0)	304 (14.4)	
Missing values	*1 (0.0)*	*0 (0)*	*1 (0.0)*	*0 (0)*	
Alcohol consumption					A vs B,C
No drinker, N (%)	5,750 (16.9)	4,813 (16.4)	937 (20.6)	542 (20.7)	
Low-risk drinker, N (%)	17,015 (59.5)	14,938 (60.6)	2,077 (51.5)	1,135 (50.7)	
High-risk drinker, N (%)	3,061 (10.2)	2,675 (10.3)	386 (9.5)	216 (9.4)	
Missing values	*4,271 (13.4)*	*3,473 (12.7)*	*798 (18.4)*	*460 (19.2)*	
PASE					A vs B,C
Quintile 1	5,794 (15.9)	4,858 (15.4)	936 (19.5)	430 (16.0)	
Quintile 2	5,768 (16.6)	5,081 (16.9)	687 (14.5)	320 (12.4)	
Quintile 3	5,772 (18.5)	5,205 (19.2)	567 (13.6)	259 (11.0)	
Quintile 4	5,760 (21.0)	5,283 (22.1)	477 (13.2)	190 (8.8)	

Quintile 5 *Missing values*	5,694 (24.2) *1,309 (3.8)*	5,263 (25.6) *209 (0.8)*	431 (14.4) *1100 (24.8)*	167 (9.7) *987 (42.1)*	
Good health status, N (%) *Missing values*	27,292 (91.1) *23 (0.1)*	23,819 (92.3) *19 (0.1)*	3,473 (82.9) *4 (0.0)*	2,000 (85.6) *2 (0.0)*	A vs B,C
No functional impairment, N (%) *Missing values*	27,061 (91.6) *157 (0.5)*	23,674 (92.8) *104 (0.4)*	3,387 (83.0) *53 (1.2)*	1,934 (83.6) *23 (1.0)*	A vs B,C
Sleep duration Short (<6h), N (%) Normal (6-8h), N (%) Long (>8h), N (%) *Missing values*	 3,963 (12.7) 24,426 (81.8) 1,637 (5.2) *71 (0.3)*	 3,245 (12.3) 21,266 (82.6) 1,331 (5.0) *57 (0.2)*	 718 (16.1) 3,160 (76.2) 306 (7.3) *14 (0.4)*	 410 (16.6) 1,779 (76.3) 160 (6.9) *4 (0.2)*	A vs B,C
Satisfactory sleep quality, N (%) *Missing values*	22,345 (74.0) *24 (0.1)*	19,366 (74.5) *16 (0.0)*	2,979 (70.1) *8 (0.2)*	1,678 (70.3) *6 (0.2)*	A vs B,C
Cardiovascular disease, N (%) *Missing values*	4,084 (10.9) *66 (0.2)*	3,169 (9.8) *37 (0.1)*	915 (18.6) *29 (0.7)*	480 (17.0) *28 (1.3)*	A vs B,C
Diabetes, N (%) *Missing values*	5,310 (15.3) *110 (0.3)*	4,261 (14.1) *72 (0.2)*	1,049 (23.3) *38 (0.8)*	558 (22.6) *32 (1.4)*	A vs B,C
Chronic obstructive pulmonary disease, N (%) *Missing values*	1,725 (4.7) *185 (0.5)*	1,362 (4.4) *127 (0.5)*	363 (7.5) *58 (1.1)*	195 (7.8) *38 (1.5)*	A vs B
Anxiety / Depression, N (%) *Missing values*	6,369 (21.1) *135 (0.4)*	5,157 (19.9) *80 (0.2)*	1,212 (29.7) *55 (1.2)*	647 (29.1) *42 (1.8)*	A vs B,C
Asthma, N (%) *Missing values*	3,984 (13.5) *140 (0.4)*	3,393 (13.4) *91 (0.3)*	591 (14.2) *49 (1.1)*	329 (14.2) *35 (1.6)*	A vs B,C
C-reactive protein levels Normal, (<1 mg/L), N (%) Mild, (1-3 mg/L), N (%) Moderate, (≥3 mg/L), N (%) High, (≥10 mg/L), N (%) *Missing values*	 10,596 (37.6) 10,126 (32.5) 5,362 (16.3) 927 (2.7) *3,086 (10.8)*	 9,474 (39.0) 8,765 (32.6) 4,414 (15.6) 732 (2.5) *2,514 (10.4)*	 1,122 (28.2) 1,361 (31.9) 948 (21.8) 195 (4.3) *572 (13.9)*	 567 (25.1) 773 (31.8) 547 (22.9) 105 (4.4) *361 (15.8)*	A vs B,C

N are crude numbers, proportions are weighted percentages that account for sampling strategy.

List of abbreviations: OSA - obstructive sleep apnea; PASE - physical activity scale for the elderly; CLSA - Canadian Longitudinal Study on Aging

Column B: Participants excluded of the analyses because they reported one or more of the following comorbidities: Alzheimer's disease; Parkinson's disease; history of stroke; history of traumatic brain injury with loss of consciousness >20 minutes; diagnosis of obstructive sleep apnea; and/or were unclassifiable based of the STOP-Obesity score because of one or more missing answers

Column C: Participants excluded of the analyses because they were unclassifiable based of the STOP-Obesity score because of one or more missing answers

eTable 2: Age-specific socio-demographic, lifestyle and clinical characteristics

		Middle-aged 45-59 years old			Younger-old 60-69 years old			Older-old 70-85 years old		
		Low-risk	High-risk	p	Low-risk	High-risk	p	Low-risk	High-risk	p
WOMEN	**Group size,** N (%)	5097 (90.2)	650 (9.8)	------	3415 (84.7)	682 (15.3)	------	2703 (82.8)	554 (17.2)	------
	Living with a spouse, N (%)	3783 (79.5)	412 (70.2)	<0.001	2211 (71.9)	397 (65.4)	<0.001	1289 (55.1)	231 (46.9)	<0.001
	Caucasian, N (%)	4623 (89.7)	543 (84.3)	<0.001	3222 (94.0)	614 (89.6)	<0.001	2636 (95.1)	514 (93.6)	<0.001
	Income									
	<20,000$, N (%)	256 (5.2)	40 (6.2)		203 (5.9)	43 (7.1)		140 (5.3)	32 (5.9)	
	20-50,000$, N (%)	1094 (22.6)	141 (23.5)		711 (21.9)	158 (23.2)		597 (23.1)	128 (24.2)	
	50-100,000$, N (%)	1676 (35.0)	211 (33.5)	<0.001	1176 (36.8)	209 (33.2)	<0.001	922 (34.8)	160 (31.1)	<0.001
	100-150,000$, N (%)	952 (19.2)	117 (18.7)		592 (18.2)	116 (18.0)		506 (19.7)	97 (20.0)	
	>150,000$, N (%)	862 (18.0)	113 (18.1)		558 (17.1)	115 (18.5)		431 (17.0)	99 (18.8)	
	Working status									
	Retired/Unemployed, N (%)	567 (9.4)	99 (11.5)		2029 (58.1)	409 (59.6)		2411 (87.5)	505 (92.8)	
	Partly retired, N (%)	326 (5.8)	41 (6.7)	<0.001	553 (16.4)	104 (16.3)	<0.001	178 (6.3)	15 (2.5)	<0.001
	Worker, N (%)	4260 (84.8)	509 (81.8)		856 (25.5)	170 (24.1)		167 (6.1)	29 (4.7)	
	Smoking status									
	No smoker, N	2760 (54.1)	286 (42.4)		1791 (51.4)	294 (41.3)		1441 (52.2)	274 (52.9)	

	(%)									
	Past smoker, N (%)	1974 (35.9)	269 (42.9)	<0.001	1448 (42.5)	327 (50.3)	<0.001	1227 (44.0)	267 (45.1)	<0.001
	Current smoker, N (%)	540 (10.0)	98 (14.7)		215 (6.1)	64 (8.4)		107 (3.8)	14 (2.0)	
	Alcohol consumption									
	No drinker, N (%)	1050 (20.7)	197 (31.6)		702 (20.0)	173 (26.7)		624 (25.6)	173 (36.7)	
	Low-risk drinker, N (%)	3036 (69.2)	286 (57.3)	<0.001	1909 (68.0)	323 (61.7)	<0.001	1412 (64.9)	230 (58.4)	<0.001
	High-risk drinker, N (%)	468 (10.2)	59 (11.1)		360 (12.0)	60 (11.6)		222 (9.6)	26 (4.9)	
	PASE score									
	Quintile 1, N (%)	499 (9.4)	119 (17.5)		539 (15.3)	177 (24.7)		935 (33.6)	235 (43.0)	
	Quintile 2, N (%)	676 (12.6)	103 (14.2)		749 (21.2)	160 (23.7)		745 (25.2)	150 (28.0)	
	Quintile 3, N (%)	814 (16.0)	110 (18.7)	<0.001	897 (26.8)	162 (26.4)	<0.001	602 (22.7)	98 (17.6)	<0.001
	Quintile 4, N (%)	1254 (25.5)	129 (19.9)		805 (23.4)	114 (15.9)		365 (13.8)	50 (9.6)	
	Quintile 5, N (%)	1874 (36.6)	183 (29.85)		454 (13.3)	66 (9.4)		117 (4.7)	14 (1.8)	
	Good health status, N (%)	4875 (94.1)	509 (78.2)	<0.001	3253 (94.3)	557 (80.8)	<0.001	2584 (93.2)	464 (83.0)	<0.001
	No functional impairment, N (%)	4888 (95.2)	550 (86.5)	<0.001	3126 (90.5)	537 (78.7)	<0.001	2231 (81.1)	335 (59.1)	<0.001
	Sleep duration									
	Short (<6h), N	663 (11.9)	154 (21.2)		420 (11.6)	138 (20.8)		352 (13.0)	118 (22.4)	

	(%)									
	Normal (6-8h), N (%)	4280 (83.4)	449 (71.1)	<0.001	2789 (80.8)	486 (69.6)	<0.001	2234 (80.0)	396 (71.1)	<0.001
	Long (>8h), N (%)	223 (4.7)	44 (7.6)		239 (7.6)	58 (9.6)		182 (7.1)	38 (6.5)	
	Satisfactory sleep quality, N (%)	3646 (71.3)	352 (54.6)	<0.001	2588 (75.1)	426 (61.9)	<0.001	2115 (76.5)	373 (66.6)	<0.001
	Health conditions									
	CVD, N (%)	141 (2.6)	56 (7.6)	<0.001	261 (7.6)	111 (16.6)	<0.001	444 (16.3)	146 (26.1)	<0.001
	Diabetes, N (%)	462 (8.4)	204 (29.3)	<0.001	443 (12.5)	219 (30.5)	<0.001	417 (14.2)	176 (30.4)	<0.001
	COPD, N (%)	174 (2.9)	63 (9.7)	<0.001	172 (4.9)	69 (9.5)	<0.001	239 (8.0)	68 (12.1)	<0.001
	Anxiety / Depression, N (%)	1178 (22.3)	289 (41.5)	<0.001	730 (21.5)	239 (40.0)	<0.001	601 (21.1)	188 (33.3)	<0.001
	Asthma, N (%)	772 (14.9)	166 (23.2)	<0.001	504 (14.1)	152 (22.5)	<0.001	336 (12.0)	103 (20.5)	<0.001
MEN	**Group size,** N (%)	4102 (81.5)	1034 (18.5)	------	3014 (75.2)	1056 (24.8)	------	2616 (76.2)	781 (23.8)	------
	Living with a spouse, N (%)	3273 (83.0)	846 (84.6)	<0.001	2404 (84.2)	868 (85.3)	<0.001	588 (81.7)	158 (84.9)	<0.001
	Caucasian, N (%)	3607 (88.2)	915 (88.9)	<0.001	2798 (93.4)	972 (91.5)	<0.001	2448 (94.5)	731 (93.5)	<0.001
	Income									
	<20,000$, N (%)	190 (4.9)	67 (7.6)		155 (5.5)	53 (5.9)		145 (5.5)	40 (6.5)	
	20-50,000$, N (%)	847 (21.8)	202 (21.5)		639 (22.2)	211 (22.2)		562 (24.0)	166 (23.6)	
	50-100,000$, N (%)	1386 (36.4)	344 (33.5)	<0.001	977 (34.6)	358 (34.5)	<0.001	866 (35.1)	259 (34.6)	<0.001
	100-150,000$,	760 (19.9)	190 (20.0)		554 (19.4)	208 (21.0)		479 (20.1)	144 (20.7)	

	N (%) >150,000$, N (%)	652 (17.0)	157 (17.5)		495 (18.3)	151 (16.4)		402 (15.3)	107 (14.5)	
	Working status Retired/Unemployed, N (%)	308 (5.4)	87 (6.6)		1449 (46.6)	544 (48.0)		2089 (79.6)	635 (82.7)	
	Partly retired, N (%)	232 (4.5)	87 (6.0)	<0.001	659 (21.8)	226 (22.9)	<0.001	347 (13.7)	103 (12.2)	<0.001
	Worker, N (%)	3554 (90.0)	860 (87.5)		904 (31.6)	283 (29.1)		179 (6.7)	43 (5.0)	
	Smoking status No smoker, N (%)	2283 (57.2)	490 (48.7)		1303 (43.2)	336 (32.0)		998 (38.1)	245 (31.0)	<0.001
	Past smoker, N (%)	1339 (31.5)	421 (40.9)	<0.001	1443 (48.0)	598 (56.2)	<0.001	1486 (57.1)	501 (64.4)	
	Current smoker, N (%)	480 (11.3)	123 (10.4)		268 (8.7)	122 (11.8)		132 (4.8)	35 (4.6)	
	Alcohol consumption No drinker, N (%)	574 (14.6)	164 (17.2)		414 (13.0)	178 (17.7)		395 (15.2)	149 (20.3)	
	Low-risk drinker, N (%)	2627 (72.9)	593 (70.4)	<0.001	1901 (72.9)	584 (64.4)	<0.001	1596 (72.5)	441 (67.0)	<0.001
	High-risk drinker, N (%)	472 (12.5)	128 (12.4)		379 (14.1)	154 (17.8)		262 (12.3)	85 (12.7)	
	PASE score Quintile 1, N (%)	374 (8.6)	134 (13.0)		485 (15.5)	247 (21.6)		817 (29.5)	297 (37.0)	
	Quintile 2, N (%)	501 (11.2)	140 (12.1)		675 (22.3)	238 (21.8)		743 (29.3)	201 (24.7)	
	Quintile 3, N	621 (15.1)	169 (15.1)	<0.001	741 (24.5)	241 (23.6)	<0.001	597 (23.5)	153 (20.3)	<0.001

	(%)									
	Quintile 4, N (%)	1012 (24.4)	264 (26.7)		653 (22.6)	200 (19.6)		346 (14.0)	91 (13.5)	
	Quintile 5, N (%)	1544 (40.7)	322 (33.1)		438 (15.2)	124 (13.4)		98 (3.7)	29 (4.5)	
	Good health status, N (%)	3852 (94.1)	859 (83.6)	<0.001	2841 (94.9)	891 (85.5)	<0.001	2457 (94.5)	677 (86.6)	<0.001
	No functional impairment, N (%)	4022 (98.4)	998 (96.9)	<0.001	2914 (97.1)	979 (93.5)	<0.001	2420 (93.2)	674 (86.4)	<0.001
	Sleep duration									
	Short (<6h), N (%)	432 (10.8)	188 (18.1)		293 (9.4)	151 (13.4)		226 (8.8)	110 (13.9)	
	Normal (6-8h), N (%)	3567 (86.9)	809 (79.4)	<0.001	2580 (85.7)	858 (81.8)	<0.001	2205 (83.6)	614 (78.3)	<0.001
	Long (>8h), N (%)	100 (2.3)	34 (2.5)		136 (4.8)	44 (4.8)		179 (7.7)	54 (7.8)	
	Satisfactory sleep quality, N (%)	3193 (77.8)	685 (66.9)	<0.001	2450 (81.3)	781 (74.8)	<0.001	2185 (84.5)	572 (73.3)	<0.001
	Health conditions									
	CVD, N (%)	222 (5.4)	11 (9.8)	<0.001	434 (14.3)	262 (25.0)	<0.001	699 (26.2)	283 (35.6)	<0.001
	Diabetes, N (%)	388 (8.8)	242 (19.6)	<0.001	507 (16.6)	398 (35.3)	<0.001	568 (22.3)	237 (30.1)	<0.001
	COPD, N (%)	97 (2.4)	44 (3.6)	<0.001	127 (3.6)	87 (7.3)	<0.001	153 (6.0)	69 (8.4)	<0.001
	Anxiety / Depression, N (%)	625 (14.8)	243 (23.4)	<0.001	396 (13.6)	222 (21.1)	<0.001	297 (11.7)	149 (19.1)	<0.001
	Asthma, N (%)	487 (12.1)	157 (16.2)	<0.001	293 (9.5)	134 (12.7)	<0.001	214 (7.8)	75 (10.5)	<0.001

N are crude numbers, proportions are weighted percentages that account for sampling strategy.

List of abbreviations: OSA - obstructive sleep apnea; PASE - physical activity scale for the elderly; CLSA - Canadian Longitudinal Study on Aging; CVD – cardiovascular disease; COPD – chronic obstructive pulmonary disease

eTable 3: Scores on the neuropsychological tests according to risk of having OSA

	Neuropsychological test	Middle-aged 45-59 years old		Younger-old 60-69 years old		Older-old 70-85 years old	
		Low risk	High risk	Low risk	High risk	Low risk	High risk
WOMEN	**Total N (weighted %)**	5174 (90.3)	653 (9.7)	3454 (84.8)	685 (15.2)	2775 (83.1)	555 (16.9)
	RAVLT Immediate recall						
	Unadjusted model	6.84 (6.79 – 6.88)	6.55 (6.42 – 6.67) *	6.42 (6.35 – 6.48)	6.16 (6.02 – 6.31) *	5.45 (5.38 – 5.52)	5.32 (5.16 – 5.47)
	Model 1	6.83 (6.78 – 6.87)	6.66 (6.53 – 6.80) *	6.40 (6.33 – 6.46)	6.28 (6.13 – 6.43)	5.44 (5.37 – 5.51)	5.38 (5.22 – 5.53)
	Model 2	6.87 (6.82 – 6.92)	6.72 (5.57 – 6.86)	6.44 (6.37 – 6.51)	6.39 (6.22 – 6.56)	5.48 (5.41 – 5.56)	5.44 (5.26 – 5.62)
	Model 3 (adjusted)	6.91 (6.85 – 6.96)	6.68 (6.50– 6.85) *	6.44 (6.36 – 6.52)	6.45 (6.24 – 6.66)	5.51 (5.42 – 5.60)	5.55 (5.32 – 5.79)
	RAVLT 5-min recall						
	Unadjusted model	5.31 (5.26 – 5.37)	4.92 (4.78 – 5.07) *	4.66 (4.58 – 4.73)	4.38 (4.22 – 4.55) *	3.62 (3.54 – 3.69)	3.40 (3.23 – 3.57)
	Model 1	5.30 (5.25 – 5.36)	5.08 (4.93 – 5.23) *	4.65 (4.58 – 4.73)	4.45 (4.28 – 4.62)	3.62 (3.54 – 3.69)	3.52 (3.34 – 3.6)
	Model 2	5.36 (5.31 – 5.42)	5.14 (4.97 – 5.31) *	4.70 (4.62 – 4.78)	4.50 (4.31 – 4.69)	3.65 (3.56 – 3.73)	3.62 (3.42 – 3.82)
	Model 3	5.40 (5.34 –	5.15 (4.95 –	4.71 (4.62 –	4.52 (4.27 –	3.65 (3.54 –	3.68 (3.41 –

	(adjusted)	5.46)	5.35) *	4.80)	4.76)	3.76)	3.94)
	Animal Fluency test						
	Unadjusted model	22.88 (22.74 – 23.02)	21.58 (21.18 – 21.98) *	20.86 (20.67 – 21.06)	19.96 (19.52 – 20.41) *	17.87 (17.66 – 18.07)	16.97 (16.52 – 17.41)*
	Model 1	22.86 (22.71 – 23.00)	21.88 (21.46 – 22.29) *	20.83 (20.63 – 21.02)	20.31 (19.86 – 20.77)	17.86 (17.65 – 18.07)	17.22 (16.76 – 17.67)*
	Model 2	22.87 (22.72 – 23.02)	22.28 (21.82 – 22.73) *	20.98 (20.77 – 21.19)	20.49 (20.99 – 21.99)	18.03 (17.81 – 18.26)	17.51 (16.99 – 18.03)
	Model 3 (adjusted)	23.07 (22.90 – 23.24)	22.40 (21.86 – 22.95) *	21.11 (20.86 – 21.36)	20.79 (20.16 – 21.41)	18.22 (17.94 – 18.50)	17.88 (17.18 – 18.58)
	Mental Alternation test						
	Unadjusted model	28.49 (28.30 – 28.68)	26.74 (26.19 – 27.29) *	26.55 (26.27 – 26.83)	25.03 (24.40 – 25.67) *	23.18 (22.86 – 23.51)	21.50 (20.78 – 22.22)*
	Model 1	28.43 (28.24 – 28.63)	27.13 (26.56 – 27.70) *	26.46 (26.17 – 25.74)	25.48 (24.82 – 26.13) *	23.21 (22.88 – 23.54)	21.74 (21.01 – 22.48)*
	Model 2	28.55 (28.35 – 28.76)	27.36 (26.72 – 27.99) *	26.62 (26.31 – 26.93)	25.61 (24.88 – 26.34) *	23.33 (22.96 – 23.70)	21.87 (21.02 – 22.73)*
	Model 3 (adjusted)	28.76 (28.53 – 28.99)	27.84 (27.08 – 28.59) *	26.69 (26.33 – 27.05)	25.48 (24.57 – 26.40) *	23.42 (22.98 – 23.86)	22.64 (21.52 – 23.75)
	Stroop 1						
	Unadjusted model	11.28 (11.22 – 11.33)	11.56 (11.40 – 11.72) *	12.20 (12.11 – 12.29)	12.52 (12.32 – 12.72) *	13.47 (13.34 – 13.61)	13.88 (13.58 – 14.17)*
	Model 1	11.29 (11.24 – 11.35)	11.41 (11.24 – 11.57)	12.22 (12.13 – 12.31)	12.40 (12.19 – 12.61)	13.50 (13.36 – 13.64)	13.85 (13.55 – 14.15)
	Model 2	11.25 (11.19 – 11.31)	11.37 (11.19 – 11.55)	12.11 (12.02 – 12.21)	12.36 (12.13 – 12.59)	13.38 (13.24 – 13.53)	13.69 (13.35 – 14.02)
	Model 3 (adjusted)	11.22 (11.16 – 11.29)	11.21 (11.00 – 11.43)	12.17 (12.05 – 12.28)	12.21 (11.92 – 12.49)	13.39 (13.21 – 13.56)	13.56 (13.13 – 13.99)
	Stroop 2						

