

Sleep Apnea is Associated With High Mortality Risk in Children With Severe Epilepsies: An Observational Analysis From Large Scale US Claims Data

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Background

- Patients with uncontrolled epilepsy experience an increased risk of mortality,¹ and commonly report comorbidities such as sleep apnea²
- Sleep apnea is a common and serious sleep disorder characterized by recurrent interruptions of breathing during sleep, which can lead to major health issues, including cardiovascular disease, cognitive impairment, and increased risk of all-cause sudden death
- The identification of sleep apnea in patients with epilepsy provides critical insights into their clinical condition, informing treatment plans and aiding in the prediction of patient outcomes²
- Notably, the presence of obstructive sleep apnea in patients with uncontrolled epilepsy is correlated with increased seizure frequency and severity, which can be ameliorated through interventions such as positive airway pressure therapy²
- However, the link between sleep apnea and mortality in individuals with uncontrolled epilepsy remains poorly understood

Objective

- This real-world study used administrative claims data to describe the excess mortality risk of sleep apnea in patients with uncontrolled epilepsy

Methods

- Patients in the Komodo US claims database were characterized as having "uncontrolled epilepsy" if two or more of the following criteria were in their claims history based on ICD-10 codes: an epilepsy-related emergency department visit or hospital admission, status epilepticus diagnosis, or generalized tonic-clonic seizures
- Mortality rates for patients with uncontrolled epilepsy were observed between January 1, 2018, to December 31, 2022
- Patients with uncontrolled epilepsy were categorized based on the presence or absence of central sleep apnea (CSA; ICD-10 codes, G47.31, G47.37) and other sleep apnea (OSA, which includes obstructive apnea; ICD-10 codes, G47.30, G47.33, G47.39)
- The primary objective was to calculate the mortality rate in patients with uncontrolled epilepsy with and without a sleep apnea claim, separately
- The secondary objective was to calculate the standardized mortality ratio (SMR) for uncontrolled epilepsy patients with and without a sleep apnea claim, separately
 - Death probabilities were compared with observed deaths in the claims data to calculate SMRs for each age group
- Patients must have qualified as having uncontrolled epilepsy in the last 3 years to be included
- Patient characteristics and comorbidities were described as exploratory objectives for patients with uncontrolled epilepsy with and without a sleep apnea claim, separately
 - Additional comorbidities were selected based on the Charlson Comorbidity Index
- Mortality rates and SMRs were smoothed by calculating rates for a 5-year window centered on the year of interest

Results

- Overall, 2,355,410 patient-years were captured from 968,993 unique patients with uncontrolled epilepsy
 - Of those, 185,458 (19.1%) patients were 1 to <18 years old, 229,448 (23.7%) were 18-35 years old, and 554,087 (57.2%) were ≥36 years old
 - Overall, 6,571 (0.7%) patients had CSA, 136,118 (14.0%) had OSA, and 826,304 (85.3%) reported no sleep apnea (NSA)
- Grouping patients according to sleep apnea classification (CSA, OSA, and NSA) demonstrates that association of other comorbidities varies across age groups, along with a tendency for comorbidities to be more common in sleep apnea groups (Figure 1)
 - Chronic pulmonary disease was the most common comorbidity reported across all age groups
 - Hemiplegia or paraplegia were more common in younger patients, and cerebrovascular disease, diabetes, and congestive heart failure were more common in older patients
- In children (1 to <18 years old), the SMR of all uncontrolled epilepsy patients was 27.7 (Table 1)
- In children with uncontrolled epilepsy, those with comorbid CSA had an SMR of 135.9 and those with comorbid OSA had an SMR of 74.2
- SMRs for other comorbidities in children with uncontrolled epilepsy were 132.3 for congestive heart failure, 74.9 for hemiplegia/paraplegia, 55.3 for cerebrovascular disease, and 44.6 for chronic pulmonary disease

QUESTION

- Is there an association between sleep apnea and age-related mortality rates in patients with uncontrolled epilepsy?