	Unadjusted model	13.84 (13.77 – 13.92)	14.79 (14.58 – 15.01) *	15.72 (15.59 – 15.85)	16.64 (16.35 – 16.93) *	18.47 (18.27 – 18.67)	19.74 (19.29 – 20.18)*
	Model 1	13.85 (13.78 – 13.92)	14.50 (14.29 – 14.72) *	15.74 (15.61 – 15.87)	16.43 (16.14 – 16.73) *	18.51 (18.31 – 18.71)	19.43 (18.98 – 19.88)*
	Model 2	13.81 (13.73 – 13.88)	14.38 (14.14 – 14.62) *	15.59 (15.46 – 15.73)	16.29 (15.97 – 16.62) *	18.27 (18.06 – 18.47)	19.20 (18.73 – 19.67)*
	Model 3 (adjusted)	13.73 (13.65 – 13.81)	14.09 (13.81 – 14.36) *	15.57 (15.42 – 15.73)	16.16 (15.76 – 16.56) *	18.18 (17.94 – 18.43)	18.90 (18.29 – 19.51)
	Stroop 3						
	Unadjusted model	21.80 (21.66 – 21.94)	23.51 (23.10 – 23.92) *	26.33 (25.89 – 26.77)	27.59 (26.59 – 28.59)	31.66 (31.23 – 32.09)	33.57 (32.63 – 34.50)*
	Model 1	21.81 (21.67 – 21.95)	22.97 (22.56 – 23.38) *	26.35 (25.89 – 26.82)	27.26 (26.20 – 28.32)	31.66 (31.24 – 32.08)	33.13 (32.20 – 34.06 *
	Model 2	21.73 (21.58 – 21.87)	22.85 (22.40 – 23.30) *	26.05 (25.52 – 26.57)	27.02 (25.78 – 28.26)	31.10 (30.65 – 31.55)	32.14 (31.09 – 33.187)
	Model 3 (adjusted)	21.55 (21.39 – 21.71)	22.33 (21.81 – 22.86) *	26.04 (25.36 – 26.72)	26.12 (24.40 – 27.84)	30.91 (30.36-31.46)	31.43 (30.05 – 32.82)
	Stroop low-interference index						
	Unadjusted model	1.24 (1.24 – 1.25)	1.30 (1.28 – 1.32) *	1.30 (1.30 – 1.31)	1.34 (1.32 – 1.36) *	1.40 (1.38 – 1.41)	1.45 (1.42 – 1.47) *
	Model 1	1.24 (1.23 – 1.24)	1.29 (1.27 – 1.30) *	1.30 (1.30 – 1.31)	1.34 (1.32 – 1.36) *	1.40 (1.38 – 1.41)	1.43 (1.40 – 1.46)
	Model 2	1.24 (1.23 – 1.25)	1.28 (1.26 – 1.30) *	1.30 (1.29 – 1.31)	1.33 (1.31 – 1.35) *	1.39 (1.38 – 1.40)	1.43 (1.40 – 1.46)
	Model 3 (adjusted)	1.24 (1.23 – 1.24)	1.27 (1.25 – 1.29) *	1.30 (1.28 – 1.31)	1.34 (1.31 – 1.36) *	1.38 (1.37 – 1.40)	1.42 (1.38 – 1.45)
	Stroop high-interference index						
	Unadjusted model	1.96 (1.95 – 1.98)	2.08 (2.05 – 2.11) *	2.18 (2.16 – 2.21)	2.23 (2.16 – 2.30)	2.40 (2.37 – 2.43)	2.46 (2.40 – 2.52)

	Model 1	1.96 (1.95 – 1.97)	2.06 (2.02 – 2.10) *	2.18 (2.15 – 2.21)	2.22 (2.15 – 2.29)	2.39 (2.37 – 2.42)	2.44 (2.37 – 2.50)
	Model 2	1.96 (1.95 – 1.97)	2.05 (2.01 – 2.09) *	2.18 (2.14 – 2.21)	2.21 (2.13 – 2.29)	2.37 (2.34 – 2.40)	2.39 (2.32 – 2.46)
	Model 3 (adjusted)	1.95 (1.94 – 1.96)	2.02 (1.98 – 2.07) *	2.16 (2.12 – 2.21)	2.16 (2.05 – 2.28)	2.34 (2.31 – 2.38)	2.36 (2.27 – 2.45)
	COWAT						
	Unadjusted model	42.72 (42.43 – 43.01)	40.51 (39.67 – 41.35) *	40.93 (40.48 – 41.38)	38.75 (37.73 – 39.76) *	38.15 (37.64 – 38.65)	35.34 (34.23 – 36.45)*
	Model 1	42.63 (42.34 – 42.93)	41.09 (40.21 – 41.97) *	40.92 (40.47 – 41.38)	39.40 (38.36 – 40.45) *	38.09 (37.58 – 38.59)	35.95 (34.83 – 37.07)*
	Model 2	42.65 (42.33 – 42.97)	41.57 (40.59 – 42.55) *	41.19 (40.70 – 41.68)	39.81 (38.65 – 40.98)	38.48 (37.92 – 39.04)	36.89 (35.59 – 38.18)
	Model 3 (adjusted)	42.99 (42.64 – 43.34)	41.99 (40.83 – 43.15)	41.15 (40.58 – 41.72)	40.00 (38.55 – 41.46)	38.59 (37.91 – 39.26)	39.09 (37.37 – 40.81)
	Choice Reaction Time Test						
	Unadjusted model	777.9 (773.9 – 782.0)	784.7 (772.8 – 796.6)	865.8 (856.6 – 874.9)	865.1 (844.4 – 885.8)	974.1 (959.8 – 988.5)	961.3 (929.7 – 992.9)
	Model 1	779.0 (774.8 – 783.2)	776.8 (764.4 – 789.2)	867.2 (857.5 – 876.9)	862.0 (839.9 – 884.1)	975.3 (960.1 – 990.4)	958.8 (925.2 – 992.3)
	Model 2	777.7 (773.1 – 782.3)	774.5 (760.5 – 788.5)	863.8 (852.9 – 874.7)	859.6 (833.9 – 885.2)	970.7 (953.2 – 988.2)	960.2 (919.4– 1000.9)
	Model 3 (adjusted)	776.4 (771.3 – 781.5)	773.9 (757.2 – 790.5)	866.5 (853.0 – 880.0)	857.4 (823.1 – 891.7)	974.3 (95412 – 994.5)	935.2 (884.4 – 986.1)
MEN	**Total N (weighted %)**	4102 (81.5)	1034 (18.5)	3014 (75.2)	1056 (24.8)	2616 (76.2)	781 (23.8)
	RAVLT Immediate recall						
	Unadjusted model	6.14 (6.09 – 6.18)	6.09 (6.00 – 6.18)	5.62 (5.55 – 5.69)	5.47 (5.36 – 5.59)	4.56 (4.48 – 4.64)	4.63 (4.48 – 4.78)

	Model 1	6.12 (6.08 – 6.17)	6.13 (6.03 – 6.22)	5.61 (5.54 – 5.68)	5.52 (5.40 – 5.63)	4.56 (4.48 – 4.64)	4.57 (4.42 – 4.72)
	Model 2	6.14 (6.09 – 6.19)	6.17 (6.07 – 6.27)	5.63 (5.56 – 5.70)	5.58 (5.46 – 5.71)	4.60 (4.51 – 4.68)	4.56 (4.40 – 4.72)
	Model 3 (adjusted)	6.12 (6.07 – 6.18)	6.16 (6.05 – 6.27)	5.65 (5.57 – 5.72)	5.62 (5.48 – 5.76)	4.60 (4.51 – 4.68)	4.58 (4.42 – 4.75)
	RAVLT 5-min recall						
	Unadjusted model	4.41 (4.36 – 4.46)	4.25 (4.15 – 4.36)	3.68 (3.60 – 3.75)	3.59 (3.46 – 3.71)	2.62 (2.53 – 2.70)	2.80 (2.65 – 2.96)
	Model 1	4.40 (4.34 – 4.45)	4.27 (4.16 – 4.38)	3.68 (3.60 – 3.76)	3.63 (3.50 – 3.76)	2.61 (2.53 – 2.70)	2.74 (2.59 – 2.90)
	Model 2	4.40 (4.34 – 4.45)	4.36 (4.24 – 4.48)	3.70- (3.62 – 3.78)	3.72 (3.58 – 3.85)	2.65 (2.56 – 2.74)	2.83 (2.66 – 3.00)
	Model 3 (adjusted)	4.38 (4.32 – 4.44)	4.37 (4.24 – 4.49)	3.71 (3.62 – 3.79)	3.70 (3.55 – 3.85)	2.64 (2.54 – 2.73)	2.76 (2.59 – 2.95)
	Animal Fluency test						
	Unadjusted model	23.22(23.06 – 23.37)	22.85 (22.54 – 23.17)	21.61 (21.38 – 21.83)	21.20 (20.81 – 21.58)	18.51 (18.25 – 18.78)	18.12 (17.64 – 18.59)
	Model 1	23.20 (23.04 – 23.36)	22.95 (22.63 – 23.27)	21.59 (21.36 – 21.83)	21.31 (20.91 – 21.70)	18.50 (18.23 – 18.77)	17.96 (17.47 – 18.44)
	Model 2	23.37 (23.20 – 23.54)	23.14 (22.80 – 23.49)	21.67 (21.42 – 21.92)	21.65 (21.22 – 22.08)	18.65 (18.37 – 18.94)	18.14 (17.62 – 18.66)
	Model 3 (adjusted)	23.37 (23.20 – 23.54)	23.18 (22.81 – 23.55)	21.74 (21.48 – 22.00)	21.76 (21.29 – 22.23)	18.68 (18.38 – 18.98)	18.27 (17.71 – 18.83)
	Mental Alternation test						
	Unadjusted model	29.97 (29.74 – 30.20)	29.62 (29.16 – 30.08)	28.30 (27.96 – 28.63)	27.46 (26.90 – 28.03) *	25.06 (24.63 – 25.50)	24.14 (23.35 – 24.92)
	Model 1	29.98 (29.76 – 30.21)	29.81 (29.35 – 30.28)	28.14 (27.79 – 28.48)	27.55 (26.97 – 28.13)	25.01 (24.57 – 25.45)	24.08 (23.27 – 24.88)

	Model 2	30.14 (29.90 – 30.38)	30.04 (29.54 – 30.54)	28.21 (27.84 – 28.57)	27.86 (27.23 – 28.50)	25.15 (24.67 – 25.63)	24.35 (23.47 – 25.23)
	Model 3 (adjusted)	30.10 (29.84 – 30.35)	30.42 (29.88 – 30.96)	28.25 (27.86 – 28.63)	27.93 (27.24 – 28.62)	25.14 (24.64 – 25.65)	24.31 (23.37 – 25.24)
	Stroop 1						
	Unadjusted model	11.64 (11.58 – 11.71)	11.65 (11.52 – 11.79)	12.64 (12.53 – 12.76)	12.76 (12.57 – 12.96)	14.22 (14.05 – 14.39)	14.40 (14.09 – 14.70)
	Model 1	11.65 (11.59 – 11.72)	11.61 (11.47 – 11.75)	12.64 (12.52 – 12.75)	12.73 (12.53 – 12.92)	14.19 (14.02 – 14.36)	14.50 (14.20 – 14.81)
	Model 2	11.55 (11.49 – 11.63)	11.52 (11.37 – 11.66)	12.61 (12.49 – 12.74)	12.59 (12.38 – 12.80)	14.16 (13.98 – 14.33)	14.30 (13.97 – 14.62)
	Model 3 (adjusted)	11.55 (11.48 – 11.62)	11.48 (11.32 – 11.63)	12.58 (12.45 – 12.70)	12.49 (12.27 – 12.71)	14.13 (13.95 – 14.31)	14.29 (13.95 – 14.62)
	Stroop 2						
	Unadjusted model	14.18 (14.09 – 14.26)	14.28 (14.10 – 14.45)	15.94 (15.78 – 16.09)	16.65 (16.40 – 16.91) *	19.14 (18.89 – 19.39)	19.66 (19.21 – 20.11)
	Model 1	14.19 (14.11 – 14.28)	14.21 (14.04 – 14.39)	15.97 (15.82 – 16.13)	16.58 (16.32 – 16.83) *	19.14 (18.89 – 19.40)	19.75 (19.30 – 20.21
	Model 2	14.09 (14.00 – 14.18)	14.08 (13.89 – 14.27)	15.96 (15.80 – 16.12)	16.33 (16.06 – 16.60)	19.05 (18.79 – 19.32)	19.58 (19.09 – 20.06)
	Model 3 (adjusted)	14.10 (14.01 – 14.19)	14.01 (13.80 – 14.21)	15.93 (15.77 – 16.09)	16.17 (15.88 – 16.46)	19.02 (18.75 – 19.30)	19.53 (19.03 – 20.04)
	Stroop 3						
	Unadjusted model	22.49 (22.31 – 22.67)	23.05 (22.68 – 23.42)	26.27 (25.95 – 26.59)	27.66 (27.12 – 28.19) *	32.49 (31.95 – 33.04)	33.95 (32.97 – 34.93)
	Model 1	22.53 (22.35 – 22.71)	22.89 (22.10 – 23.27)	26.32 (26.00 – 26.64)	27.45 (26.91 – 28.00) *	32.43 (31.88 – 32.97)	34.21 (33.23– 35.20)
	Model 2	22.31 (22.12 – 22.50)	22.68 (22.29 – 23.08)	26.28 (25.95 – 26.61)	27.06 (26.49 – 27.63)	32.21 (31.65 – 32.77)	33.65 (32.63 – 34.68)
	Model 3 (adjusted)	22.34 (22.14 – 22.53)	22.57 (22.15 – 22.99)	26.25 (25.91 – 26.59)	26.79 (26.18 – 27.40)	32.12 (31.54 – 32.69)	33.68 (32.62 – 34.75)

	Stroop low-interference index						
	Unadjusted model	1.23 (1.22 – 1.23)	1.24 (1.23 – 1.25)	1.28 (1.27 – 1.29)	1.32 (1.30 – 1.33) *	1.36 (1.35 – 1.38)	1.40 (1.37 – 1.42)
	Model 1	1.23 (1.22 – 1.24)	1.24 (1.22 – 1.25)	1.28 (1.27 – 1.29)	1.32 (1.30 – 1.33) *	1.36 (1.35 – 1.38)	1.39 (1.37 – 1.42)
	Model 2	1.23 (1.22 – 1.24)	1.23 (1.22 – 1.25)	1.28 (1.27 – 1.29)	1.31 (1.29 – 1.33) *	1.36 (1.35 – 1.38)	1.39 (1.37 – 1.42)
	Model 3 (adjusted)	1.23 (1.23 – 1.24)	1.23 (1.22 – 1.24)	1.28 (1.27 – 1.29)	1.31 (1.29 – 1.33)	1.36 (1.35 – 1.38)	1.39 (1.36 – 1.42)
	Stroop high-interference index						
	Unadjusted model	1.96 (1.94 – 1.97)	2.00 (1.97 – 2.03)	2.12 (2.09 – 2.14)	2.19 (2.15 – 2.23) *	2.32 (2.28 – 2.35)	2.40 (2.34 – 2.46)
	Model 1	1.96 (1.94 – 1.97)	2.00 (1.97 – 2.02)	2.12 (2.10 – 2.14)	2.18 (2.14 – 2.22) *	2.32 (2.28 – 2.35)	2.40 (2.34 – 2.46)
	Model 2	1.96 (1.94 – 1.97)	1.99 (1.96 – 2.03)	2.12 (2.10 – 2.14)	2.17 (2.13 – 2.21)	2.30 (2.27 – 2.34)	2.39 (2.33 – 2.46)
	Model 3 (adjusted)	1.96 (1.95 – 1.98)	1.99 (1.96 – 2.02)	2.12 (2.10 – 2.15)	2.17 (2.12 – 2.21)	2.30 (2.27 – 2.34)	2.40 (2.33 – 2.47)
	COWAT						
	Unadjusted model	40.64 (40.32 – 40.96)	40.05 (39.39 – 40.70)	39.34 (38.84 – 39.84)	37.85 (37.01 – 38.69) *	36.19 (35.54 – 36.84)	34.29 (33.13 – 35.45)
	Model 1	40.65 (40.33 – 40.98)	40.17 (39.50 – 40.85)	39.13 (38.61 – 39.64)	38.22 (37.36 – 39.08)	36.20 (35.54 – 36.85)	34.35 (33.17 – 35.53)
	Model 2	40.88 (40.53 – 41.22)	40.71 (39.99 – 41.44)	39.37 (38.82 – 39.91)	38.72 (37.79 – 39.66)	36.21 (35.52 – 36.90)	34.75 (33.49 – 36.01)
	Model 3 (adjusted)	40.81 (40.45 – 41.17)	40.86 (40.09 – 41.63)	39.46 (38.89 – 40.03)	39.10 (38.08 – 40.11)	36.26 (35.54 – 36.99)	34.88 (33.54 – 36.21)
	Choice Reaction Time Test						

	Unadjusted model	755.1 (750.1 – 760.1)	759.4 (749.2 – 769.6)	837.2 (828.3 – 846.1)	852.5 (837.5 – 867.4)	914.2 (901.9 – 926.5)	931.6 (909.6 – 953.6)
	Model 1	755.1 (750.5 – 759.8)	756.3 (746.8 – 765.9)	837.0 (827.8 – 846.3)	852.4 (836.8 – 868.0)	916.7 (903.9 – 929.6)	937.3 (914.1 – 960.6)
	Model 2	751.1 (746.2 – 756.1)	751.2 (740.9 – 761.5)	837.6 (827.7 – 847.6)	852.1 (835.0 – 869.2)	916.4 (902.8 – 930.0)	916.4 (895.6 – 945.3)
	Model 3 (adjusted)	750.4 (745.3 – 755.6)	748.2 (737.2 – 759.3)	835.5 (825.0 – 845.9)	850.7 (832.1 – 869.4)	913.9 (899.6 – 928.1)	917.1 (890.7 – 943.4)

RAVLT: Rey auditory verbal learning test; COWAT: Controlled oral word association test.

Model 1 includes socio-demographic variables (age, education, income, working status, marital status, ethnicity); Model 2 includes Model 1 + lifestyle variables (smoking, alcohol, physical activity, sleep quality, sleep duration); Model 3 includes Model 2 + clinical variables (cardiovascular disease, diabetes, chronic obstructive pulmonary disease, anxiety-depression symptoms, asthma, functional status, general health perception, menopausal status, levels of C-reactive protein concentration) covariables.

All results are presented as adjusted means with 95% confidence intervals.

All p-values were FDR-adjusted for multiple comparisons

*: FDR-adjusted p-value is significant (<0.05)

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2.3 Article 4

Article 4 : Age- and sex-specific associations between obstructive sleep apnea risk and cognitive decline in middle-aged and older adults: A 3-year longitudinal analysis of the Canadian Longitudinal Study on Aging

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Contribution : Pour cet article, j'ai procédé à une revue de la littérature, effectué les analyses statistiques, interprété les résultats, rédigé et révisé de manière critique le manuscrit.

Abstract

Background: Whether obstructive sleep apnea (OSA) increases the risk of cognitive decline and how sex and age influence this association is not clear. Here, we characterized the sex- and age-specific associations between OSA risk and 3-year cognitive changes in middle-aged and older adults.

Methods: We included 24,819 participants aged 45-85 (52% women) from the Canadian Longitudinal Study on Aging. OSA risk was measured at baseline using the STOP combined to body mass index (STOP-B). Neuropsychological tests assessed memory, executive functioning, and psychomotor speed at baseline and at 3-year follow-up. We conducted age- and sex-specific linear mixed models to estimate the predictive role of baseline STOP-B score on 3-year cognitive changes.

Results: Men at high-risk for OSA aged 45-59 years showed a steeper decline in psychomotor speed (+13.2 [95%CI: -1.6, 27.9]) compared to men at low-risk. Men at high-risk for OSA aged 60-69 showed a steeper decline in mental flexibility (-1.2 [-1.9, -0.5]) and processing speed (+0.6 [0.3, 0.9]) than those at low-risk. Women at high-risk for OSA aged 45-59 showed a steeper decline in processing speed (+0.1 [-0.2, 0.4]) than women at low-risk, while women at high-risk ≥70 years had a steeper decline in memory (-0.2 [-0.6, 0.1]) and processing speed (+1.0 [0.4, 1.5]).

Conclusions: Associations between OSA risk and cognitive decline over 3 years depend on age and sex. Being at high-risk for OSA is associated with a generalized cognitive decline in attention and processing speed, while a memory decline is specific to older women (≥70 years).

1. Introduction

1.1 OSA and cognition

Obstructive sleep apnea (OSA) is a serious public health issue, as 6 to 17% of the general adult population and up to 49% of adults aged 40-85 present with a moderate to severe form of the

disease (Senaratna et al., 2017). OSA often goes undiagnosed. In a Canadian study, only 3% of adults reported a diagnosis (Public Health Agency of Canada., 2010), while a quarter are at high-risk (Thompson, Legault, Moullec, Baltzan, et al., 2022). Even when diagnosed, only 58% accept the continuous positive airway pressure (CPAP) treatment (Lee et al., 2017). Amongst those, only 41% remain compliant to their treatment after one year (Lee et al., 2017).

OSA leads to sleep fragmentation and intermittent hypoxia, which induce excessive daytime sleepiness and cognitive dysfunctions (Gosselin et al., 2019). Numerous brain structures are sensitive to OSA-related hypoxemia and sleep fragmentation (Shi et al., 2017; Weng et al., 2014), such as the prefrontal and parietal cortex and the hippocampi. Cognitive domains relying on these regions, such as memory, executive function and processing speed, are affected in adults with OSA (Bucks et al., 2013; Gagnon et al., 2014). Memory problems in the context of OSA in late middle-aged and older adults thus require special attention, as they could represent a neurodegenerative process leading to abnormal cognitive decline and Alzheimer's disease (AD) (Dubois et al., 2016). It is essential to determine which risk factors for OSA are associated with increased cognitive decline in middle-aged and older adults to identify individuals who should be screened and treated in priority.

Several large cross-sectional and longitudinal cohort studies showed lower cognitive performance in OSA patients as compared to non-OSA participants (Duan et al., 2022; Kaur et al., 2021; Marchi et al., 2023; Ramos et al., 2015; Shieu et al., 2022; Thompson, Legault, Moullec, Martineau-Dussault, et al., 2022; Ward et al., 2022; Yaffe et al., 2011), but others did not (Allen et al., 2020; Lee et al., 2022; Lutsey et al., 2016, 2018; Parker et al., 2021). Different methodologies used to identify OSA participants (e.g., questionnaires, self-reported diagnosis, national registry, objective measures) may explain part of the heterogeneity. Cross-sectional studies using the STOP-Bang (Shieu et al., 2022) and the Berlin (Addison-Brown et al., 2014) screening questionnaires found that being at high-risk for OSA is associated with an increased risk of cognitive impairment and dementia. Some cross-sectional and longitudinal studies using objective in-home testing or in-laboratory polysomnography recordings support these findings (Kaur et al., 2021; Ramos et al., 2015; Ward et al., 2022; Yaffe et al., 2011), but most studies

show a limited (Blackwell et al., 2015; Saint Martin et al., 2015) or absence of association (Allen et al., 2020; Lee et al., 2022; Lutsey et al., 2016, 2018; Parker et al., 2021; Suemoto et al., 2021). Moreover, most longitudinal studies assessing the relationship between OSA and cognitive decline found that OSA (based on insurance databases or self-reported diagnosis) was associated with a 1.6 to 2.2-times greater risk of presenting with mild cognitive impairment (MCI) over time (Chang et al., 2013; Duan et al., 2022; Lee et al., 2019) and an earlier MCI or AD onset of approximately 10 years (Osorio et al., 2015). Screening participants using questionnaires rather than including only diagnosed OSA cases could capture particularly symptomatic patients and/or with severe OSA who might present more important OSA-related cognitive decline.

Participants' individual characteristics could influence the association between OSA and the risk of cognitive decline (Legault et al., 2021). Age should be considered, as it is the main risk factor for dementia (Lindsay et al., 2002) and an important risk factor for OSA (Kryger et al., 2011). Results from previous studies suggest a steeper cognitive decline in older (> 60 years (Lee et al., 2022); > 65 years (Kaur et al., 2021); > 70 years (Chang et al., 2013); > 75 years (Marchi et al., 2023)) than in younger-old adults with OSA. However, one study showed the reverse pattern, where OSA-related cognitive decline was only observed in middle aged-adults (50-59 years (Chang et al., 2013)). The impact of OSA on cognitive decline might follow a non-linear trend with age. In fact, conditions affecting cognition and showing different prevalence according to age (e.g., high blood pressure (Mossello & Simoni, 2015), menopause (Scheyer et al., 2018), subclinical neurodegeneration due to early AD (Jack et al., 2010)) may blur the association between OSA and cognition in some age groups. Using multiple age groups might allow a better understanding of the role of age as a moderator in the association between OSA and cognitive decline, as the independent effects of several variables on the brain and their interaction with OSA could vary with age.

While the symptomatology of OSA and its impact on diurnal functioning is sex-specific (Bonsignore et al., 2019; Lozo et al., 2017), the effect of sex on the association between OSA

and cognitive function is still unclear and has been investigated in only a few cohorts, yielding inconsistent results. Some cross-sectional studies have found that women with OSA or at high-risk for OSA were more likely to show cognitive impairment than men with a similar OSA status (Bade et al., 2014; Blackwell et al., 2011; Foley et al., 2003; Qiu et al., 2022; Ramos et al., 2015; Spira et al., 2008; Thompson, Legault, Moullec, Martineau-Dussault, et al., 2022), while some longitudinal studies found the opposite (Lee et al., 2022; Marchi et al., 2023). Indeed, longitudinal data from the HypnoLaus study show a stronger association between AHI and oxygen desaturation index (ODI) and a steeper cognitive decline in men than women (Marchi et al., 2023).

The present study characterized the age- and sex-specific association between OSA risk, as determined by the STOP-B score, and 3-year change in cognitive performance. We hypothesized that participants at high-risk of OSA would present a steeper 3-year cognitive decline than those at low-risk. Moreover, we hypothesized that this relationship would be more pronounced in women compared to men. Finally, we expect that comparing more than two groups will allow us to highlight age effects, which could possibly be non-linear. Since our approach to assess cognitive outcomes is semi-exploratory, findings should be interpreted carefully and may not be definitive evidence for cognitive decline.

2. Material and methods

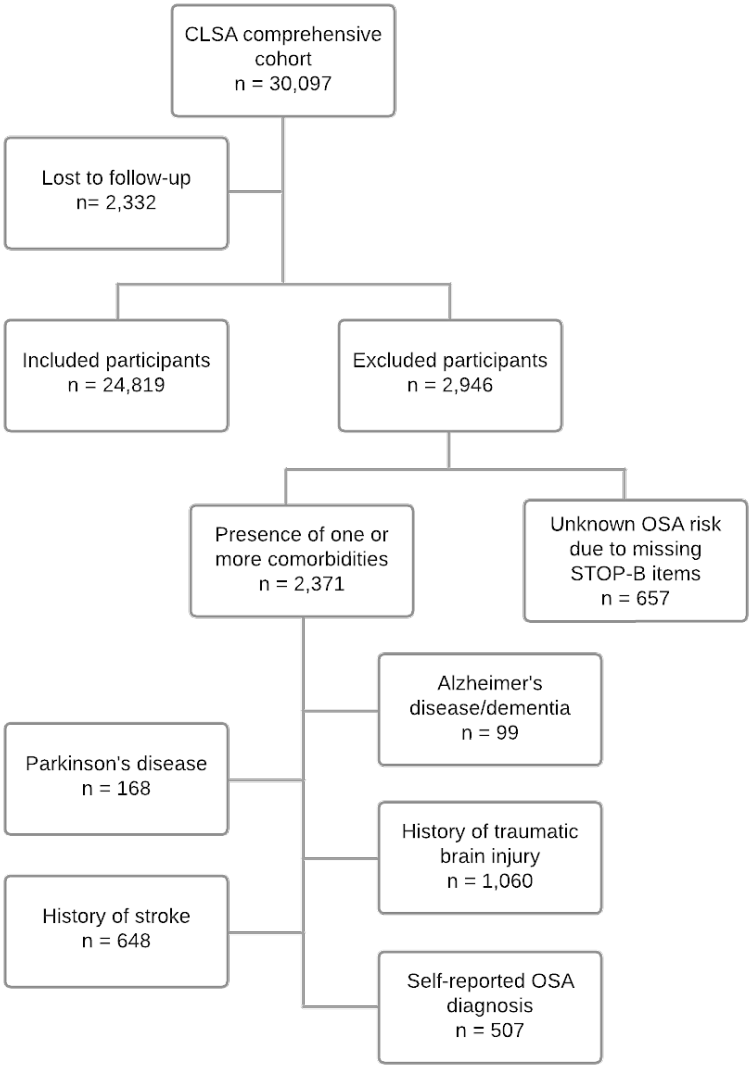
2.1 Study design and participants

We used data from the Canadian Longitudinal Study on Aging (CLSA) comprehensive cohort, a national-based, prospective study on healthy aging. Recruiting methods and cohort characteristics were described previously (Raina et al., 2019; Raina et al., 2009). Baseline data were collected from 30,097 participants between 2011 and 2015, while follow-up data were collected from 27,765 participants between 2015 to 2018. Participants were recruited through telephone random digit dialling (n = 25,968; 10% response rate) or provincial healthcare registration databases (n = 4,129; 9% response rate).

The CLSA comprehensive cohort inclusion criteria were (1) being 45-85 years old at baseline, (2) being fluent in English or French, (3) living within 25 km of a data collection site, and (4) being able to give informed consent and understand instructions. Exclusion criteria for the present study included having dementia or neurologic conditions (AD, Parkinson's disease and stroke), or traumatic brain injury with loss of consciousness for 20 minutes, either at baseline or follow-up. We also excluded participants reporting sleep apnea at baseline or follow-up from the main analyses as we had no information regarding possible treatment. However, they were included in sensitivity analyses (see below). A total of 24,819 participants were included in our analyses (Figure 1).

The CLSA is overseen by a McMaster University collaborative Research Ethics Board forum. Participation in the CLSA cohort is voluntary, and all individuals provided written informed consent. Our study was approved by the Research Ethics Board of the Centre intégré universitaire de santé et services sociaux du Nord de l'Ile-de-Montréal (REB 2018-1584).

Figure 1. Flowchart illustrating the inclusion and exclusion of participants



2.4 Measures

2.2.1 OSA risk classification

To assess participants' OSA risk, we used five items of the STOP-Bang: **S**noring; **T**iredness, sleepiness, or fatigue; **O**bserved apneas; high blood **P**ressure; and **B**ody mass index (BMI) > 35 kg/m^2 (details available in the supplemental material).

The STOP questionnaire has a sensitivity of 79.5% and a specificity of 48.6% in detecting severe OSA in adults aged 18 and over (Chung et al., 2008), and a better validity in predicting OSA in

women than in men (Horvath et al., 2018; Pataka et al., 2020). However, a meta-analysis found that age was positively associated with sensitivity (Chiu et al., 2017). Adding **B**MI, **A**ge, **N**eck circumference, and sex (labelled as **G**ender in the original tool) to form the STOP-Bang score increases its sensitivity to 100% in detecting severe OSA (Chung et al., 2008). Since neck circumference was unavailable in the CLSA, we used the STOP-B score with a maximum value of 5 and stratified our analyses according to age and sex. Recent systematic reviews have shown that a STOP-Bang score ≥3 has a sensitivity between 88% (Chen et al., 2021) and 94% (Pivetta et al., 2021) for detecting moderate-to-severe OSA and a negative predictive value reaching 93% (Chen et al., 2021). Hence, participants scoring ≥3 on the STOP-B were considered at high-risk for OSA.

2.2.2 Neuropsychological assessment

CLSA-trained interviewers administered the neuropsychological testing battery following a standardized order. Three domains were assessed: verbal memory (Rey Auditory Verbal Learning Test (RAVLT))(Rey, 1964), executive functions (Animal Fluency test (Survey of Health Ageing and Retirement in Europe (SHARE), 2005), Mental Alternation test (Teng, 1995), Stroop test (Victoria version) (Bayard et al., 2011; Troyer et al., 2006) and Controlled Oral Word Association test; COWAT) (Spreen & Benton, 1977) and psychomotor speed (Choice reaction time) (Gallacher et al., 2013).

The RAVLT assessed memory, learning, and retention. Participants were asked to recall common nouns from a list of 15 heard five consecutive times (one word per second). The number of remembered words in the first immediate recall trial and the 5-min delayed recall trial were reported.

The Animal Fluency Test assessed semantic word fluency, while the Controlled Oral Word Association test assessed phonemic word fluency. Participants were asked to name as many animals (Animal Fluency test) or words beginning with a specific letter (F-, A-, S-; COWAT) as possible during 60-sec trials. The number of words generated were reported.

The Mental Alternation Test assessed mental flexibility and processing speed by asking participants to generate matched pairs of ordered numbers and letters over a 30-sec trial. The number of correct matched pairs was reported.

The Stroop test (Victoria version) assessed processing speed and inhibition. Participants were presented with printed cards and were asked to name the color of dots (condition 1), words (condition 2), and the color of the ink in which a color word is printed (condition 3). The time was reported for the three conditions in seconds. We also calculated the interference index to isolate the inhibition component of the test. The low interference index corresponded to the time for condition 2 / the time for condition 1, and the high interference index corresponded to the time for condition 3 / the time for condition 1.

Finally, the Choice Reaction Time assessed participants' psychomotor speed by asking them to touch an interactive computer screen where a target appeared as quickly as possible. The mean latency over 60 trials was reported in milliseconds.

2.2.3 Covariates

We selected covariates based on the literature, clinical relevance, and availability in the CLSA. We described them previously (Thompson, Legault, Moullec, Martineau-Dussault, et al., 2022) and detailed reference categories in the supplemental material.

2.3 Statistical analysis

We conducted age and sex-specific Linear Mixed Models (LMM) between OSA risk and neuropsychological test scores in six separate groups. We formed age groups based on the literature (Hedden & Gabrieli, 2004: middle-aged, 45-59 years; younger-old, 60-69 years; older-old, ≥70 years). Model 1 only accounted for sociodemographic variables, while we additionally added lifestyle-related variables in Model 2 and clinical variables in Model 3 (fully adjusted). Fixed effects were baseline OSA risk and covariables, and random effects were the individuals (id).

After verifying the number of missing values and the profile of participants with missing values, we conducted multiple imputations on the entire dataset. We performed the statical analyses using RStudio. We used the package *lmerTest* to conduct the LMMs and *mice* for the multiple imputations (details available in the supplemental material). The level of significance was set at $p < 0.05$.

2.3.1 Sensitivity analyses

Sensitivity analyses were conducted to assess the robustness of our findings. First, we ran the models on the entire sample without stratification by age and sex. Second, we examined the impact of including participants who reported an OSA diagnosis (n= 464) on our results.

3. Results

3.1 Description of the sample

Table 1 presents the sex- and age-specific characteristics of the sample (detailed description of the sample is presented in Table S1). Of the participants, 52% were women. The sample was divided into three age categories: 42.6% were middle-aged (45-59 years), 31.9% were young-old (60-69 years), and 25.5% were older-old adults (70 years and over). Additionally, 7.5% of the sample were classified as being at high-risk for OSA.

In general, participants lost to follow-up were more likely to show sociodemographic, lifestyle and clinical characteristics associated with an increased risk of OSA and cognitive impairment (see Table S2 for details). They did not differ from those included in the analyses in terms of sex, sleep satisfaction, asthma, or anxious-depressive symptoms.

Regarding STOP-B items, participants lost to follow-up were less likely to report snoring ($p < 0.001$) and observed apneas ($p = 0.008$), but more likely to report tiredness ($p = 0.017$). Participants did not differ on the presence of high blood pressure and high BMI. They did not differ on the OSA risk category.

Table 1. Description of the sample according to sex, age and OSA risk at baseline

		Middle-aged: 45-59 years		Younger-old: 60-69 years		Older-old: 70-85 years	
		Low-risk	**High-risk**	**Low-risk**	**High-risk**	**Low-risk**	**High-risk**
Men	**Group size, n (%)**	4494 (91.2)	433 (8.8)	3443 (89.1)	422 (10.9)	2894 (92.9)	221 (7.1)
	Snoring (S), n (%)	1359 (30.2)	376 (86.8)	890 (25.8)	351 (83.2)	533 (18.4)	178 (80.5)
	Daytime tiredness, sleepiness or fatigue (T), n (%)	225 (5.0)	122 (28.2)	204 (5.9)	110 (26.1)	209 (7.2)	94 (42.5)
	Observed apneas (O), n (%)	601 (13.4)	344 (79.4)	429 (12.5)	333 (78.9)	306 (10.6)	176 (79.6)
	High blood pressure (P), n (%)	862 (19.2)	356 (82.2)	1165 (33.8)	382 (90.5)	1338 (46.2)	203 (91.9)
	BMI > 35 kg/m^2 (B), n (%)	190 (4.2)	226 (52.2)	122 (3.5)	196 (46.4)	67 (2.3)	64 (29.0)
	Age (mean (SD))	52.75 (4.00)	53.67 (3.81)	64.16 (2.82)	64.46 (2.94)	76.08 (4.16)	75.42 (4.28)
	Post-secondary education, n (%)	3825 (85.1)	340 (78.5)	2786 (81.0)	334 (79.3)	2170 (75.4)	163 (74.1)
Women	**Group size, n (%)**	5344 (94.7)	297 (5.3)	3752 (92.4)	309 (7.6)	3034 (94.5)	176 (5.5)
	Snoring (S), n (%)	844 (15.8)	242 (81.5)	603 (16.1)	244 (79.0)	339 (11.2)	128 (72.7)
	Daytime tiredness, sleepiness or fatigue (T), n (%)	272 (5.1)	114 (38.4)	193 (5.1)	98 (31.7)	208 (6.9)	68 (38.6)
	Observed apneas (O), n (%)	260 (4.9)	172 (57.9)	181 (4.8)	185 (59.9)	111 (3.7)	94 (53.4)
	High blood pressure (P), n (%)	868 (16.2)	233 (78.5)	1184 (31.6)	266 (86.1)	1454 (47.9)	163 (92.6)
	BMI > 35 kg/m^2 (B), n (%)	381 (7.1)	210 (70.7)	296 (7.9)	216 (69.9)	146 (4.8)	105 (59.7)
	Age (mean (SD))	52.84 (4.01)	53.68 (3.83)	64.19 (2.82)	64.15 (2.77)	76.18 (4.18)	75.77 (4.40)
	Post-secondary education, n (%)	4503 (84.3)	226 (76.1)	2898 (77.4)	203 (66.1)	2016 (66.5)	109 (61.9)

Note: n are crude numbers, proportions are weighted to account for the sampling strategy. BMI: Body mass index ; SD: standard deviation

2.5 Cognitive changes over time in the whole sample

We first examined 3-year cognitive change regardless of OSA risk in the whole sample. Performance worsened on the Mental Alternation test (-0.5 pair [95%CI: -0.6, -0.5]), AFT (-0.2 word [-0.3, -0.2]), and the three Stroop conditions (dot: +0.4 sec [0.3 – 0.4]; word: +0.5 sec [0.4, 0.5]; color: +0.6 sec [0.5, 0.7]), while it improved on the RAVLT immediate recall (+0.7 word [0.6, 0.7]), RAVLT delayed 5-min recall (+0.6 word [0.6 – 0.6]), COWAT (+0.7 word [0.6, 0.8]), Stroop indices (low interference: -0.01 [-0.01, 0.0]; high interference: -0.01 [-0.01, 0.0]), and Choice Reaction Time (-6.3 msec [-8.5, -4.1]).

3.3 Association between OSA risk and 3-year cognitive change

Table 2 presents the cognitive scores obtained at baseline and 3-year follow-up in middle-aged, younger-old and older-old men and women, based on their OSA risk levels. The results we report were obtained using the fully adjusted model (Model 3) that accounts for sociodemographic, lifestyle-related and clinical variables. The statistical significance level did not change across the different models (Model 1: sociodemographic variables only; Model 2: sociodemographic and lifestyle-related variables). More detailed results for Models 1 and 2 are available upon request. Figures 2 to 6 present the cognitive changes according to OSA risk and age groups in men and women.

Men at high-risk for OSA aged 45-59 years showed a steeper decrease in processing speed, as demonstrated by longer reaction times on the Choice Reaction Time (+13.2 ms [-1.6 – 27.9]; figure 2), but a greater improvement on the COWAT test than those at low-risk for OSA (+1.8 word [1.0 – 2.6]; figure 3). Among men aged 60-69 years, those at high-risk for OSA showed a steeper decline of cognitive scores than those at low-risk for OSA on the Mental Alternation test (-1.2 pair [-1.9 - -0.5]; figure 4) and the Stroop test, condition 1 (dots) (+0.6 sec [0.3 – 0.9]; figure 5). There was no significant association between OSA risk and cognitive change in men aged 70 and over.

Women aged 45-59 years at high-risk for OSA showed a steeper decline of cognitive scores than those at low-risk for OSA on the Stroop test, condition 1 (dots) (+0.1 sec [-0.2 – 0.4]; figure 5). Women aged 60-69 at high-risk for OSA improved their performance on the Mental Alternation test (+0.8 par [0.0 – 1.6]; figure 4), whereas those at low-risk for OSA showed a decline in performance. Women aged 70 years and over at high-risk for OSA had a steeper decline in cognitive scores on the RAVLT delayed 5-min recall (-0.2 word [-0.6 – 0.1]; figure 6) and the Stroop test, condition 1 (dots) (+1.0 sec [0.4 – 1.5]; figure 5) compared to those at low-risk for OSA.

Table 2. Cognitive scores according to sex, age and OSA risk

	Neuropsychological variable	**Low-risk OSA** (unadjusted mean (SD))		**High-risk OSA** (unadjusted mean (SD))		**Estimate** (95% CI)
		Baseline	Follow-up	Baseline	Follow-up	
Middle-aged men (45-59 years)	Group size, n	4494		433		
	RAVLT immediate recall (nb of words)	6.1 (1.8)	6.9 (2.0)	6.0 (1.6)	6.7 (1.8)	P = 0.5
	RAVLT 5-min delayed recall (nb of words)	4.3 (2.0)	5.0 (2.2)	4.1 (1.9)	4.7 (2.1)	P = 0.6
	Mental Alternation test (nb of pairs)	29.6 (8.8)	29.4 (7.5)	29.1 (8.8)	29.0 (7.6)	P = 0.6
	Animal Fluency test (nb of words)	22.8 (5.9)	22.6 (5.6)	22.6 (5.7)	22.4 (5.7)	P = 0.6
	COWAT (nb of words)	40.5 (12.5)	41.4 (12.2)	39.3 (12.0)	41.3 (12.2)	+1.8 (1.0 – 2.6) †
	Stroop 1 (dot ; sec)	11.7 (3.0)	12.1 (3.2)	11.8 (2.5)	12.2 (2.7)	P = 0.7
	Stroop 2 (word ; sec)	14.2 (3.3)	14.6 (3.3)	14.6 (3.2)	15.2 (3.5)	P = 0.5
	Stroop 3 (color of ink; sec)	22.7 (6.6)	22.8 (6.7)	23.7 (7.2)	24.0 (7.7)	P = 0.5
	Stroop low interference index	1.2 (0.2)	1.2 (0.2)	1.3 (0.2)	1.3 (0.2)	P = 0.9
	Stroop high interference index	2.0 (0.5)	1.9 (0.5)	2.0 (0.5)	2.0 (0.6)	P = 0.9
	Choice Reaction Time (ms)	744.9 (150.8)	741.7 (130.3)	746.3 (191.2)	756.5 (143.2)	+13.2 (-1.6 – 27.9) †
Younger-old men (60-69 years)	Group size, n	3443		422		
	RAVLT immediate recall (nb of words)	5.6 (1.7)	6.1 (1.9)	5.5 (1.6)	6.1 (1.8)	P = 0.4
	RAVLT 5-min delayed recall (nb of words)	3.6 (1.9)	4.1 (2.0)	3.6 (1.8)	4.0 (2.0)	P = 0.4
	Mental Alternation test (nb of pairs)	27.8 (8.4)	27.6 (7.4)	27.3 (8.9)	26.4 (8.1)	-1.2 (-1.9 - -0.5) †
	Animal Fluency test (nb of	21.1 (5.7)	20.9 (5.3)	20.9 (5.9)	20.8 (5.3)	P = 0.7

	words)					
	COWAT (nb of words)	38.9 (12.7)	39.7 (12.1)	38.3 (12.3)	38.8 (12.5)	P = 0.5
	Stroop 1 (dot ; sec)	12.8 (2.9)	12.9 (3.1)	12.8 (3.2)	13.4 (3.4)	+0.6 (0.3 – 0.9) †
	Stroop 2 (word ; sec)	16.2 (4.7)	16.7 (4.3)	16.8 (4.7)	17.5 (5.0)	P = 0.5
	Stroop 3 (color of ink; sec)	26.7 (7.6)	27.2 (9.1)	28.3 (10.3)	29.1 (11.6)	P = 0.8
	Stroop low interference index	1.3 (0.3)	1.3 (0.2)	1.3 (0.2)	1.3 (0.3)	P = 0.4
	Stroop high interference index	2.1 (0.6)	2.2 (0.6)	2.2 (0.6)	2.2 (0.7)	P = 0.2
	Choice Reaction Time (ms)	818.5 (174.7)	807.1 (148.3)	826.5 (226.1)	822.8 (165.5)	P = 0.5
Older-old men (70 years and older)	Group size, n	2894		221		
	RAVLT immediate recall (nb of words)	4.7 (1.6)	4.9 (1.8)	4.5 (1.7)	4.8 (1.8)	P = 0.9
	RAVLT 5-min delayed recall (nb of words)	2.7 (1.7)	2.8 (1.9)	2.5 (1.8)	2.6 (1.8)	P = 0.5
	Mental Alternation test (nb of pairs)	25.0 (8.7)	23.9 (7.7)	23.3 (8.1)	22.7 (7.6)	P = 0.7
	Animal Fluency test (nb of words)	18.4 (5.4)	17.9 (5.2)	17.3 (5.0)	17.2 (5.0)	P = 0.4
	COWAT (nb of words)	36.3 (12.9)	36.6 (12.5)	32.1 (12.2)	33.0 (12.8)	P = 0.3
	Stroop 1 (dot ; sec)	14.2 (3.5)	14.7 (4.0)	14.7 (3.9)	15.2 (4.4)	P = 0.6
	Stroop 2 (word ; sec)	19.1 (5.0)	20.0 (7.1)	20.5 (5.8)	21.5 (6.6)	P = 0.6
	Stroop 3 (color of ink; sec)	32.5 (10.9)	34.3 (13.7)	34.7 (11.1)	36.2 (15.0)	P = 0.7
	Stroop low interference index	1.4 (0.3)	1.4 (0.4)	1.4 (0.3)	1.4 (0.3)	P = 0.7
	Stroop high interference index	2.3 (0.7)	2.4 (0.8)	2.4 (0.7)	2.4 (0.8)	P = 0.3
	Choice Reaction Time (ms)	883.3 (193.8)	880.0 (159.3)	913.9 (191.2)	929.0 (276.2)	P = 0.1
Middle-aged	Group size, n	5344		297		
	RAVLT immediate recall	6.8 (1.8)	7.9 (2.1)	6.6 (1.8)	7.5 (2.0)	P = 0.2

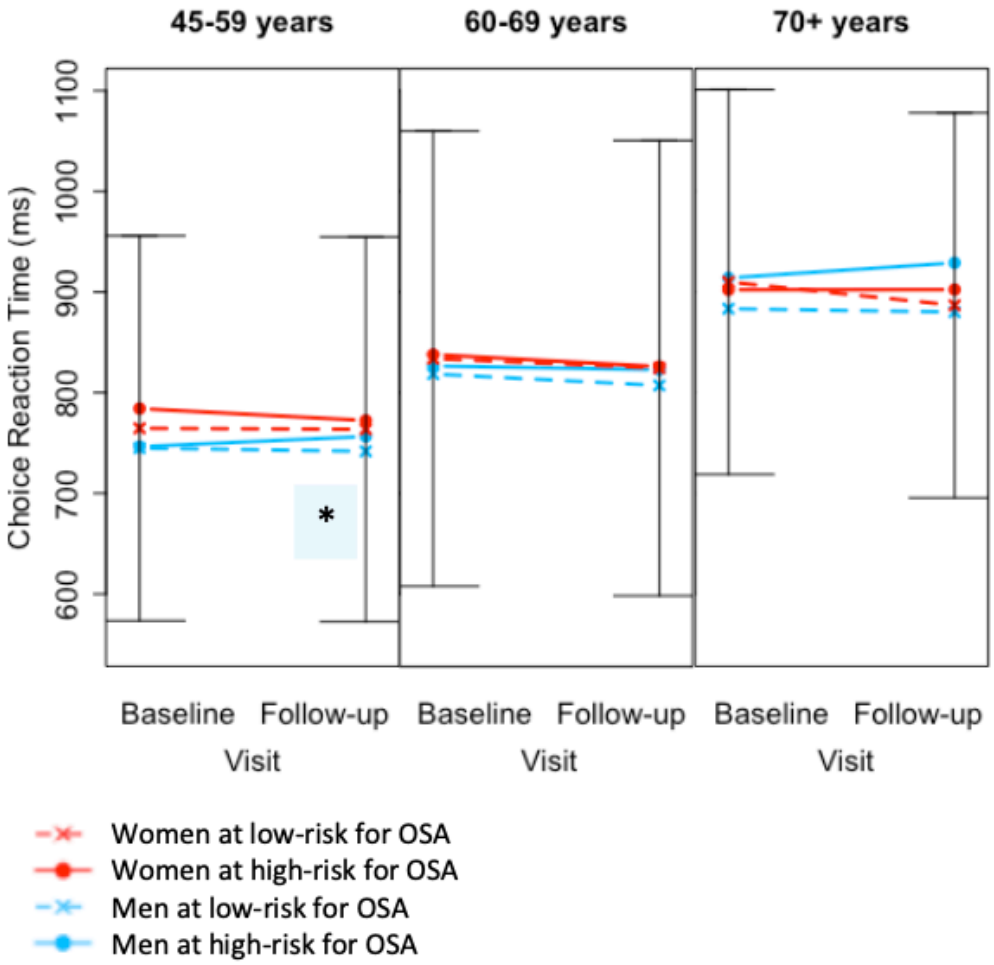
women (45-59 years)	(nb of words)					
	RAVLT 5-min delayed recall (nb of words)	5.2 (2.2)	6.2 (2.3)	4.9 (2.0)	5.7 (2.4)	P = 0.2
	Mental Alternation test (nb of pairs)	28.3 (7.9)	28.2 (6.8)	26.5 (8.2)	26.3 (6.7)	P = 0.8
	Animal Fluency test (nb of words)	22.6 (5.9)	22.5 (5.5)	21.6 (5.9)	21.4 (5.6)	P = 0.5
	COWAT (nb of words)	42.7 (12.2)	43.7 (12.1)	40.5 (11.5)	40.9 (11.3)	P = 0.3
	Stroop 1 (dot ; sec)	11.3 (2.4)	11.7 (2.6)	11.8 (2.7)	11.8 (2.3)	+0.1 (-0.2 – 0.4)†
	Stroop 2 (word ; sec)	14.0 (3.2)	14.4 (3.1)	15.2 (3.7)	15.3 (3.4)	P = 0.1
	Stroop 3 (color of ink; sec)	22.1 (6.0)	22.3 (6.4)	23.9 (6.6)	24.3 (6.7)	P = 0.5
	Stroop low interference index	1.3 (0.2)	1.2 (0.2)	1.3 (0.3)	1.3 (0.2)	P = 0.8
	Stroop high interference index	2.0 (0.5)	2.0 (0.5)	2.1 (0.6)	2.1 (0.5)	P = 0.1
	Choice Reaction Time (ms)	764.6 (148.0)	763.6 (132.7)	784.2 (147.2)	772.3 (127.5)	P = 0.2
Younger-old women (60-69 years)	Group size, n	3752		309		
	RAVLT immediate recall (nb of words)	6.4 (1.8)	7.2 (2.0)	6.1 (1.9)	7.0 (2.0)	P = 0.9
	RAVLT 5-min delayed recall (nb of words)	4.6 (2.1)	5.4 (2.1)	4.2 (2.0)	5.1 (2.2)	P = 0.8
	Mental Alternation test (nb of pairs)	26.3 (7.8)	25.8 (6.9)	24.7 (8.7)	25.2 (6.7)	+0.8 (0.0 – 1.6) †
	Animal Fluency test (nb of words)	20.6 (5.6)	20.5 (5.2)	19.6 (5.7)	19.6 (5.4)	P = 0.9
	COWAT (nb of words)	41.0 (12.5)	42.1 (12.1)	37.3 (12.8)	38.1 (12.8)	P = 1.0
	Stroop 1 (dot ; sec)	12.2 (2.6)	12.6 (3.8)	12.6 (3.4)	13.0 (3.4)	P = 1.0
	Stroop 2 (word ; sec)	15.8 (4.1)	16.1 (3.8)	16.8 (4.4)	17.1 (4.3)	P = 0.8
	Stroop 3 (color of ink; sec)	26.3 (12.4)	26.2 (8.3)	27.5 (8.3)	28.0 (8.3)	P = 0.6
	Stroop low interference	1.3 (0.3)	1.3 (0.2)	1.4 (0.2)	1.3 (0.3)	P = 0.8

	index					
	Stroop high interference index	2.2 (0.8)	2.2 (0.6)	2.2 (0.6)	2.2 (0.6)	P = 0.8
	Choice Reaction Time (ms)	833.8 (167.3)	824.4 (143.0)	837.8 (197.1)	825.8 (147.5)	P = 1.0
Older-old women (70 years and over)	Group size, n	3034		176		
	RAVLT immediate recall (nb of words)	5.5 (1.7)	5.8 (2.0)	5.4 (1.9)	5.7 (2.0)	P = 0.8
	RAVLT 5-min delayed recall (nb of words)	3.6 (2.0)	3.8 (2.1)	3.6 (1.9)	3.3 (2.1)	-0.2 (-0.6 – 0.1) †
	Mental Alternation test (nb of pairs)	23.1 (8.2)	22.1 (7.2)	21.0 (7.7)	20.7 (6.9)	P = 0.2
	Animal Fluency test (nb of words)	17.7 (5.2)	17.3 (5.0)	16.2 (5.1)	16.4 (5.2)	P = 0.1
	COWAT (nb of words)	37.9 (12.5)	38.1 (12.2)	33.9 (12.0)	33.4 (11.9)	P = 0.1
	Stroop 1 (dot ; sec)	13.5 (3.4)	13.8 (3.6)	13.9 (3.4)	14.7 (4.0)	+1.0 (0.4 – 1.5) †
	Stroop 2 (word ; sec)	18.5 (4.9)	19.1 (5.4)	20.3 (5.8)	21.2 (9.0)	P = 0.2
	Stroop 3 (color of ink; sec)	31.6 (10.4)	32.5 (12.4)	34.3 (12.5)	36.3 (14.0)	P = 0.2
	Stroop low interference index	1.4 (0.3)	1.4 (0.3)	1.5 (0.4)	1.5 (0.5)	P = 0.3
	Stroop high interference index	2.4 (0.7)	2.4 (0.7)	2.5 (0.8)	2.5 (0.9)	P = 1.0
	Choice Reaction Time (ms)	910.0 (276.2)	886.7 (157.9)	902.2 (207.3)	902.4 (169.8)	P = 0.2

† Significant when controlling for sociodemographic, lifestyle and medical variables (model 3). Lower scores represent worse performance at the RAVLT immediate and 5-min delayed recall, Mental Alternation test, Animal fluency test and COWAT. Higher scores represent worse performance at the Stroop test (three conditions and two indexes) and Choice Reaction Time.

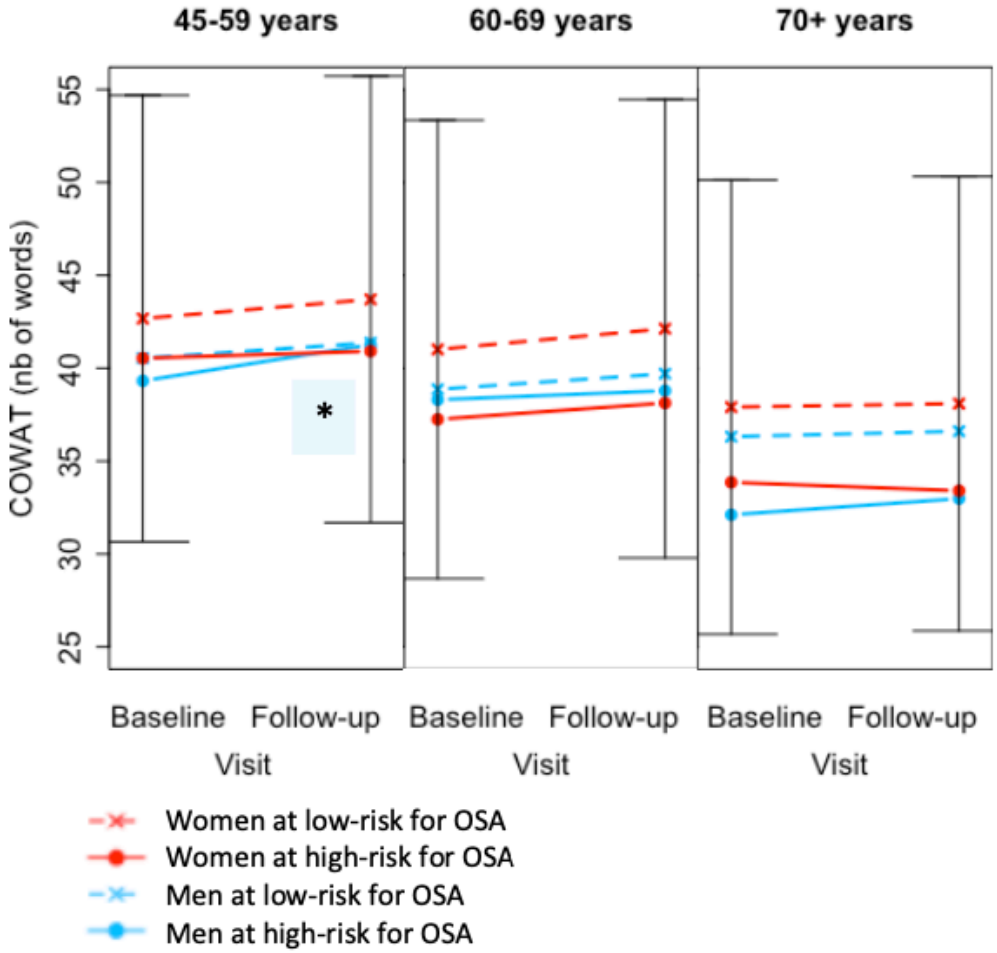
Note: n are crude numbers. RAVLT: Rey Auditory Verbal Learning Test; COWAT: Controlled Oral Word Association Test.

Figure 2. Choice Reaction Time according to OSA risk, age, and sex



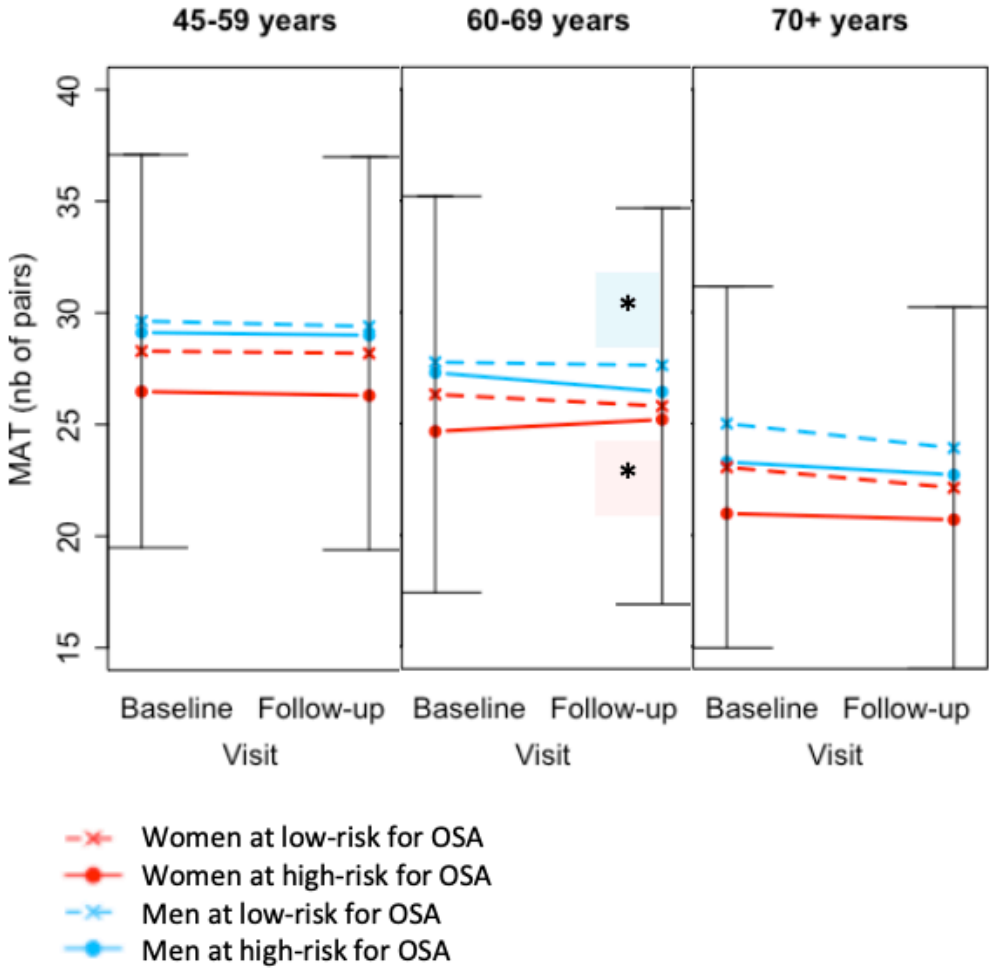
Legend: Figure 6 presents scores obtained on the Choice Reaction Time at baseline and follow-up according to OSA risk, age, and sex. Asterisks highlighted in pink represent significant associations in women; asterisks highlighted in blue represent significant associations in men. Error bars represent standard errors. Results are significant at $p < 0.05$.

Figure 3. Controlled Oral Word Association Test according to OSA risk, age, and sex



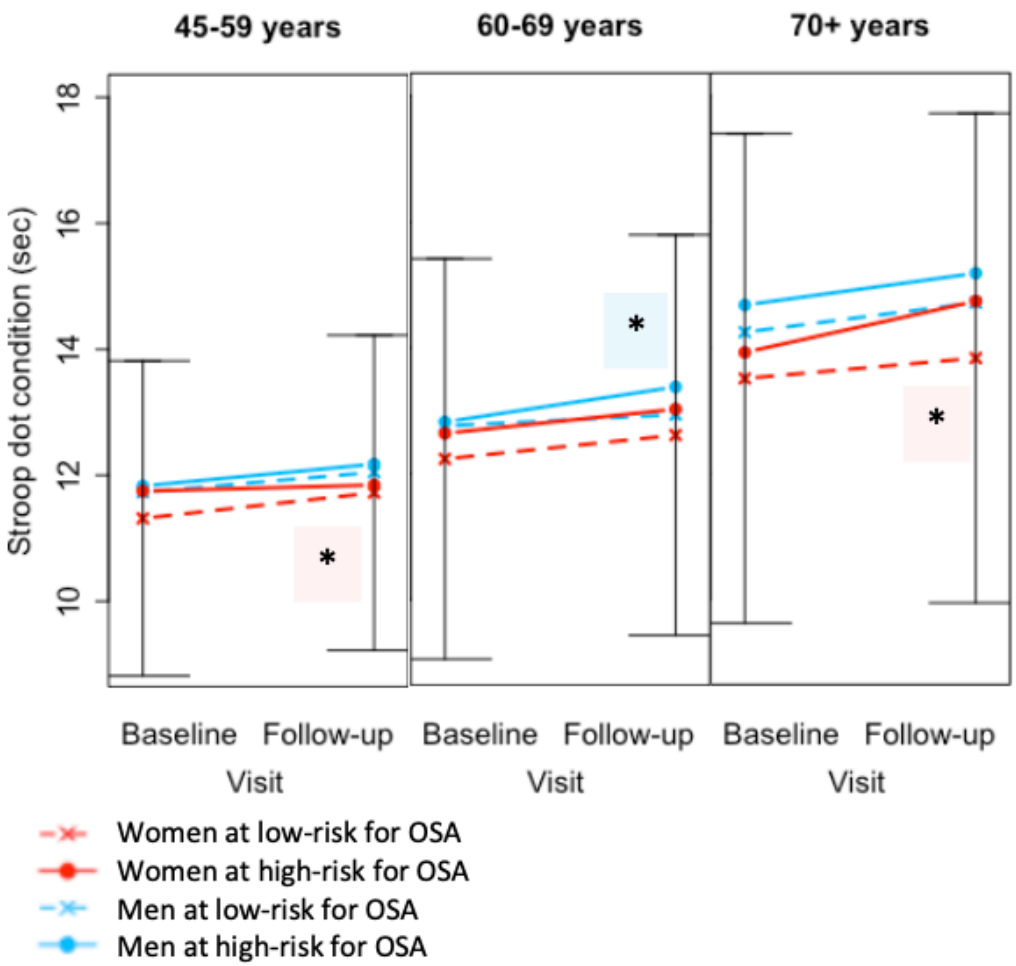
Legend: Figure 4 presents scores obtained on the Controlled Oral Word Association Test (COWAT) at baseline and follow-up according to OSA risk, age, and sex. Asterisks highlighted in pink represent significant associations in women; asterisks highlighted in blue represent significant associations in men. Error bars represent standard errors. Results are significant at $p < 0.05$.

Figure 4. Mental Alternation Test according to OSA risk, age, and sex



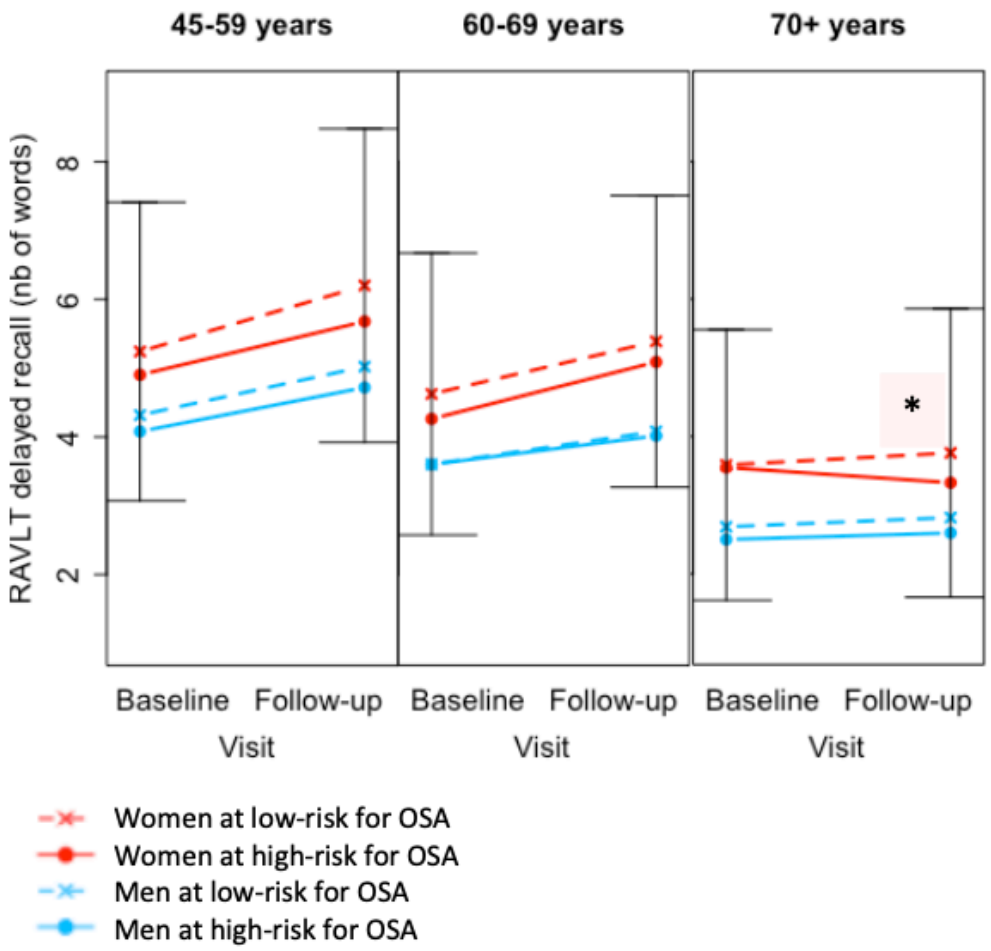
Legend: Figure 3 presents scores obtained on the Mental Alternation Test (MAT) at baseline and follow-up according to OSA risk, age, and sex. Asterisks highlighted in pink represent significant associations in women; asterisks highlighted in blue represent significant associations in men. Error bars represent standard errors. Results are significant at $p < 0.05$.

Figure 5. Stroop test, dot condition, according to OSA risk, age, and sex



Legend: Figure 5 presents scores obtained on the Stroop test, dot condition, at baseline and follow-up according to OSA risk, age, and sex. Asterisks highlighted in pink represent significant associations in women; asterisks highlighted in blue represent significant associations in men. Error bars represent standard errors. Results are significant at $p < 0.05$.

Figure 6. Rey Auditory Verbal Learning Test delayed recall according to OSA risk, age, and sex



Legend: Figure 2 presents scores obtained on the Rey Auditory Verbal Learning Test (RAVLT) delayed recall at baseline and follow-up according to OSA risk, age, and sex. Asterisks highlighted in pink represent significant associations in women; asterisks highlighted in blue represent significant associations in men. Error bars represent standard errors. Results are significant at $p < 0.05$.

2.6 Sensitivity analyses

Table S3 presents the cognitive scores obtained at baseline and follow-up in the whole sample excluding participants with a self-reported diagnosis of OSA, and Table S4 presents those results when participants with an OSA diagnosis are included. Similar results were obtained in both

cases, where high-risk of OSA is associated with a steeper improvement of performance on the RAVLT 5-minute delayed recall.

4. Discussion

In this study of 24,819 Canadians, we investigated the association between OSA risk, as measured by the STOP-B, and 3-year cognitive change. Our results reveal that sex and age significantly impact associations between risk of OSA and cognitive decline. Although being at high-risk of OSA was associated with improvement in verbal episodic memory performance over time when considering the whole sample, highly heterogeneous results were obtained when stratifying for age and sex. Indeed, women at high-risk for OSA aged 70 years and over showed a steeper decline in verbal episodic memory (RAVLT delayed recall) and processing speed tasks (Stroop condition 1) than those at low-risk, while no such association was observed in men that age. Men and women at high-risk for OSA also showed greater age-specific decline in processing speed and attention (men aged 60-69 and women aged 45-59), psychomotor speed (men aged 45-59) and mental flexibility (men aged 60-69). The present study highlights the importance of considering moderating factors, especially age and sex, when studying the complex association between OSA and cognitive decline.

Most of the significant effects we found were in attention and mental flexibility, which is similar to what was reported in previous studies (Blackwell et al., 2011; Olaithe & Bucks, 2013; Saint Martin et al., 2015). Tests targeting attention and mental flexibility used in the present study also require processing speed (e.g., Controlled Oral Word Association Test, Mental Alternation Test, Stroop Test). Therefore, part of the decline observed in attention and mental flexibility may be attributed to a decrease in processing speed. These cognitive functions also depend on the prefrontal cortex, which is highly vulnerable to OSA (Gosselin et al., 2019; Marchi et al., 2020). Specifically, sleep fragmentation and intermittent hypoxemia interfere with brain structure and function through oxidative stress and neuroinflammation, leading to neuronal death (D. C. Lim & Pack, 2014). Therefore, attention and executive function, especially mental

flexibility, seem to be cognitive domains vulnerable to OSA, in middle-aged and older individuals.

The association between OSA risk and a steeper decline in psychomotor speed, processing speed and attention in middle-aged men and women may be due to the independent effect of OSA on cognitive functioning specific to this age group. In older age groups, the increased prevalence of multiple health conditions (e.g.: cardiovascular diseases, hypertension, and neurodegenerative diseases) (Prince et al., 2015) can explain more cognitive performance variability than in the middle-aged group and therefore, mask OSA's role in cognitive decline. In addition, the age-specific prevalence and impact of these health conditions could also be sex-specific, which could explain the differences in the link between OSA risk and cognitive functioning in each group. For example, hypertension and depression are more prevalent in apneic women, while type 2 diabetes and ischaemic heart disease are more prevalent in men with OSA (Mokhlesi et al., 2016).

There is an increasing interest in understanding the role of comorbidities and how they interact with OSA to explain cognitive impairments. On one hand, to better understand the role of comorbidities in the detection of OSA using questionnaires, a study analyzed the contribution of each STOP-Bang variable to capture OSA (Morinigo et al., 2022). Their results show that neck circumference, observed apneas, high blood pressure and BMI were the best predictors of OSA (Morinigo et al., 2022). These results suggest that snoring and observed apneas alone are not sufficient to predict OSA, and that it is relevant to include comorbidities in screening questionnaires. On the other hand, to isolate the role of OSA and better understand the impact of comorbidities on cognition, a preliminary study (n= 27) compared the cognitive performance of apneic and non-apneic heathy middle-aged men without comorbidities. Results show that those with OSA had poorer executive functioning, visuospatial memory, vigilance, sustained attention, psychomotor and impulse control than those without OSA (Gnoni et al., 2023). Hence, more research is needed to better understand the role of comorbidities in the association between OSA and cognitive decline.

A possible explanation for the age-specific steeper decline we observed in middle-aged participants at high-risk for OSA compared to those at low-risk could be that older adults are less sensitive to sleep deprivation's deleterious impact on the brain (Scullin & Bliwise, 2015). As regards to OSA specifically and in agreement with this hypothesis, a systematic review reported no association between OSA and cognitive impairment in older adults at cross-section (Bubu et al., 2020). Finally, research has shown that advanced age may protect OSA patients against the detrimental effects of intermittent hypoxia on vascular health (*e.g.*, myocardial infarction and stroke; Beaudin et al., 2017). This may be because older adults might experience less respiratory events and nocturnal hypoxemia than younger adults because of the greater sleep fragmentation and reduced total sleep time that occur with aging (Beaudin et al., 2017).

We found that older women at high-risk for OSA were the only group showing a decline in episodic memory performance. This suggests that post-menopausal women may be at higher risk for cognitive decline when they present a sleep disorder. Importantly, the prevalence of OSA is higher in post-menopausal (21%) than pre-menopausal women (3%) (Heinzer et al., 2018; Thompson, Legault, Moullec, Baltzan, et al., 2022) likely due to morphological changes (such as increased waist and neck circumferences (Heinzer et al., 2018; Polesel et al., 2015)) and ovarian hormonal effect on the upper airway dilator muscles (Jehan et al., 2015). The loss of ovarian hormones at menopause may have long-term effects on the brain and has been associated with lower cognitive scores in attention, executive function, and memory (Gervais et al., 2017). Such long-term effects could explain why we found a memory decline in women at high-risk for OSA aged 70 and over, but not in those aged 60-69. Since both sleep and cognitive function are sensitive to ovarian hormones, the concomitant presence of OSA and the loss of ovarian hormones could lead to decreased cognitive performances.

Alterations of the medial temporal lobe (MTL) could be involved in the memory decline observed in older women at high-risk for OSA. The MTL subregions (e.g., hippocampus and entorhinal cortex) are essential for memory processes (Squire & Zola-Morgan, 1991), but are sensitive to tau pathology (Braak & Braak, 1991; Marks et al., 2017) and hypoxemia (Bartsch et al., 2015). Past studies reported that women with OSA exhibit more important white matter

damage (Macey et al., 2012), cortical thinning (Macey, Haris, et al., 2018), and both smaller and larger hippocampal volumes than men with OSA (Macey, Prasad, et al., 2018; Martineau-Dussault et al., 2022). Larger MTL volumes were likely the result of neuroinflammation and extracellular edema, as the use of free-water corrected volumes eliminated these associations (Martineau-Dussault et al., 2022). Another recent study found that more severe OSA was associated with lower entorhinal cortex and hippocampal volumes in cognitively unimpaired amyloid-positive participants, but not in those who were amyloid-negative (André et al., 2023). Interestingly, sex-stratified analysis showed that the links between OSA severity and MTL atrophy were significant in women only and were especially driven by amyloid-positive women (André et al., 2023). In addition, lower hippocampal volumes at baseline were associated with reduced memory performance at 21-month follow-up (André et al., 2023). These results suggest that in women, OSA may be harmful for MTL integrity, which could lead to memory decline.

Limitations

The main strength of the present study is its large sample size and comprehensive neuropsychological battery. However, this study has limitations. First, it lacked objective sleep measures, and while the STOP and STOP-Bang have shown good sensitivity and negative predictive value, they might have mainly captured male and symptomatic OSA patients. Second, the association between OSA and cognition might have been weakened due to loss to follow-up of 2,332 participants, who were mostly at low-risk for OSA but presented many risk factors for cognitive decline. Third, to ensure that we did not falsely attribute neurodegenerative processes to OSA, we excluded participants reporting a neurodegenerative or neurologic disease such as AD (Liguori et al., 2021), Parkinson's disease (Elfil et al., 2021) and stroke (Arzt et al., 2005) at baseline or follow-up. However, these conditions are of particular interest to consider when investigating the link between OSA and cognition and should be addressed in future studies. Fourth, while some of our results reached the level of statistical significance ($p < 0.05$), they do not seem to be clinically significant and should be interpreted with caution in clinical settings. Fifth, our results without stratification by age and sex show surprising improvement in performance in two groups (men aged 45-59 (COWAT) and women aged 60-69 (Mental

Alternation test)). This might be due to a general practice effect in longitudinal cohorts, meaning there are improvements in certain cognitive performances due to repeated evaluation using the same tests (Öijerstedt et al., 2022). Sixth, the time of day of the neuropsychological testing was not specified in the CLSA protocol. Since cognitive performance may vary across the day, participants tested at different times of day between baseline and follow-up could show changes in cognitive performance independent from OSA.

Clinical implications

Since the OSA-related memory decline observed in women aged 70 and over could suggest underlying neurodegenerative processes, older women should be screened and treated as a priority as they might present a higher risk of MCI and AD.

CPAP therapy has been associated with improvement in cerebral function (L'Heureux et al., 2021), a lower risk of AD diagnosis (Dunietz et al., 2021) and later onset of MCI compared to untreated OSA (Osorio et al., 2015), and effective screening and treatment of OSA is therefore crucial to limit brain alterations and prevent the development of OSA-related cognitive impairment.

A review highlighted that CPAP-related improvements in cognitive functioning are most prominent in attention and in middle-aged adults with more severe OSA and sleepiness (Mullins et al., 2020). However, it is not clear if the effects of CPAP are similar in individuals with mild or asymptomatic OSA, and whether clinicians should recommend early use of CPAP to those at risk for OSA or cognitive decline (e.g., individuals presenting vascular comorbidities, *APOE4* carriers, or relatives of individuals with familial AD). Thus, studies are needed in these populations to guide clinical decision-making. The present study may help select patients based on age and sex for inclusion in randomized controlled trials.

Conclusion

Our findings indicate that being at high-risk for OSA is associated with a generalized cognitive decline in attention and processing speed, but a memory decline specific to older women (≥70 years) at follow-up. The variability we observed within our cohort based on cognitive domains,

age, and sex could explain the discrepancies between previous studies. While we do not yet completely understand the long-term cognitive consequences of OSA in relation to individual characteristics, our results suggest that OSA could be an age-specific risk factor for cognitive decline, which would depend on sex in older age.

Disclaimer

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Conflict of interest

Authors have no competing interests to declare.

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Supplemental material

Material and methods

Measures

Snoring, observed apneas, and high blood pressure were self-reported through yes/no questions: "Do you snore loudly? By "loudly" I mean louder than talking or loud enough to be heard through closed doors"; "Has anyone ever observed you stop breathing in your sleep?"; "Has a doctor ever told you that you have high blood pressure or hypertension?" Participants were given one point for every question answered with "yes". Tiredness was assessed using the question, "Over the last month, how often do you find it difficult to stay awake during your normal waking hours when you want to?" Participants were given one point if they answered ≥3 times per week. Finally, participants with a BMI > 35 kg/m^2 were given an additional point.

Covariates

Reference categories were not having a spouse, not being white from European origin, having an income < $20,000 CAD, having no post-secondary education, being completely retired, being a current smoker, being a regular drinker, having a short sleep duration, having a good sleep, being in the lowest physical activity quartile, not having chronic health conditions, not having functional impairment, having a good health perception, having normal levels of systemic inflammation (normal (<1 mg/L), mild (1-3 mg/L), moderate (3-10 mg/L) and high (>10 mg/L)), and being non-menopausal.

Statistical analyses

Multiple Imputation

We conducted multiple imputation to account for missing values of the following items: marital status (0.01% missing), ethnicity (0.06% missing), income (2.12% missing), education (0.09% missing), retirement status (0.06% missing), drinking status (0.85% missing), sleep duration (0.08% missing), sleep quality (0.03% missing), PASE score (1.16% missing), cardiovascular problems (0.34% missing), diabetes (0.19% missing), COPD (0.27% missing), asthma (0.19%

missing), anxious-depressive symptoms (0.21% missing), CESD10 score (0.17% missing), functional status (0.09% missing), general health perception (0.04% missing) and hs-CRP level (3.94% missing).

Table S1. Detailed description of the sample according to sex, age group and OSA risk as measured with the STOP-B score

		Middle-aged: 45-59 years		Younger-old: 60-69 years		Older-old: 70-85 years		Missing values	
		Low-risk	High-risk	Low-risk	High-risk	Low-risk	High-risk	n	%
Men	**Group size, n (%)**	4494 (91.2)	433 (8.8)	3443 (89.1)	422 (10.9)	2894 (92.9)	221 (7.1)		
	Age (mean (SD))	52.75 (4.00)	53.67 (3.81)	64.16 (2.82)	64.46 (2.94)	76.08 (4.16)	75.42 (4.28)	0	0,0
	Living with a spouse, n (%)	3583 (79.8)	355 (82.0)	2765 (80.3)	341 (80.8)	2246 (77.6)	183 (82.8)	2	0,0
	White from European origin, n (%)	4138 (92.1)	411 (94.9)	3280 (95.4)	394 (93.6)	2751 (95.3)	212 (95.9)	14	0,1
	Income, n (%)							526	4,1
	< $20,000	115 (2.6)	17 (4.0)	99 (3.0)	19 (4.8)	80 (2.9)	12 (5.7)		
	$20,000-$50,000	393 (9.1)	33 (7.7)	587 (17.8)	84 (21.0)	712 (26.2)	66 (31.4)		
	$50,000-$100,000	1150 (26.5)	127 (29.8)	1327 (40.3)	163 (40.8)	1240 (45.7)	87 (41.4)		
	$100,000-$150,000	1251 (28.8)	108 (25.4)	722 (21.9)	77 (19.2)	439 (16.2)	31 (14.8)		
	> $150,000	1432 (33.0)	141 (33.1)	556 (16.9)	57 (14.2)	242 (8.9)	14 (6.7)		
	Post-secondary education, n (%)	3825 (85.1)	340 (78.5)	2786 (81.0)	334 (79.3)	2170 (75.4)	163 (74.1)	22	0,2
	Retirement, n (%)							14	0,1
	Retired/unemployed	343 (7.6)	36 (8.3)	1656 (48.2)	221 (52.5)	2294 (79.3)	181 (81.9)		
	Partly retired	269 (6.0)	35 (8.1)	755 (22.0)	84 (20.0)	394 (13.6)	28 (12.7)		
	Worker	3874 (86.4)	362 (83.6)	1028 (29.9)	116 (27.6)	205 (7.1)	12 (5.4)		
	Smoking status, n (%)							0	0,0
	Current smoker	519 (11.5)	50 (11.5)	306 (8.9)	39 (9.2)	136 (4.7)	9 (4.1)		
	Non smoker	2477 (55.1)	199 (46.0)	1436 (41.7)	143 (33.9)	1096 (37.9)	66 (29.9)		
	Former smoker	1498 (33.3)	184 (42.5)	1701 (49.4)	240 (56.9)	1662 (57.4)	146 (66.1)		
	Drinking status, n (%)							211	1,6

	Regular drinker	3688 (83.5)	316 (74.4)	2813 (82.8)	324 (78.3)	2298 (81.2)	154 (72.3)		
	Occasional drinker	351 (7.9)	59 (13.9)	272 (8.0)	41 (9.9)	224 (7.9)	33 (15.5)		
	Non drinker	377 (8.5)	50 (11.8)	314 (9.2)	49 (11.8)	307 (10.9)	26 (12.2)		
	Sleep duration, n (%)							19	0,1
	Short (< 6h)	483 (10.8)	92 (21.3)	347 (10.1)	62 (14.8)	277 (9.6)	37 (16.8)		
	Normal (6-8h)	3896 (86.8)	322 (74.7)	2941 (85.5)	347 (82.6)	2423 (83.9)	171 (77.7)		
	Long (> 8h)	111 (2.5)	17 (3.9)	150 (4.4)	11 (2.6)	189 (6.5)	12 (5.5)		
	Unsatisfactory sleep quality, N (%)	1016 (22.6)	174 (40.2)	656 (19.1)	126 (29.9)	506 (17.5)	62 (28.2)	7	0,1
	PASE score, N (%)							287	2,2
	Quintile 1	427 (9.8)	68 (15.8)	428 (12.7)	86 (20.8)	703 (25.0)	65 (31.7)		
	Quintile 2	643 (14.7)	69 (16.0)	656 (19.4)	75 (18.1)	706 (25.1)	54 (26.3)		
	Quintile 3	690 (15.8)	70 (16.3)	789 (23.3)	78 (18.8)	631 (22.4)	34 (16.6)		
	Quintile 4	900 (20.6)	93 (21.6)	841 (24.9)	99 (23.9)	559 (19.9)	38 (18.5)		
	Quintile 5	1717 (39.2)	130 (30.2)	666 (19.7)	76 (18.4)	215 (7.6)	14 (6.8)		
	Cardiovascular problems, n (%)	252 (5.6)	64 (14.9)	531 (15.5)	113 (27.0)	808 (28.3)	84 (38.4)	84	0,7
	Diabetes, n (%)	483 (10.8)	127 (29.5)	643 (18.7)	182 (43.3)	647 (22.5)	78 (35.5)	47	0,4
	COPD, n (%)	109 (2.4)	25 (5.8)	157 (4.6)	35 (8.4)	164 (5.7)	12 (5.5)	66	0,5
	Asthma, n (%)	542 (12.1)	83 (19.2)	349 (10.2)	57 (13.6)	240 (8.3)	23 (10.5)	47	0,4
	Anxious-depressive symptoms, n (%)	747 (16.7)	135 (31.2)	561 (16.4)	133 (31.7)	292 (10.1)	36 (16.3)	51	0,4
	CESD10 score (mean (SD))	4.74 (4.19)	6.24 (5.32)	4.19 (3.99)	5.39 (4.79)	4.11 (3.69)	5.16 (4.08)	43	0,3
	Functional impairment (%)	82 (1.8)	18 (4.2)	113 (3.3)	36 (8.6)	219 (7.6)	37 (16.9)	23	0,2
	Unsatisfactory health status (%)	290 (6.5)	93 (21.5)	202 (5.9)	74 (17.5)	171 (5.9)	41 (18.6)	9	0,1
	Hs-CRP level, n (%)							977	7,6

	Normal	2298 (55.6)	123 (30.8)	1622 (51.2)	116 (30.7)	1198 (45.2)	68 (33.8)		
	Mild	1270 (30.7)	151 (37.8)	1054 (33.2)	166 (43.9)	954 (36.0)	73 (36.3)		
	Moderate	485 (11.7)	110 (27.5)	427 (13.5)	74 (19.6)	412 (15.6)	52 (25.9)		
	High	79 (1.9)	16 (4.0)	67 (2.1)	22 (5.8)	85 (3.2)	8 (4.0)		
Women	**Group size, n (%)**	5344 (94.7)	297 (5.3)	3752 (92.4)	309 (7.6)	3034 (94.5)	176 (5.5)		
	Age (mean (SD))	52.84 (4.01)	53.68 (3.83)	64.19 (2.82)	64.15 (2.77)	76.18 (4.18)	75.77 (4.40)	0	0,0
	Living with a spouse, n (%)	3881 (72.7)	173 (58.4)	2357 (62.8)	161 (52.1)	1378 (45.4)	68 (38.6)	5	0,0
	White from European origin, n (%)	4990 (93.4)	272 (91.9)	3608 (96.2)	296 (95.8)	2940 (96.9)	165 (93.8)	7	0,1
	Income, n (%)							985	7,6
	< $20,000	174 (3.4)	23 (8.2)	192 (5.5)	37 (13.4)	242 (9.2)	29 (18.1)		
	$20,000-$50,000	619 (12.2)	63 (22.4)	1002 (28.8)	103 (37.2)	1137 (43.1)	84 (52.5)		
	$50,000-$100,000	1664 (32.7)	94 (33.5)	1422 (40.8)	98 (35.4)	940 (35.7)	39 (24.4)		
	$100,000-$150,000	1284 (25.2)	68 (24.2)	544 (15.6)	21 (7.6)	222 (8.4)	7 (4.4)		
	> $150,000	1348 (26.5)	33 (11.7)	325 (9.3)	18 (6.5)	94 (3.6)	1 (0.6)		
	Post-secondary education, n (%)	4503 (84.3)	226 (76.1)	2898 (77.4)	203 (66.1)	2016 (66.5)	109 (61.9)	14	0,1
	Retirement, n (%)							62	0,5
	Retired/unemployed	593 (11.1)	47 (16.0)	2207 (59.1)	182 (58.9)	2652 (88.0)	160 (92.0)		
	Partly retired	344 (6.5)	18 (6.1)	597 (16.0)	45 (14.6)	191 (6.3)	5 (2.9)		
	Worker	4386 (82.4)	229 (77.9)	931 (24.9)	82 (26.5)	172 (5.7)	9 (5.2)		
	Smoking status, n (%)							0	0,0
	Current smoker	548 (10.3)	46 (15.5)	232 (6.2)	24 (7.8)	102 (3.4)	4 (2.3)		
	Non smoker	2824 (52.8)	126 (42.4)	1927 (51.4)	137 (44.3)	1574 (51.9)	91 (51.7)		
	Former smoker	1972 (36.9)	125 (42.1)	1593 (42.5)	148 (47.9)	1358 (44.8)	81 (46.0)		
	Drinking status, n (%)							360	2,8

	Regular drinker	4004 (76.7)	179 (61.9)	2717 (74.2)	177 (58.4)	2017 (69.3)	88 (52.1)		
	Occasional drinker	723 (13.9)	69 (23.9)	533 (14.6)	69 (22.8)	483 (16.6)	45 (26.6)		
	Non drinker	493 (9.4)	41 (14.2)	410 (11.2)	57 (18.8)	411 (14.1)	36 (21.3)		
	Sleep duration, n (%)							26	0,2
	Short (< 6h)	690 (12.9)	76 (25.9)	474 (12.7)	67 (21.8)	402 (13.3)	45 (25.9)		
	Normal (6-8 h)	4406 (82.6)	197 (67.2)	3006 (80.2)	213 (69.2)	2429 (80.3)	112 (64.4)		
	Long (> 8h)	240 (4.5)	20 (6.8)	267 (7.1)	28 (9.1)	195 (6.4)	17 (9.8)		
	Unsatisfactory sleep quality, n (%)	1601 (30.0)	150 (50.5)	970 (25.9)	127 (41.1)	731 (24.1)	56 (32.0)	7	0,1
	PASE score, n (%)							242	1,9
	Quintile 1	827 (15.8)	74 (25.5)	738 (20.0)	131 (42.8)	1162 (39.0)	89 (52.4)		
	Quintile 2	860 (16.4)	60 (20.7)	893 (24.2)	70 (22.9)	785 (26.4)	43 (25.3)		
	Quintile 3	943 (18.0)	44 (15.2)	886 (24.0)	54 (17.6)	599 (20.1)	23 (13.5)		
	Quintile 4	1116 (21.3)	55 (19.0)	768 (20.8)	33 (10.8)	327 (11.0)	10 (5.9)		
	Quintile 5	1488 (28.4)	57 (19.7)	406 (11.0)	18 (5.9)	106 (3.6)	5 (2.9)		
	Cardiovascular problems, n (%)	161 (3.0)	25 (8.4)	303 (8.1)	66 (21.5)	516 (17.2)	47 (27.0)	81	0,6
	Diabetes, n (%)	530 (9.9)	107 (36.0)	509 (13.6)	132 (42.9)	499 (16.5)	76 (43.4)	32	0,2
	COPD, n (%)	180 (3.4)	34 (11.5)	189 (5.1)	33 (10.9)	261 (8.7)	22 (12.6)	65	0,5
	Asthma, n (%)	793 (14.9)	99 (33.7)	551 (14.7)	78 (25.7)	375 (12.4)	31 (17.7)	47	0,4
	Anxious-depressive symptoms, n (%)	1531 (28.7)	162 (54.5)	1057 (28.3)	132 (42.9)	591 (19.6)	60 (34.5)	50	0,4
	CESD10 score (mean (SD))	5.45 (4.83)	8.32 (5.84)	5.10 (4.62)	8.12 (5.93)	5.51 (4.39)	7.39 (5.62)	50	0,4
	Functional impairment (%)	283 (5.3)	61 (20.7)	360 (9.6)	88 (28.8)	617 (20.4)	80 (45.5)	41	0,3
	Unsatisfactory health status (%)	316 (5.9)	76 (25.6)	225 (6.0)	79 (25.6)	209 (6.9)	35 (20.0)	8	0,1
	Hs-CRP level, n (%)							1 395	10,8

	Normal	2389 (49.8)	32 (12.5)	1377 (40.7)	29 (10.9)	931 (34.9)	24 (15.8)		
	Mild	1465 (30.6)	65 (25.4)	1198 (35.4)	86 (32.3)	1040 (39.0)	57 (37.5)		
	Moderate	810 (16.9)	122 (47.7)	699 (20.7)	111 (41.7)	611 (22.9)	62 (40.8)		
	High	130 (2.7)	37 (14.5)	109 (3.2)	40 (15.0)	84 (3.2)	9 (5.9)		
	Post-menopausal, n (%)	2715 (56.4)	149 (62.3)	3098 (98.9)	233 (97.5)	2273 (98.4)	111 (97.4)	2 065	16,0

Note: n are crude numbers, proportions are weighted to account for the sampling strategy. SD: standard deviation

Table S2. Comparison of participant characteristics for those included in the follow-up to those lost to follow-up

	Lost to follow-up	Present at follow-up	p
Group size, N (%)	1628	24819	
Age (mean (SD))	65.47 (11.21)	62.40 (10.07)	<0.001
Female sex (%)	841 (51.7)	12912 (52.0)	0.794
Living with a spouse, N (%)	999 (61.4)	17491 (70.5)	<0.001
White from European origin, N (%)	1485 (91.4)	23457 (94.6)	<0.001
Income, N (%)			<0.001
< $20,000	157 (10.6)	1039 (4.5)	
$20,000-$50,000	487 (32.8)	4883 (20.9)	
$50,000-$100,000	454 (30.6)	8351 (35.8)	
$100,000-$150,000	237 (15.9)	4774 (20.5)	
> $150,000	151 (10.2)	4261 (18.3)	
Post-secondary education, N (%)	1112 (68.5)	19573 (79.0)	<0.001
Retirement, N (%)			<0.001
Retired/unemployed	846 (52.4)	10572 (42.7)	
Partly retired	152 (9.4)	2765 (11.2)	
Worker	616 (38.2)	11406 (46.1)	
Smoking status, N (%)			<0.001
Current smoker	247 (15.2)	2015 (8.1)	
Non smoker	671 (41.2)	12096 (48.7)	
Former smoker	710 (43.6)	10708 (43.1)	
Drinking status, N (%)			<0.001
Regular drinker	1049 (66.9)	18775 (77.4)	
Occasional drinker	249 (15.9)	2902 (12.0)	
Non drinker	271 (17.3)	2571 (10.6)	
Sleep duration, N (%)			<0.001

Short (< 6h)	252 (15.5)	3052 (12.3)	
Normal (6-8h)	1265 (78.0)	20463 (82.6)	
Long (> 8h)	105 (6.5)	1257 (5.1)	
Unsatisfactory sleep quality, N (%)	419 (25.7)	6175 (24.9)	0.464
PASE score, N (%)			<0.001
Quintile 1	396 (33.5)	4798 (19.8)	
Quintile 2	277 (23.4)	4914 (20.2)	
Quintile 3	187 (15.8)	4841 (19.9)	
Quintile 4	165 (13.9)	4839 (19.9)	
Quintile 5	158 (13.4)	4898 (20.2)	
Cardiovascular problems, N (%)	286 (17.7)	2970 (12.0)	<0.001
Diabetes, N (%)	325 (20.0)	4013 (16.2)	<0.001
COPD, N (%)	151 (9.3)	1221 (4.9)	<0.001
Asthma, N (%)	216 (13.4)	3221 (13.0)	0.730
Anxious-depressive symptoms, N (%)	391 (24.2)	5437 (22.0)	0.043
CESD10 score (mean (SD))	6.23 (5.14)	5.04 (4.50)	<0.001
Functional impairment (%)	232 (14.3)	1994 (8.1)	<0.001
Unsatisfactory health status (%)	256 (15.7)	1811 (7.3)	<0.001
Hs-CRP level, N (%)			<0.001
Normal	547 (39.6)	10207 (45.5)	
Mild	460 (33.3)	7579 (33.8)	
Moderate	313 (22.6)	3975 (17.7)	
High	62 (4.5)	686 (3.1)	
Snoring, N (%)	279 (17.1)	6087 (24.5)	<0.001
Tiredness, N (%)	153 (9.4)	1917 (7.7)	0.017
Observed apneas, N (%)	172 (10.6)	3192 (12.9)	0.008
High blood pressure, N (%)	525 (32.2)	8474 (34.1)	0.124

BMI > 35 kg/m^2 , N (%)	128 (7.9)	2219 (8.9)	0.151
STOP-B score (categorical), N (%)			<0.001
0 (low-risk)	832 (51.1)	10724 (43.2)	
1 (low-risk)	488 (30.0)	8634 (34.8)	
2 (low-risk)	180 (11.1)	3603 (14.5)	
3 (high-risk)	107 (6.6)	1430 (5.8)	
4 (high-risk)	17 (1.0)	381 (1.5)	
5 (high-risk)	4 (0.2)	47 (0.2)	
High risk OSA, N (%)	128 (7.9)	1858 (7.5)	0.610
STOP-B score (continuous; mean (SD))	1.77 (0.98)	1.88 (0.98)	<0.001

Note: Reference categories were not having a spouse, not being white from European origin, having an income < $20,000, having no post-secondary education, being completely retired, being a current smoker, being a regular drinker, having a short sleep duration, having a good sleep, being in the lowest physical activity quartile, not having chronic health conditions, not having functional impairment, having a good health perception, having normal levels of systemic inflammation (normal (<1 mg/L), mild (1-3 mg/L), moderate (3-10 mg/L) and high (>10 mg/L)), not presenting STOP-B items, and not presenting high risk OSA. N are crude numbers, proportions are weighted to account for the sampling strategy. SD: standard deviation.

Table S3. Cognitive scores according to OSA risk in the whole sample, excluding participants with a self-reported OSA diagnosis

	Neuropsychological variable	**Low-risk OSA** (unadjusted mean (SD))		**High-risk OSA** (unadjusted mean (SD))		**Estimate** (95% CI)
		Baseline	Follow-up	Baseline	Follow-up	
Whole sample	Group size, N	22961		1858		
	RAVLT immediate recall	6.0 (1.9)	6.7 (2.2)	5.8 (1.8)	6.4 (2.0)	P = 0.3
	RAVLT 5-min delayed recall	4.2 (2.2)	4.8 (2.4)	3.9 (2.0)	4.4 (2.3)	+0.5 (0.4 – 0.6) †
	Mental Alternation test	27.1 (8.5)	26.7 (7.6)	26.1 (8.9)	25.9 (7.8)	P = 0.5
	Animal Fluency test	20.9 (6.0)	20.7 (5.7)	20.3 (6.0)	20.2 (5.8)	P = 0.6
	COWAT	40.0 (12.7)	40.8 (12.4)	37.5 (12.5)	38.5 (12.6)	P = 0.7
	Stroop 1 (dot)	12.4 (3.1)	12.8 (3.5)	12.7 (3.3)	13.1 (3.4)	P = 0.3
	Stroop 2 (word)	15.9 (4.5)	16.4 (4.9)	16.8 (4.9)	17.3 (5.5)	P = 0.6
	Stroop 3 (color)	26.1 (9.8)	26.6 (10.2)	27.7 (10.0)	28.4 (11.2)	P = 0.4
	Stroop low interference index	1.3 (0.3)	1.3 (0.3)	1.3 (0.3)	1.3 (0.3)	P = 0.3
	Stroop high interference index	2.1 (0.6)	2.1 (0.6)	2.2 (0.6)	2.2 (0.7)	P = 0.8
	Choice Reaction Time	814.2 (192.1)	805.5 (152.5)	820.5 (204.0)	818.6 (178.8)	P = 0.08

† Significant when controlling for sociodemographic, lifestyle and medical variables.

Table S4. Cognitive scores according to OSA risk in the whole sample, including participants with a self-reported OSA diagnosis

	Neuropsychological variable	**Low-risk OSA** (unadjusted mean (SD))		**High-risk OSA** (unadjusted mean (SD))		**Estimate** (95% CI)
		Baseline	Follow-up	Baseline	Follow-up	
Whole sample	Group size, N	23206		2077		
	RAVLT immediate recall	6.0 (1.9)	6.7 (2.2)	5.8 (1.8)	6.4 (2.1)	P = 0.2
	RAVLT 5-min delayed recall	4.2 (2.2)	4.8 (2.4)	3.9 (2.0)	4.4 (2.3)	+0.5 (0.4 – 0.6) †
	Mental Alternation test	27.1 (8.5)	26.7 (7.6)	26.4 (8.8)	26.0 (7.7)	P = 0.9
	Animal Fluency test	20.9 (6.0)	20.7 (5.7)	20.5 (6.0)	20.4 (5.7)	P = 0.7
	COWAT	40.0 (12.7)	40.8 (12.4)	37.8 (12.4)	38.7 (12.6)	P = 0.8
	Stroop 1 (dot)	12.4 (3.1)	12.8 (3.5)	12.7 (3.2)	13.1 (3.4)	P = 0.2
	Stroop 2 (word)	15.9 (4.5)	16.4 (4.9)	16.7 (4.8)	17.2 (5.4)	P = 0.5
	Stroop 3 (color)	26.1 (9.7)	26.6 (10.2)	27.6 (9.8)	28.3 (11.2)	P = 0.2
	Stroop low interference index	1.3 (0.3)	1.3 (0.3)	1.3 (0.3)	1.3 (0.3)	P = 0.3
	Stroop high interference index	2.1 (0.6)	2.1 (0.6)	2.2 (0.6)	2.2 (0.7)	P = 0.8
	Choice Reaction Time	814.0 (191.7)	805.5 (152.5)	818.4 (199.0)	816.0 (174.3)	P = 0.1

† Significant when controlling for sociodemographic, lifestyle and medical variables.

Chapitre 3 – Discussion générale

3.1 Résultats généraux des études

L'objectif général de cette thèse était de caractériser le rôle de caractéristiques individuelles dans le risque de présenter de l'AOS et des possibles troubles cognitifs associés à l'AOS. Dans l'article 2, nous avons estimé la prévalence canadienne des hommes et des femmes âgés de 45 ans et plus qui sont à haut risque d'AOS et nous avons caractérisé l'association entre l'AOS et les comorbidités, la ménopause et l'inflammation systémique. Nous avons estimé une prévalence d'AOS de 13,1 % chez les femmes et de 21,9% chez les hommes. Le facteur le plus important associé au risque d'AOS était un niveau élevé d'inflammation systémique, et cette association était 1,3 à 2,3 fois plus élevée chez les femmes que chez les hommes. Le risque d'AOS augmentait également avec l'âge, les maladies cardiovasculaires, le diabète, les symptômes anxio-dépressifs, l'asthme, l'arthrite et, chez les femmes, le statut post-ménopausique. Cette étude montre que près d'un Canadien sur cinq âgé de plus de 45 ans présente les facteurs de risque d'AOS. Elle suggère de sensibiliser le grand public aux facteurs de risque et aux impacts de l'AOS ainsi que d'intégrer le dépistage de l'AOS parmi les procédures cliniques standard. Par exemple, les médecins de famille pourraient intégrer à leurs questionnaires de suivi des questions tel que : « Ronflez-vous bruyamment? » et « Quelqu'un vous a-t-il déjà vu cesser de respirer pendant votre sommeil? ».

L'article 3 a permis de caractériser les associations entre le risque d'AOS et les performances cognitives selon l'âge et le sexe et a clarifié le rôle médiateur du niveau d'inflammation systémique dans cette association. Notre étude a montré que les femmes âgées de 45 à 69 ans à haut risque d'AOS obtenaient des scores plus faibles que celles à bas risque d'AOS à des tests évaluant la mémoire verbale épisodique, l'attention et les fonctions exécutives. Nous avons également montré que l'inflammation systémique modérait certaines associations entre le risque d'AOS et l'attention et la mémoire épisodique. De ce fait, nous avons observé une association plus forte entre le risque d'AOS et certains scores cognitifs chez les participants ayant un niveau élevé d'inflammation systémique. De plus, l'inflammation systémique médiait plusieurs associations, en particulier celles observées chez les femmes ainsi que celles observées dans les domaines cognitifs de l'attention et des fonctions exécutives. En effet, une

inflammation systémique élevée expliquait une partie des associations significatives entre le risque d'AOS et la performance cognitive. Cette étude met en lumière l'inflammation systémique comme mécanisme possible pour expliquer le lien entre l'AOS et le fonctionnement cognitif.

L'article 4 a caractérisé les associations entre le risque d'AOS et le changement dans les performances cognitives après trois ans selon l'âge et le sexe. De manière générale, nous avons montré qu'un risque élevé d'AOS était associé à un déclin plus abrupte des performances dans les domaines de l'attention et de la vitesse de traitement de l'information. Nous avons également identifié un déclin plus abrupte des performances mnésiques des femmes âgées de 70 ans et plus à haut risque d'AOS en comparaison à celles à bas risque. Notre étude renforce l'idée que l'AOS devrait être considérée comme un facteur modifiable précoce de déclin cognitif et souligne la nécessité de développer des interventions adaptées qui tiennent compte des différences d'âge et de sexe dans la relation entre l'AOS et le fonctionnement cognitif.

Cette thèse constitue l'étude populationnelle la plus vaste (N= 27,210 participants) estimant la prévalence d'AOS et caractérisant le risque associé de présenter des troubles et un déclin cognitif selon le sexe tout en focalisant sur les adules âgés de 45-85 ans, qui pourraient différer des adultes plus jeunes en termes de prévalence et de déterminants d'AOS.

Les sections suivantes souligneront les implications de nos résultats.

3.2 ÉLCV et études épidémiologiques

3.2.1 Impacts des études épidémiologiques comme l'ÉLCV

Depuis environ vingt ans, un nombre croissant d'études s'intéressent au lien entre l'AOS et le fonctionnement cognitif. Celles-ci comptent des centaines, voire des milliers, de participants (Blackwell et al., 2011; Yaffe et al., 2011). Ces études menées sur d'aussi vastes échantillons offrent une grande puissance statistique permettant de tester l'effet de nombreuses variables et de contrôler pour l'effet de plusieurs autres, ce qui n'est pas possible dans de plus petits

échantillons. De plus, en dressant des portraits des populations, les études épidémiologiques représentent un outil particulièrement important pour les décideurs des politiques de santé publique. La cohorte de l'Étude longitudinale canadienne sur le vieillissement (ÉLCV), étudiée dans le cadre de cette thèse, fait partie de ces initiatives de recherche présentant un grand potentiel de généralisation des résultats. En caractérisant les participants de la cohorte compréhensive de l'ÉLCV au tout début du suivi, cette thèse pourra servir de base pour les études futures qui s'intéresseront aux prochains suivis prévus tous les trois ans pendant 20 ans. Précisément, nous avons caractérisé les participants au niveau du risque d'AOS, de l'inflammation systémique, de plusieurs conditions de santé et des performances cognitives. Le portrait que nous avons dressé chez plus de 27,000 Canadiens âgés de 45 ans et plus est généralisable à une grande partie de la population canadienne.

Considérant que le domaine de la santé est le plus coûteux pour les gouvernements provinciaux du Canada (Institut canadien d'information sur la santé, 2022) et étant donné le vieillissement de la population, une telle initiative est un excellent investissement. Ultimement, la meilleure compréhension des trajectoires de vieillissement qui découlera des résultats obtenus dans le cadre de l'ÉLCV facilitera l'adoption rapide de pratiques cliniques, de programmes d'interventions et de politiques visant l'amélioration de la santé, l'augmentation de la qualité et de la durée de la vie et le vieillissement optimal (Raina et al., 2009). De plus, le suivi de 20 ans prévu dans le protocole de l'ÉLCV permettra de caractériser de manière longitudinale les facteurs de risque et de protection de problèmes de santé et de déclin cognitif.

3.2.2 Forces et limites de l'ÉLCV

Le protocole de cette thèse incluait 30 097 participants de la cohorte compréhensive de l'ÉLCV. L'ÉLCV a été lancée afin d'améliorer notre compréhension de la complexité des transitions et des trajectoires de vieillissement (Raina et al., 2009). Précisément, elle vise à mieux comprendre comment les facteurs biologiques, physiques, psychologiques, sociaux et environnementaux, individuellement et en combinaison, influencent la santé et le bien-être des personnes âgées canadiennes (Raina et al., 2009). Ainsi, l'ÉLCV collecte de l'information sur une variété de

domaines relatifs à la santé tel que la génétique, les habitudes de vie, la cognition, l'inflammation, la santé physique et les variables psychosociales (Raina et al., 2009).

3.2.2.1 Protocole

Les données collectées dans le cadre de cette vaste étude nationale incluaient des questions sur le sommeil et la santé, des prises de sang et des tests neuropsychologiques. Le protocole incluait des visites à domicile (questionnaires et courts tests neuropsychologiques) ainsi que des visites aux sites de collecte de données (examen physique, prise de sang et batterie de tests neuropsychologiques). Cette variété de données nous a permis de caractériser efficacement les participants ainsi que leur risque de présenter de l'AOS ainsi que des possibles troubles cognitifs associés. Précisément, les prises de sang nous ont permis de caractériser le rôle de l'inflammation systémique dans la présentation de l'AOS et dans son association avec le fonctionnement cognitif. Il est à noter que bien que seule la CRP eût été dosée au moment des analyses, d'autres marqueurs tels que l'interleukine 6 et le facteur de nécrose tumorale sont maintenant disponibles. Les données auto-rapportées sur la santé (ex : conditions de santé concomitantes) nous ont permis d'identifier lesquelles étaient associées à un plus grand risque de présenter de l'AOS. Elles nous ont également permis de contrôler pour leur effet dans notre investigation de l'association entre l'AOS et les troubles cognitifs, en plus de contrôler pour les variables socio-démographiques et celles associées aux habitudes de vie.

Le vaste échantillon de cette étude nationale nous a également permis d'avoir la puissance statistique nécessaire pour effectuer des analyses statistiques stratifiées selon l'âge et spécifiques au sexe. De plus, le suivi effectué tous les trois ans au sein de cette étude longitudinale prospective permet d'examiner le changement au niveau du fonctionnement cognitif en lien avec le risque d'AOS au fil du temps.

3.2.2.2 Batterie neuropsychologique

La batterie neuropsychologique diversifiée de l'ÉLCV nous a permis d'examiner une variété de domaines cognitifs en lien avec le risque d'AOS. Plusieurs études de grandes cohortes ont utilisé des mesures de fonctionnement cognitif global (ex : MMSE), des échelles de sévérité de démence (ex : Clinical Dementia Rating) ou des diagnostics de démence (établis par des

cliniciens dans le cadre de l'étude ou auto-rapportés par les participants). Ces mesures sont toutefois peu sensibles et spécifiques, et sont susceptibles d'identifier un déclin cognitif qu'en stade déjà modéré ou avancé (Arevalo-Rodriguez et al., 2021).

À l'inverse, les tests neuropsychologiques ciblant des domaines cognitifs précis permettent d'identifier des troubles cognitifs plus précocement et de manière plus précise. Dans le cadre de cette thèse, l'utilisation d'une batterie neuropsychologique évaluant la mémoire verbale, les fonctions exécutives (flexibilité mentale, fluence verbale, vitesse de traitement, inhibition et attention) et la vitesse psychomotrice nous a permis d'identifier les domaines cognitifs les plus à risque de montrer un déclin lié à l'AOS.

3.2.2.3 Limites de l'ÉLCV

Toutefois, l'ÉLCV, tout comme plusieurs autres vastes études épidémiologiques, présente certaines limites. En collectant une panoplie d'informations sur une variété de domaines au sein de vastes échantillons, ce type de protocole de recherche devient rapidement dispendieux. Les équipes de recherche se butent ainsi rapidement à un défi : trouver la balance entre la quantité de domaines de recherche inclus dans la collecte de données et la précision des informations collectées. Dans le cas de l'ÉLCV, le sommeil a été sélectionné comme domaine d'intérêt, mais seules des informations subjectives ont été collectées. Ce faisant, les implications cliniques et la généralisation des résultats sont plus limitées que si des mesures objectives avaient été collectées. L'ÉLCV et les autres études grandes cohortes nationales devraient ainsi inclure des mesures ambulatoires tel qu'un oxymètre afin d'évaluer avec une plus grande sensibilité la présence d'AOS.

De plus, la cohorte compréhensive de l'ÉLCV a été échantillonnée afin d'inclure une proportion de femmes et d'hommes représentative de la population canadienne, ce qui permet une généralisation des résultats à l'ensemble de la population canadienne. Toutefois, plus de 90% de l'échantillon de la cohorte était caucasienne, ce qui limite la généralisation des résultats dans les autres groupes ethniques. De plus, les personnes résidant sur des réserves fédérales des Premières nations ou dans d'autres établissements des Premières nations dans les provinces ont été exclues de l'échantillonnage, et les participants recrutés résidaient dans les régions

urbaines situées à 25-50 km des sites de collecte de données, limitant la généralisation des résultats dans les populations rurales.

3.3 Femmes et ménopause

La santé des femmes est malheureusement encore mal comprises, et l'AOS ne fait pas exception. Ainsi, des efforts doivent être déployés afin d'adapter le dépistage ainsi que la prise en charge aux spécificités des femmes, particulièrement celles ménopausées.

3.3.1 Dépistage de l'AOS chez les femmes

Les femmes apnéiques semblent présenter des symptômes différents de ceux des hommes. Malheureusement, ce sont les symptômes présentés par les hommes apnéiques qui sont reconnus comme étant cardinaux et qui, ainsi, sont inclus dans les questionnaires de dépistage de l'AOS : le ronflement, la sensation de souffle coupé et l'observation d'apnées par le partenaire de lit. Les symptômes rapportés par les femmes ne correspondent toutefois pas à cette présentation clinique, et inclus des maux de tête, de la fatigue, de la dépression, de l'anxiété et de l'insomnie (Bonsignore et al., 2019; Lozo et al., 2017). Conséquemment, ces questionnaires identifient correctement les hommes apnéiques, mais pourraient avoir du mal à identifier les femmes apnéiques (Bonsignore et al., 2019). Ces dernières pourraient alors se retrouver sans diagnostic et donc, sans traitement. Dans le contexte spécifique de cette thèse, il est possible que les résultats obtenus auprès des femmes identifiées à haut risque d'AOS ne soient généralisables qu'aux femmes apnéiques qui présentent des symptômes semblables aux hommes, et non à l'ensemble des femmes apnéiques. Les questionnaires de dépistage devraient être revus afin d'inclure les symptômes typiquement rapportés par les deux sexes.

3.3.2 Rôle de la ménopause dans l'association entre l'AOS et la cognition

La prévalence de l'AOS chez les femmes augmente à la suite de la ménopause, notamment en raison de changements morphologiques (Heinzer et al., 2018). La ménopause augmente non seulement le risque de présenter de l'AOS, mais pourrait également augmenter le risque de

développer des troubles cognitifs associés à l'AOS. D'ailleurs, les résultats de l'article 3 montrent que les femmes âgées de 45 à 69 ans à haut risque d'AOS avaient des performances mnésiques, attentionnelles et exécutives inférieures à celles à bas risque d'AOS.

Bien que nos analyses de modération n'aient pas été en mesure de mettre en lumière un effet modérateur du statut ménopausique sur l'association entre le risque d'AOS et la performance cognitive, nos analyses de régression montrent que les femmes non-ménopausées avaient de meilleures performances à des tâches de fonctions exécutives que les femmes ménopausées. D'ailleurs, la perte d'hormones ovariennes à la ménopause est associée à des scores cognitifs plus faibles dans plusieurs domaines tels que l'attention, les fonctions exécutives et la mémoire (Gervais et al., 2017). Étant donné que le sommeil et le fonctionnement cognitif sont tous deux sensibles aux hormones ovariennes, la présence d'AOS jumelée à la perte d'hormones ovariennes à la ménopause pourrait entraîner une diminution des performances cognitives. Spécifiquement, cette perte d'hormones pourrait exacerber les troubles du sommeil et potentialiser leur impact sur le fonctionnement cognitif. Cependant, très peu d'études se sont penchées sur cette question à ce jour (pour des revues, voir Carrier et al., 2017; Gervais et al., 2017).

Une étude effectuée chez des rates a révélé que la privation de sommeil altérait les performances de la mémoire uniquement chez les rates ovariectomisés, mais pas chez celles dont les gonades étaient intactes (Esmaeilpour et al., 2015). De plus, dans une étude de Saletu (2003), les femmes ménopausées utilisant une hormonothérapie substitutive pendant deux mois ont amélioré à la fois la qualité subjective et objective (tendance) du sommeil, l'indice d'apnée/hypopnée (IAH), ainsi que l'attention soutenue et la vitesse de traitement. Ces résultats suggèrent que les hormones ovariennes sont bénéfiques pour le sommeil et protègent le cerveau des jeunes femmes contre les effets néfastes des troubles du sommeil (Gervais et al., 2017).

Un mécanisme qui pourrait expliquer le lien entre la perte d'hormones ovariennes, l'AOS et le déclin cognitif est le stress oxydatif. Tel que décrit précédemment, les apnées génèrent une hypoxie intermittente, qui à son tour peut induire un stress oxydatif, c'est-à-dire un déséquilibre

entre les activités des enzymes pro-oxydantes et antioxydantes (Boukari et al., 2017). Fait intéressant, l'estradiol et la progestérone sont bien connus comme médicaments antioxydants et pourraient avoir des effets protecteurs contre le stress oxydatif induit par l'AOS (Boukari et al., 2017). En effet, une étude chez des rates ovariectomisées exposées à une hypoxie intermittente chronique a montré que celles traitées à l'estradiol étaient protégées des effets de l'hypoxie intermittente sur le cerveau (Laouafa et al., 2017). Ces résultats suggèrent que les hormones ovariennes pourraient agir comme des médicaments antioxydants pour protéger le cerveau des jeunes femmes contre l'impact possiblement délétère de l'hypoxie intermittente.

Ainsi, il pourrait y avoir un effet d'interaction entre le risque d'AOS et la ménopause sur le fonctionnement cognitif, mais d'autres études sont nécessaires pour confirmer cette hypothèse. Si tel est le cas, les hormones ovariennes pourraient être utilisées comme médicament antioxydant afin de réduire le stress oxydatif occasionné par l'AOS et ainsi, prévenir le déclin cognitif des femmes apnéiques. Les futures études devraient examiner à la fois les effets indépendants et synergiques de la ménopause et de l'AOS sur le fonctionnement cognitif afin d'améliorer le dépistage la prise en charge des femmes apnéiques ménopausées.

3.4 Mesures à intégrer dans les études futures

Le rôle de l'inflammation systémique a été étudié dans le cadre des articles de cette thèse, mais d'autres mécanismes pourraient expliquer les associations entre l'AOS et le déclin cognitif. La présente section présentera des marqueurs qu'il serait intéressant d'inclure dans les futures études investiguant le lien entre l'AOS et la cognition chez les personnes d'âge moyen et âgées. Précisément, il sera question de l'inflammation systémique, les biomarqueurs de la MA, c'est-à-dire l'amyloïde et la protéine tau, ainsi que le facteur de risque génétique ApoE4.

3.4.1 Inflammation systémique

La fragmentation du sommeil et l'hypoxémie intermittente caractéristiques de l'AOS peuvent provoquer de l'inflammation systémique (Polsek et al., 2018). Ainsi, plusieurs études ont mis en évidence des niveaux élevés d'inflammation (protéine C-Réactive (CRP), interleukines (IL),

fibrinogène et vitesse de sédimentation des érythrocytes élevées) chez les personnes apnéiques, en particulier les femmes (Bouloukaki et al., 2017). Dans un échantillon de 74 jeunes adultes militaires, les niveaux d'IL-6 étaient plus élevés chez les participants avec AOS modérée à sévère en comparaison aux participants avec AOS légère ainsi qu'aux participants contrôles (Motamedi et al., 2018). Puisque l'hypertension était peu fréquente chez ces jeunes participants, il est possible d'attribuer ces niveaux élevés d'inflammation à l'AOS (Motamedi et al., 2018). De manière consistante, les résultats de l'article 2 de cette thèse montrent qu'un niveau élevé de CRP était le facteur le plus fortement associé au risque d'AOS, particulièrement chez les femmes.

La réponse inflammatoire consécutive à l'AOS pourrait expliquer le développement de troubles cognitifs. Les résultats de l'article 3 de la présente thèse montrent qu'un niveau élevé de CRP médie certaines associations entre le risque d'AOS et la performance en fonctions exécutives des personnes âgées de moins de 70 ans, appuyant le rôle de l'inflammation systémique comme mécanisme expliquant le lien entre l'AOS et les troubles cognitifs. Ces résultats complémentent les résultats d'une étude récente montrant une interaction entre les niveaux de base de CRP et la fragmentation du sommeil sur la prédiction du risque de démence plus élevé 13 ans plus tard (Baril et al., 2021).

Davantage d'études incluant des mesures objectives d'AOS devraient investiguer le rôle de l'inflammation dans l'association entre l'AOS et le fonctionnement cognitif afin de déterminer si un niveau inflammatoire élevé augmente le risque de troubles cognitifs des personnes apnéiques. Tel que mentionné précédemment, nous avons analysé uniquement la CRP dans le cadre de nos études, mais d'autres marqueurs sont maintenant disponibles dans l'ÉLCV (ex : interleukine 6 et facteur de nécrose tumorale). Il serait pertinent d'investiguer le rôle de ces autres marqueurs puisqu'ils pourraient être indépendamment associés à la sévérité de l'AOS et au sexe (Bouloukaki et al., 2017). Par exemple, une étude a montré que les femmes apnéiques avaient des niveaux plus élevés de CRP, de fibrinogène et de vitesse de sédimentation des érythrocytes alors que les hommes apnéiques avaient des niveaux plus élevés d'acide urique (Bouloukaki et al., 2017). Ainsi, il serait pertinent d'investiguer le rôle de différents marqueurs

d'inflammation systémique dans l'association entre l'AOS et le fonctionnement cognitif en fonction du sexe.

3.4.2 Biomarqueurs de la maladie d'Alzheimer

Les deux principaux processus neuropathologiques caractéristiques de la maladie d'Alzheimer (MA) sont l'accumulation extracellulaire de plaques de peptide bêta-amyloïde et l'accumulation intracellulaire de protéine tau hyperphosphorylée formant des dégénérescences neurofibrillaires (Braak & Braak, 1991). Ces deux mécanismes favorisent la mort neuronale et l'apparition de déficits cognitifs (Jack et al., 2010). Un nombre grandissant d'études s'intéresse aux liens entre le sommeil et les biomarqueurs de la MA (Liguori et al., 2021; Lucey et al., 2019; Mander et al., 2016). Notamment, plusieurs études ont montré une augmentation des niveaux d'amyloïde et de tau en cas de privation (Barthélemy et al., 2020; Ju et al., 2017; Ooms et al., 2014), de fragmentation (Lim et al., 2013) et de courte durée (Spira et al., 2013; Winer et al., 2021) de sommeil.

3.4.2.1 Amyloïde et AOS

En ce qui a trait à l'AOS, sa sévérité a été associée de manière transversale et longitudinale à une augmentation des dépôts amyloïdes, observable par une augmentation des niveaux d'amyloïde dans le sang (Bu et al., 2015; Huang et al., 2023; Kang et al., 2022) et une réduction des niveaux d'amyloïde dans le liquide céphalorachidien (Bubu et al., 2019; Cui et al., 2022; Kang et al., 2022; Liguori et al., 2017; Sharma et al., 2018). Cette accumulation se ferait préférentiellement au niveau du cortex cingulaire postérieur et du précunéus, deux régions typiquement affectées dans la MA (André et al., 2020). De manière intéressante, l'accumulation d'amyloïde dépendrait de l'âge, de l'IMC et de la sévérité de l'AOS (Cui et al., 2022). En effet, l'amyloïde s'accumulerait davantage dans le cerveau des personnes apnéiques âgées de plus de 67 ans, celles ayant un IMC de plus de 27,6 et celles présentant de l'AOS modérée à sévère (Cui et al., 2022). L'effet du sexe n'a pas été investigué dans cette étude.

L'accumulation d'amyloïde chez les personnes apnéiques pourrait être une conséquence de 1) l'hyperactivité neuronale consécutive à la perturbation du sommeil (Bero et al., 2011); 2) la

perturbation de l'activité du système glymphatique, responsable de nettoyer le cerveau des déchets accumulés au cours de la journée, en raison de la réduction du sommeil à ondes lentes et de l'augmentation de la pression intrathoracique et intracrânienne en réponse aux apnées et hypopnées (Xie et al., 2013). L'accumulation d'amyloïde pourrait aussi être une conséquence de l'inflammation systémique (Kinney et al., 2018; Polsek et al., 2018). En effet, une activation chronique des cellules de la microglie (qui jouent un rôle de défense et de réparation dans le système nerveux) pourrait avoir pour effet de libérer des produits proinflammatoires tels que des espèces réactives de l'oxygène et des cytokines, ce qui faciliterait l'accumulation de la pathologie amyloïde et tau (Kinney et al., 2018; Polsek et al., 2018).

3.4.2.2 Protéine tau et AOS

L'AOS a également été associée à des niveaux élevés de tau périphérique (Bu et al., 2015; Ju et al., 2016; Liguori et al., 2017; Motamedi et al., 2018; Osorio et al., 2014), ce qui traduit une augmentation de la pathologie tau, mais l'association longitudinale n'est pas bien établie (Bubu et al., 2019; Sharma et al., 2018). Toutefois, l'AOS pourrait accélérer l'accumulation longitudinale de tau dans le liquide céphalorachidien chez les personnes cognitivement saines et celles présentant un trouble cognitif léger (TCL) (Bubu et al., 2019). De manière intéressante, dans un échantillon de 74 jeunes adultes militaires avec peu de comorbidités mentionné précédemment, les niveaux de tau périphériques étaient plus élevés chez les participants avec AOS modérée à sévère en comparaison aux participants avec AOS légère ainsi qu'aux participants contrôles (Motamedi et al., 2018), ce qui suggère qu'une plus grande sévérité d'AOS est associée à une augmentation plus importante de la pathologie tau.

Bien que les mécanismes liant la pathologie tau et l'AOS ne soient pas encore bien compris, une récente étude chez les rongeurs suggère un rôle causal de l'hypoxémie intermittente (Kazim et al., 2022). En effet, dans cette étude, les souris exposées à une hypoxie intermittente chronique pendant huit semaines ont montré une augmentation de l'ensemencement et de la propagation de la protéine tau en comparaison aux souris ayant une quantité normale d'oxygène (Kazim et al., 2022). Également, les perturbations du sommeil associés à l'AOS (ex : fragmentation du sommeil) pourraient également être impliquées puisque les éveils corticaux répétitifs

pourraient altérer la clairance de l'amyloïde dans le liquide interstitiel (Sun et al., 2022). De manière intéressante, les niveaux de tau périphérique ont été associés à la fois à l'IAH et à l'IDO ainsi qu'à la somnolence diurne excessive (Sun et al., 2022). Étant donné la disponibilité récente des outils technologiques permettant d'analyser les marqueurs sanguins de protéine tau (Ossenkoppele et al., 2022), les résultats obtenus à ce jour devront être corroborés dans le cadre d'études futures.

3.4.2.3 Amyloïde, tau et déclin cognitif

L'accumulation de pathologie amyloïde et tau sont associées au développement et à la progression de la MA. Une étude longitudinale (moyenne de suivi de 2,5 ans) de l'*Alzheimer's Disease Neuroimaging Initiative (ADNI)* a montré une plus grande augmentation annuelle des niveaux d'amyloïde et d'agrégation de tau cérébraux chez les personnes apnéiques cognitivement saines et présentant un TCL en comparaison à ceux des participants sans AOS, mais pas chez celles présentant une MA (Bubu et al., 2019). Cela suggère que l'effet de l'AOS sur les biomarqueurs de la MA serait atténué aux stades plus avancés de la maladie, possiblement en raison d'un effet plafond du niveau de la pathologie amyloïde (Bubu et al., 2019; Jack et al., 2010).

3.4.2.4 Biomarqueurs dans les études épidémiologiques futures

Au cours des dernières années, la sensibilité des tests de biomarqueurs sanguins s'est grandement améliorée, permettant de détecter des anomalies physiologiques aux stades pré-cliniques de la MA, parfois des décennies avant l'apparition des troubles cognitifs (Leuzy et al., 2022). Inclure des tests sanguins dans de vastes études épidémiologiques permettrait d'identifier des anomalies physiologiques liées à l'AOS qui apparaitraient en amont des troubles cognitifs afin d'identifier les individus cognitivement sains les plus à risque de développer une démence. Si les niveaux d'amyloïde et de tau avaient été disponibles dans l'ÉLCV, il aurait été possible d'investiguer leur potentiel rôle médiateur ou modérateur de l'association entre le risque d'AOS et le déclin cognitif. En se basant sur la littérature actuelle, il aurait été attendu que les participants à haut risque d'AOS ayant des niveaux élevés d'amyloïde et de tau

présentent un déclin cognitif plus marqué que ceux à haut risque d'AOS ayant de faibles niveaux de ces biomarqueurs.

Toutefois, une étape nécessaire pour favoriser l'implémentation de ces tests en pratique clinique est la validation de la valeur pronostique de ces biomarqueurs au niveau individuel (Ossenkoppele et al., 2022). Considérant cette limite et le fait que la présence de biomarqueurs n'est pas suffisante pour prédire le développement de la démence (Jack et al., 2010), il est primordial de cibler les participants particulièrement à risque de démence pour ces tests. Pour ce faire, plus de recherche est nécessaire afin d'identifier les combinaisons de facteurs, par exemple des caractéristiques individuelles et des habitudes de vie, qui caractérisent ces personnes.

3.4.3 ApoE4

L'apolipoprotéine E (apoE) est une protéine impliquée dans le transport du cholestérol et dans la croissance et la réparation du système nerveux pendant le développement ou après une blessure (Poirier et al., 1993; Strittmatter et al., 1993). L'allèle 4 (apoE4) représente le principal facteur de risque génétique de la MA (Poirier et al., 1993). Même si la présence de l'apoE4 seule ne serait pas suffisante pour engendrer un déclin cognitif, elle représente probablement un facteur de susceptibilité interagissant avec d'autres influences génétiques et environnementales pour augmenter le risque de déclin cognitif (Oviedo et al., 2018) ; un de ces facteurs pourrait être l'AOS.

Chez les personnes avec AOS, la présence de l'apoE4 serait associée à davantage de troubles cognitifs en comparaison à celles sans cet allèle (Cosentino et al., 2008; Nikodemova et al., 2013; O'Hara et al., 2005; Spira et al., 2008). Ces résultats pourraient s'expliquer par la vulnérabilité des porteurs de l'apoE4 aux blessures du système nerveux central de différentes origines, telles que le stress oxydatif associé à l'AOS (Nikodemova et al., 2013; O'Hara et al., 2005). Une étude américaine de 1 387 participants de la *National Alzheimer's Coordinating Center Uniform Dataset (NACC UDC)* a d'ailleurs montré une interaction entre la présence d'AOS auto-rapportée et d'apoE4 en lien avec plus d'hypersignaux de la matière blanche (Turner et al., 2023).

Davantage d'études sont nécessaires afin de déterminer si les personnes apnéiques porteuses de l'apoE4 présentent réellement un risque accru de déclin cognitif et de démence. Les vastes études épidémiologiques telles que l'ÉLCV devraient inclure cette mesure dans leur protocole afin de caractériser les participants sur le plan génétique et de déterminer si l'apoE4 interagit avec des facteurs de risque, notamment l'AOS, pouvant mener au déclin cognitif ou à la démence. Dans l'ÉLCV, les échantillons de sang ont été collectés, mais n'ont pas encore été génotypés. Si cette information avait été disponible, nous aurions pu caractériser le rôle de l'apoE dans l'association entre le risque de présenter de l'AOS et le déclin cognitif. Nous nous serions attendus à ce que les participants à haut risque d'AOS ayant l'allèle 4 présentent un déclin cognitif plus marqué que ceux à haut risque d'AOS ayant l'allèle 2 ou 3.

Bref, intégrer des mesures inflammatoires et génétiques ainsi que des biomarqueurs dans le cadre de futures études épidémiologiques permettrait de mieux comprendre les mécanismes qui lient l'AOS au déclin cognitif. Ultimement, cela améliorerait l'identification des individus les plus à risque de démence et leur prise en charge précoce afin de prévenir ou de ralentir le déclin cognitif.

3.5 Avenues de traitement et d'intervention

3.5.1 Traitement par CPAP

Le traitement par CPAP permet de réduire les événements respiratoires et ainsi, de diminuer les éveils répétés, la somnolence diurne, la pression artérielle moyenne, les marqueurs d'inflammation, les anomalies des cellules endothéliales (Jelic & Le Jemtel, 2008) et le nombre d'événements cardiovasculaires mortels et non mortels (Marin et al., 2005).

3.5.1.1 Effet du CPAP sur la cognition

L'amélioration de l'hypoxie intermittente et de la fragmentation du sommeil par le CPAP entraîne une amélioration de la circulation sanguine (Jonas et al., 2017) et, ainsi, des modifications cérébrales neuroanatomiques (Mullins et al., 2020) et fonctionnelles (L'Heureux

et al., 2021). Par exemple, l'utilisation du CPAP pendant 18 mois par des personnes apnéiques âgées entre 56 et 82 ans a permis d'augmenter le flux sanguin cérébral relatif (tendance) dans des régions du lobe temporal médian (L'Heureux et al., 2021). De plus, le traitement par CPAP a été associé à des augmentations de volume de la matière grise après un mois (Rosenzweig et al., 2016) et trois mois (Canessa et al., 2011), ainsi qu'à un renversement presque complet des anomalies de la matière blanche après douze mois (Castronovo et al., 2014).

En retour, ces modifications cérébrales peuvent être associées à une amélioration du fonctionnement cognitif. En effet, une étude rétrospective canadienne menée auprès de 171 personnes apnéiques avec troubles cognitifs (MA, TCL, démence vasculaire, TCL vasculaire ou démence mixte; âge moyen = 70 ans) suggère que l'utilisation du CPAP est associée à une amélioration du fonctionnement cognitif (Costa et al., 2023). Précisément, une bonne adhérence au CPAP ($\geq$ 4h/nuit pendant 7 jours/semaine) pour une durée de 2 à 12 mois était associée à de meilleurs scores au *Montreal Cognitive Assessment* (MoCA; 2,3 points) et au *Mini Mental State Examination* (MMSE; 1,2 points) en comparaison à une mauvaise adhérence ou une absence d'utilisation du CPAP (Costa et al., 2023). Une autre étude a montré que l'utilisation du CPAP pendant six mois (âge moyen de 50 ans) était associée à une amélioration de la mémoire de travail, de l'attention soutenue, des capacités visuospatiales et des fonctions exécutives (D'Rozario et al., 2022). Toutefois, un large essai contrôlé randomisé multicentrique n'a montré aucun effet du traitement par CPAP sur la cognition après six mois (Kushida et al., 2012). Cette absence d'effet pourrait être attribuable au bas âge des participants (moyenne de 52 ans et de 51 ans dans les groupes actifs et contrôles, respectivement), à l'absence de troubles cognitifs au début de l'étude ainsi qu'à la faible symptomatologie, notamment au niveau de la fatigue. Ainsi, il est possible que le CPAP ait des effets bénéfiques sur la cognition particulièrement des personnes apnéiques plus âgées, particulièrement lorsqu'elles ont des troubles cognitifs ainsi que des symptômes diurnes de l'AOS.

Également, le traitement par CPAP a été associé à un risque plus faible de diagnostic de MA (Dunietz et al., 2021) et à l'apparition plus tardive de TCL par rapport à l'AOS non traitée (82 ans contre 72 ans ; Osorio et al., 2015). Chez les patients atteints de MA modérée et d'AOS sévère,

le traitement par CPAP a été associé à un déclin cognitif plus lent sur trois ans par rapport aux patients non traités (Troussière et al., 2014), et à une amélioration significative de la vitesse de traitement psychomoteur/cognitif chez les patients avec un TCL après un an (Richards et al., 2019). Toutefois, une étude rétrospective n'a pas montré d'association entre le traitement par CPAP et la progression vers la MA ou le déclin cognitif après 2,8 ans (Skiba et al., 2020). Il est possible d'attribuer cette absence de relation au jeune âge des participants (âgés de 18 ans et plus) ainsi qu'au critère faible utilisé pour statuer de la présence d'AOS (IAH $\geq$ 5) (Skiba et al., 2020). L'ensemble de ces résultats suggère que le CPAP pourrait possiblement retarder le diagnostic de TCL et de MA spécifiquement chez les personnes plus âgées présentant une forme modérée à sévère d'AOS.

3.5.1.2 Mécanismes neurophysiologiques

L'amélioration du fonctionnement cognitif à la suite du traitement par CPAP pourrait s'expliquer par l'amélioration de la somnolence qui découle du traitement (Costa et al., 2023). Le traitement par CPAP pendant six mois a d'ailleurs été associé à une amélioration des symptômes auto-rapportés de somnolence, de dépression, d'anxiété et de stress ainsi que de la qualité de vie en lien avec le sommeil (D'Rozario et al., 2022). Le traitement par CPAP améliorerait également les anomalies de l'électrophysiologie du cerveau associées à l'AOS, notamment en augmentant la puissance spectrale dans la bande de fréquences delta durant le sommeil lent ainsi que la densité des fuseaux de sommeil (D'Rozario et al., 2022). Considérant le rôle important de ces oscillations dans les processus d'apprentissage et de mémoire (Feld & Diekelmann, 2015; Gosselin, 2020), il ne serait pas étonnant que leur augmentation se traduise par une amélioration du fonctionnement cognitif (D'Rozario et al., 2022), mais cette hypothèse reste à être vérifiée.

Le traitement par CPAP pourrait également limiter les troubles cognitifs liés à l'AOS en prévenant l'inflammation systémique induite par l'hypoxémie intermittente (Dandan-Zong et al., 2023). Une étude récente a montré que des niveaux élevés d'inflammation systémique (mesurés par les marqueurs IL-6/IL-8) de patients apnéiques étaient associés à une plus grande sévérité d'AOS (mesurée par l'IAH et l'IDO) et à de plus faibles scores cognitifs (mesurés par le

MMSE et le MoCA) (Dandan-Zong et al., 2023). Après un traitement par CPAP de 12 semaines, les niveaux d'inflammation ont significativement baissé et les performances cognitives ont augmenté chez les patients présentant de l'AOS sévère (Dandan-Zong et al., 2023). Ces résultats suggèrent que les marqueurs d'inflammation systémique pourraient devenir de nouvelles cibles thérapeutiques intéressantes pour prévenir et traiter les troubles cognitifs liés à l'AOS (Dandan-Zong et al., 2023). Puisque les résultats de l'article 3 de cette thèse montrent qu'un niveau élevé d'inflammation systémique (mesuré par la CRP) médie certaines associations entre le risque d'AOS et les scores de fonctions exécutives, il aurait également été intéressant d'évaluer le rôle du CPAP dans cette association. Précisément, il aurait été pertinent de comparer les niveaux d'inflammation des personnes à haut risque d'AOS traitées par CPAP et des personnes non traitées. Il aurait été attendu que les personnes à haut risque d'AOS traitées par CPAP montrent des niveaux d'inflammation plus faibles que celles non traitées. L'ÉLCV devrait inclure une question sur le traitement par CPAP afin de permettre d'investiguer cette relation. De plus, le traitement par CPAP pourrait diminuer la charge amyloïde des personnes apnéiques. De ce fait, une étude a montré que les patients traités par CPAP depuis plus d'un an présentaient des niveaux d'amyloïde semblables aux contrôles alors que les patients non traités montraient des niveaux faibles dans le liquide cérébro-spinal, reflétant une accumulation importante dans le cerveau (Liguori et al., 2017). Une étude récente a également montré que les niveaux périphériques d'amyloïde et de tau de patients apnéiques étaient significativement plus bas après un an de traitement par CPAP que ceux observés un an plus tôt (Sun et al., 2022).

Bref, le traitement par CPAP est une piste thérapeutique prometteuse qui pourrait potentiellement protéger le cerveau des effets délétères de l'AOS. Son impact sur le cerveau et la cognition peut toutefois varier en fonction de divers facteurs tels que le nombre d'années d'AOS non-traitée, la sévérité de l'AOS, le degré d'hypoxémie, la réserve cognitive et le statut cognitif (Hoyos et al., 2022). Malheureusement, il n'a pas été possible d'évaluer l'impact du traitement par CPAP dans le cadre des articles de cette thèse puisque l'ÉLCV n'a pas collecté d'information à ce sujet. Il serait pertinent que les prochaines études épidémiologiques collectent de l'information sur le traitement de l'AOS afin de pouvoir comparer les apnéiques

traités et non traités sur le plan cognitif et ainsi, déterminer si le traitement par CPAP limite ou retarde le déclin cognitif associé à l'AOS.

3.5.1.3 Faible adhérence au CPAP

Malheureusement, seulement 41% des patients apnéiques qui ont reçu un diagnostic utilisent toujours le CPAP après un an (Lee et al., 2017). Les patients qui n'adhèrent pas au traitement rapportent qu'ils n'en voient pas le besoin, que l'appareil est incommode ou inconfortable et qu'il est coûteux (Lee et al., 2017).

Au Québec, un remboursement du CPAP par le programme de la *Régie de l'assurance maladie du Québec (RAMQ)* résulterait sans doute à une augmentation du nombre de patients apnéiques traités. Ainsi, un traitement plus accessible pourrait résulter en une diminution des conséquences possibles de l'AOS sur la santé telles que les maladies cardiovasculaires, l'hypertension et le diabète (Marin et al., 2005). Également, la réduction de la somnolence entraînée par le CPAP pourrait augmenter la productivité au travail et réduire le taux d'absentéisme ainsi que le nombre d'accidents de travail et de la route (Sassani et al., 2004). Bref, en contexte de rareté de main d'œuvre, un remboursement du traitement par CPAP par la RAMQ est souhaitable afin de prévenir des événements de santé liés à l'AOS et ainsi contribuer à désengorger le système de santé. Un premier pas dans cette direction a été fait en avril 2023 : le ministre de la santé, Christian Dubé, a annoncé un financement de 1,8 million de dollars pour le remboursement des appareils CPAP (Association pulmonaire du Québec, 2023). Bien que les échéanciers ne soient pas encore connus à ce jour, les personnes à faible revenu auront accès au remboursement en priorité (Assemblée nationale du Québec, 2023).

3.5.2 Exercice physique et perte de poids

Bien que l'efficacité du traitement par CPAP soit éprouvée, le niveau d'acceptation et d'adhérence au CPAP est faible chez les patients apnéiques. Ce faisant, il est nécessaire de proposer d'autres avenues afin de limiter les conséquences possibles de l'AOS sur la santé cérébrale. L'une de ces options est l'exercice physique.

3.5.2.1 Obésité et inactivité physique

Tel que mentionné précédemment, l'obésité est le plus grand facteur de risque d'AOS (Carter & Watenpaugh, 2008). Une revue systématique portant sur l'activité physique et l'AOS suggère que les patients avec AOS présenteraient de faibles niveaux d'activité physique, possiblement en raison d'un cercle vicieux, avec l'inactivité physique menant à une prise de poids pouvant conduire au développement de l'AOS, associé à de la fatigue et de la somnolence, ce qui contribue en retour à l'inactivité physique. À l'inverse, selon une revue systématique et méta-analyse, l'intégration d'un programme d'exercices physiques serait liée à une diminution subséquente de l'IAH et des symptômes de somnolence (Mendelson et al., 2018). La diminution de la symptomatologie de l'AOS liée à l'activité physique pourrait être attribuable à la diminution de tissus adipeux, à l'augmentation de la force et de la résistance à la fatigue des dilatateurs des voies aériennes supérieures, à une diminution de la résistance nasale et à une augmentation de la stabilité respiratoire lors du sommeil profond (Kline et al., 2011).

Ensuite, l'inactivité physique serait le facteur de risque de démence le plus important aux États-Unis, en Europe et en Angleterre alors qu'environ le tiers de la population adulte de ces régions serait physiquement inactive (Norton et al., 2014). Les troubles cognitifs pourraient être une manifestation de l'obésité elle-même ou d'une ou plusieurs de ses comorbidités associées (Fernando et al., 2019). Les résultats issus d'une étude longitudinale sur 36 ans montrent que l'obésité à l'âge adulte moyen augmenterait le risque de démence, même en contrôlant pour l'influence du diabète et d'autres comorbidités vasculaires (Whitmer et al., 2008). Les adipocytes sécrètent des cytokines pro-inflammatoires qui peuvent affecter la plasticité synaptique et neuronale et être impliquées dans les processus neurodégénératifs (Miller & Spencer, 2014), alors que l'inflammation liée à l'obésité entraîne un stress oxydatif, jouant lui aussi un rôle dans les processus neurodégénératifs (Barnham et al., 2004). Il serait intéressant que les études futures investiguent les interactions potentielles entre l'AOS et l'obésité sur le fonctionnement cognitif et le risque de démence.

Dans le cadre de l'ÉLCV, l'absorptiométrie à rayons X en double énergie (DXA) a été utilisée afin de déterminer la composition corporelle des participants, permettant notamment d'établir le

pourcentage de masse adipeuse. Cette information, plus précise que l'IMC, serait pertinente à utiliser dans le cadre d'études futures portant sur le lien entre l'AOS. Par exemple, il serait intéressant d'investiguer si l'activité physique et le pourcentage de masse adipeuse sont indépendamment associés à la présence et à la sévérité de l'AOS, et si ces variables jouent un rôle modérateur ou médiateur dans l'association entre l'AOS et le fonctionnement cognitif.

3.5.2.2 Bénéfices de l'activité physique sur le cerveau

De manière encourageante, les résultats issus d'essais contrôlés randomisés suggèrent que des personnes âgées inactives, bien qu'en bonne santé générale, améliorent leur fonctionnement cognitif et voient le risque de déclin cognitif diminuer lorsqu'elles entament un programme d'exercices, même de basse intensité (Baumgart et al., 2015). L'activité physique promouvrait la santé vasculaire en diminuant la pression sanguine, les lipides, l'obésité et les marqueurs d'inflammation, favoriserait la plasticité cérébrale et la neurogenèse et améliorerait l'apport en oxygène au cerveau (Hamer & Chida, 2008). Une étude menée chez des hommes âgés entre 60 et 70 ans (IMC entre 25 et 35 kg/m^2) a d'ailleurs montré que l'amélioration des performances en fonctions exécutives à la suite d'un programme d'activité physique de huit semaines était accompagnée d'augmentations concomitantes du flux sanguin cérébral (ce qui implique une augmentation de l'oxygénation) dans les lobes frontaux ainsi qu'une augmentation du métabolisme du glucose (Kleinloog et al., 2019). Fait important, le taux de glucose métabolique cérébral dépend du débit sanguin cérébral, de l'apport d'oxygène et du métabolisme neuronal (Ueno-Pardi et al., 2022). Une augmentation du métabolisme du glucose associée à une augmentation du flux sanguin cérébral pourrait ainsi traduire une amélioration de l'activité synaptique, ce qui expliquerait l'amélioration des fonctions exécutives (Ueno-Pardi et al., 2022). Finalement, l'activité physique serait associée à de plus faibles niveaux de biomarqueurs de la MA dans le liquide céphalorachidien tels que la protéine tau et la bêta-amyloïde (Liang et al., 2010). Ainsi, les auteurs d'une revue de littérature sur l'effet de l'activité physique sur la cognition et le fonctionnement cérébral des personnes âgées suggèrent l'activité physique comme intervention prometteuse afin de prévenir le déclin cognitif et les maladies neurodégénératives (Bherer et al., 2013).

3.5.2.3 Activité physique, fonctionnement cognitif et AOS

En ce qui a trait à l'AOS, le rôle de l'activité physique en lien avec le fonctionnement cognitif a été peu étudié à ce jour. Une étude menée chez des personnes âgées entre 30 et 65 ans en surpoids (IMC entre 27 et 42 kg/m^2) a montré qu'un programme d'exercice physique de six semaines permettait d'améliorer les fonctions exécutives des personnes ayant une AOS modérée à sévère, mais pas de celles ayant une AOS légère (Kubitz et al., 2023). Une étude récente supporte ces résultats, montrant une amélioration des fonctions exécutives et de l'attention chez les personnes âgées entre 40 et 65 ans (IMC < 40 kg/m^2) ayant une AOS modérée à sévère ayant suivi un programme d'activité physique pour une durée de six mois (Ueno-Pardi et al., 2022). De manière intéressante, cette étude a montré que le programme d'activité physique était aussi associé à une amélioration des capacités physiques et à une réduction de l'IAH (Ueno-Pardi et al., 2022), bien que l'étude de Kubitz et al. (2023) n'ait pas montré de telles améliorations. L'étude de Ueno-Pardi et al. (2022) a également montré que le programme d'activité physique était associé à une augmentation du taux de glucose métabolique cérébral dans le lobe frontal droit, ce qui pourrait expliquer l'amélioration des fonctions exécutives et de l'attention. Bref, ces résultats suggèrent que l'activité physique, possiblement via l'amélioration du taux de glucose métabolique, pourrait modérer l'association entre l'AOS et les fonctions exécutives, avec les personnes présentant de l'AOS plus sévère bénéficiant le plus des bienfaits de l'exercice physique sur le fonctionnement cognitif.

L'activité physique représente ainsi une avenue de traitement intéressante pour les personnes apnéiques puisqu'elle pourrait améliorer les symptômes d'AOS et le fonctionnement cognitif, et potentiellement retarder le déclin cognitif. Toutefois, plus d'études sont nécessaires pour le confirmer. Dans le cadre de l'ÉLCV, l'activité physique a été quantifiée en utilisant le questionnaire *Physical Activity Scale for the Elderly (PASE)* (Washburn et al., 1993), qui mesure les activités de loisirs, domestiques et liées au travail. Le score obtenu au PASE correspond à des coefficients de dépense énergétique calculés pour chaque activité selon le temps consacré et l'intensité (Raina et al., 2008). Nous avons utilisé ces scores comme covariables afin de contrôler pour l'effet de l'activité physique sur le lien entre le risque d'AOS et le fonctionnement cognitif. Toutefois, il aurait été intéressant d'investiguer son rôle potentiellement médiateur ou

modérateur. Étant donné l'effet protecteur de l'activité physique sur la santé cognitive, il aurait été attendu que les personnes à haut risque d'AOS ayant un score élevé au PASE obtiennent de meilleures performances cognitives que les personnes à haut risque d'AOS ayant un score plus faible au PASE.

3.5.3 Programmes de prévention

Considérant les enjeux que posent le vieillissement de la population ainsi du manque des ressources humaines au sein du système de la santé, il devient primordial de proposer à la population des programmes de prévention de la démence afin de limiter le recours aux soins médicaux. Ces programmes de prévention devraient cibler une variété de facteurs de risque tels que l'obésité, l'hypertension, le diabète et les troubles du sommeil. Ainsi, des interventions multimodales devraient combiner l'activité physique à l'amélioration d'autres habitudes de vie tel que le sommeil. De tels programmes pourraient permettre de prévenir des conditions de santé telles que les maladies cardiovasculaires et des troubles cognitifs tels que ceux associés à la MA.

À Montréal, le Centre ÉPIC de l'Institut de Cardiologie de Montréal offre des programmes qui visent la promotion de la santé et l'acquisition de saines habitudes de vie (Institut de cardiologie de Montréal, n.d.). En plus d'offrir une programmation diversifiée d'activités physiques d'intensités variées (ex : yoga, musculation, danse, cardio vélo, aqua forme), le Centre ÉPIC offre des ateliers de réduction de stress, des consultations en nutrition ainsi qu'une cuisine école (Institut de cardiologie de Montréal, n.d.). Il regroupe également plusieurs équipes de recherche, notamment dans le domaine de la cognition et de l'exercice. Il serait pertinent que le sommeil soit intégré aux programmes de prévention du centre ÉPIC comme habitude de vie modifiable. En effet, davantage d'études sont nécessaires afin de mieux comprendre l'interaction entre les troubles du sommeil, particulièrement l'AOS, et les habitudes de vie telles que l'activité physique et le tabagisme. De plus, les personnes apnéiques devraient être incluses dans ce type d'étude et encouragées à participer aux programmes de prévention implémentés dans des centres tel qu'ÉPIC afin de possiblement réduire leur symptomatologie et leur risque de déclin cognitif.

3.6 Limites des études présentées dans cette thèse

Une limite méthodologique globale de cette thèse est que les trois articles sont basés sur la même cohorte de participants testés dans le cadre d'un seul protocole de recherche. De futures études devraient ainsi tenter de répliquer les résultats obtenus dans une autre cohorte de participants.

3.6.1 Questionnaire STOP-B comme mesure proxy de l'AOS

Dans le cadre de cette thèse, le risque d'AOS a été estimé en utilisant des variantes du questionnaire validé STOP (Chung et al., 2008). Cet outil est une mesure indirecte de l'AOS, et a possiblement identifié les personnes les plus symptomatiques et celles ayant une AOS particulièrement sévère comme étant à haut risque d'AOS. Aussi, tel que décrit précédemment, le STOP évalue des symptômes typiquement masculins (ex : ronflement et apnées observées par le ou la partenaire de lit), ce qui pourrait limiter sa capacité à identifier les femmes à haut risque d'AOS. De plus, la circonférence du cou n'a pas été mesurée dans le cadre de l'ÉLCV, ce qui nous a empêché d'utiliser le STOP-Bang, qui a de meilleures valeurs prédictives que le STOP (Chung et al., 2008; Nagappa et al., 2015). Puisque la circonférence du cou est un prédicteur d'AOS aussi important que l'âge (Marti-Soler et al., 2016), la prévalence de haut risque d'AOS rapportée dans cette thèse est possiblement sous-estimée.

Toutefois, afin de maximiser la sensibilité des questionnaires, nous avons établi le seuil limite des variantes du STOP en se basant sur des récentes méta-analyses et des études comparant des données de polysomnographie à un score ≥ 3 au STOP-Bang (Chen et al., 2021; Chiu et al., 2017; Pivetta et al., 2021; Zheng et al., 2021). Ces études suggèrent qu'utiliser un seuil limite de 3 pour détecter l'AOS modérée à sévère montre une sensibilité entre 88% (Chen et al., 2021) et 94% (Pivetta et al., 2021) avec une valeur prédictive négative de 93% (Chen et al., 2021). Utiliser ce même seuil limite sur une variante du STOP (scores de 0 à 5) le rend plus sévère que le STOP-Bang (scores de 0 à 8), ce qui a l'avantage de réduire le nombre de faux négatifs.

Les variantes du STOP utilisées dans le cadre de cette thèse ont permis d'étudier le risque d'AOS dans un vaste échantillon alors que des mesures objectives n'auraient pas pu être recueillies. La polysomnographie étant coûteuse et difficile à implémenter dans des grandes cohortes, un questionnaire validé tel que le STOP était la meilleure mesure à utiliser comme proxy de l'AOS. De plus, cet outil peut être facilement transposé au contexte clinique.

3.6.2 Absence de données sur la sévérité de l'AOS

L'utilisation d'une mesure indirecte d'AOS nous a permis d'estimer sa prévalence, mais nous n'avons eu accès à aucune information quant à la sévérité de l'AOS. Des mesures ambulatoires auraient pu être recueillies, par exemple en utilisant un oxymètre au domicile des participants. Ce type d'outil nous aurait permis de mesurer notamment l'IAH et la saturation en oxygène, puis de prendre en considération ces indices de sévérité d'AOS dans nos analyses.

3.6.3 Absence de données sur le diagnostic et le traitement de l'AOS

L'ÉLCV n'a pas demandé aux participants s'ils avaient déjà reçu un diagnostic d'AOS par un clinicien ni s'ils utilisaient un traitement par pression positive continue. Ce faisant, certains participants présentant de l'AOS pourraient avoir été mal classifiés comme étant à bas risque d'AOS après avoir rapporté une absence de symptômes aux variantes du questionnaire STOP, simplement parce que leurs symptômes ont été réduits ou éliminés par le traitement par pression positive continue. Afin de limiter l'impact de cette variable potentiellement confondante, nous avons exclu les participants qui ont rapporté un diagnostic d'AOS à la question « Avez-vous d'autres conditions physiques ou mentales de longue durée qui ont été diagnostiquées par un professionnel de la santé ? Si oui, veuillez préciser. »

3.6.4 Absence de données sur les niveaux hormonaux et la périménopause

L'ÉLCV a demandé aux participantes « Avez-vous traversé la ménopause, ce qui signifie que vos menstruations se sont arrêtées pendant au moins un an et n'ont pas recommencé? ». Les participantes ayant répondu « non » pourraient donc être en périménopause et subir d'importantes fluctuations hormonales. Ainsi, l'absence de mesures objectives de niveaux

hormonaux résulte en un groupe hétérogène de femmes classifiées comme étant non-ménopausées. Considérant le rôle des hormones ovariennes dans le sommeil et le fonctionnement cognitif, les études futures devraient mesurer le niveau de ces hormones afin d'investiguer leur rôle dans l'association entre l'AOS et le fonctionnement cognitif.

3.7 Conclusion

Cette thèse contribue à identifier des caractéristiques individuelles associées à un plus grand risque de présenter de l'AOS et des possibles troubles cognitifs associés. Le protocole de recherche utilisé dans le cadre de cette thèse est le premier à investiguer les effets de l'âge et du sexe sur le fonctionnement cognitif en lien avec le risque d'AOS dans une aussi grande cohorte et en utilisant une batterie de tests neuropsychologiques diversifiée. De plus, le devis longitudinal utilisé permet une meilleure caractérisation des changements cognitifs à travers le temps.

Le vieillissement de la population et le manque de ressources humaines au sein du réseau de la santé posent un défi important pour les décennies à venir. Il est ainsi primordial de comprendre quels facteurs influencent le vieillissement optimal. Les troubles du sommeil, particulièrement l'AOS, pourraient avoir des effets délétères sur le cerveau, et les personnes apnéiques pourraient présenter un risque accru de développer des troubles cognitifs tel que ceux associés à la MA. Dans le cadre de cette thèse, nous avons brossé un portrait actuel de la prévalence du haut risque d'AOS et de ses facteurs de risque dans la population canadienne. De plus, nous avons montré que l'association entre le risque d'AOS et la performance cognitive variait selon le sexe, l'âge et les domaines cognitifs, les femmes à haut risque d'AOS étant particulièrement susceptibles de développer des troubles cognitifs.

Ces études jettent les bases pour comprendre le rôle d'autres caractéristiques individuelles qui augmentent ou réduisent le risque de présenter de l'AOS et des possibles troubles cognitifs associés à l'AOS. Cette thèse a un impact clinique significatif en soulignant l'importance de considérer les caractéristiques individuelles dans l'évaluation et la prise en charge de patients présentant des facteurs de risque d'AOS. Dans un contexte de vieillissement de la population et de manque de main d'œuvre, des efforts devraient être concentrés sur l'amélioration de l'accès au traitement de l'AOS ainsi que sur la mise sur pieds de programmes de prévention de l'AOS et des troubles cognitifs.

En somme, cette thèse supporte l'association entre l'AOS et le développement de troubles cognitifs et de déclin cognitif dans certaines tranches de la population. Les prochaines larges

études épidémiologiques devraient inclure à la fois des mesures objectives de sommeil, des biomarqueurs ainsi qu'une diversité de tests neuropsychologiques.

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