INVESTIGATION

- Using United States (US) administrative claims data from January 1, 2018, to December 31, 2022, standardized mortality ratios (SMRs) were calculated for patients with uncontrolled epilepsy with or without sleep apnea
- SMRs were also calculated for other comorbidities of interest
- Patients must have qualified as having uncontrolled epilepsy in the last 3 years to be included

CONCLUSIONS

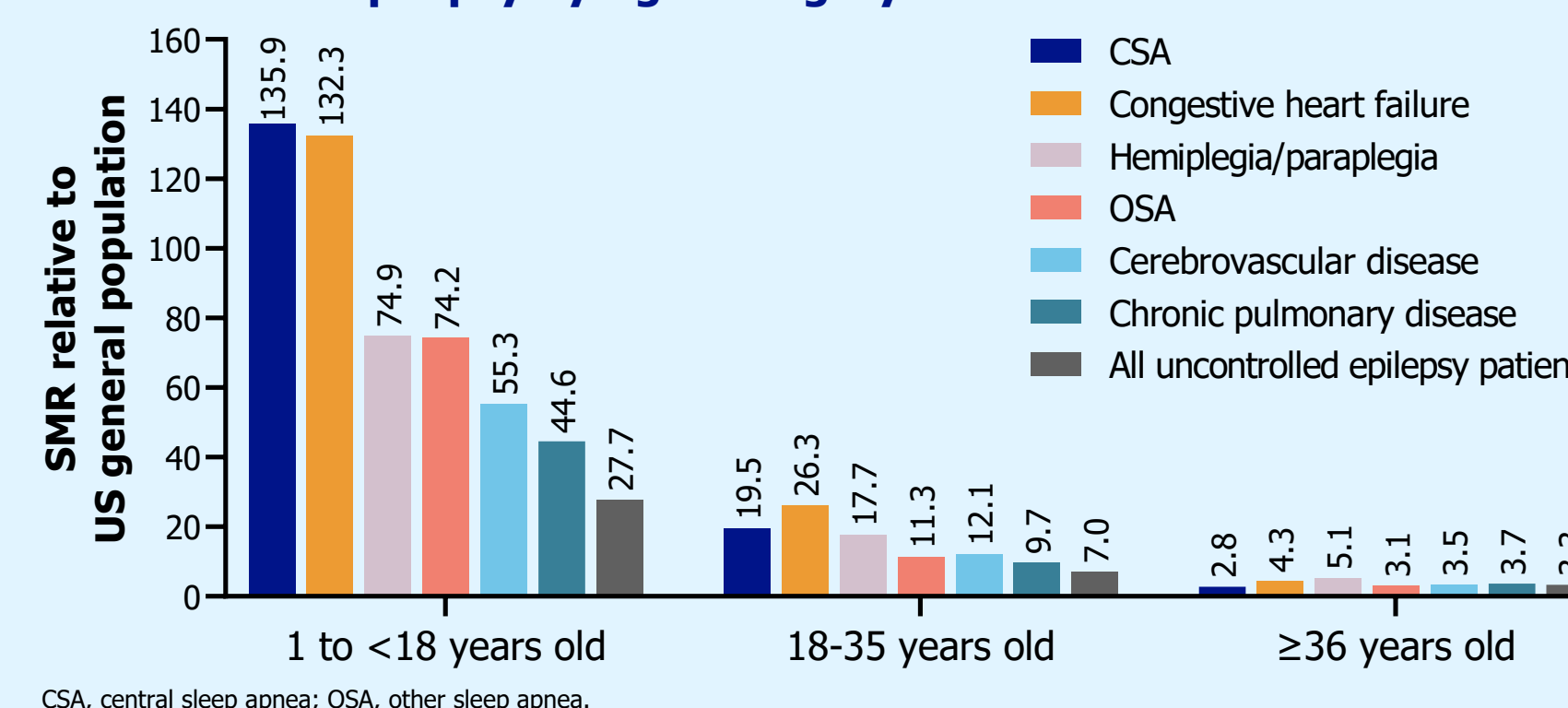
- Pediatric and adult patients with uncontrolled epilepsy experience increased mortality relative to the US general population
- Mortality tends to be more strongly associated with comorbidities, such as rare comorbidities like CSA and congestive heart failure, in pediatric patients
- This real-world study using administrative claims data shows that any sleep apnea comorbidity is an important and potentially actionable comorbidity associated with increased mortality in children and young adults with uncontrolled epilepsy

Overview

RESULTS

- Overall, 2,355,410 patient-years were captured from 968,993 unique patients with uncontrolled epilepsy
- In children (1 to <18 years old) with uncontrolled epilepsy, those with central sleep apnea (CSA) had an SMR of 135.9 and those with other sleep apnea (OSA) had an SMR of 74.2 (Figure)
- A young child with uncontrolled epilepsy and comorbid central sleep apnea has a mortality risk comparable to a 50-year-old patient with uncontrolled epilepsy

Figure. Standardized Mortality Ratio for Select Comorbidities in Patients With Uncontrolled Epilepsy by Age Category

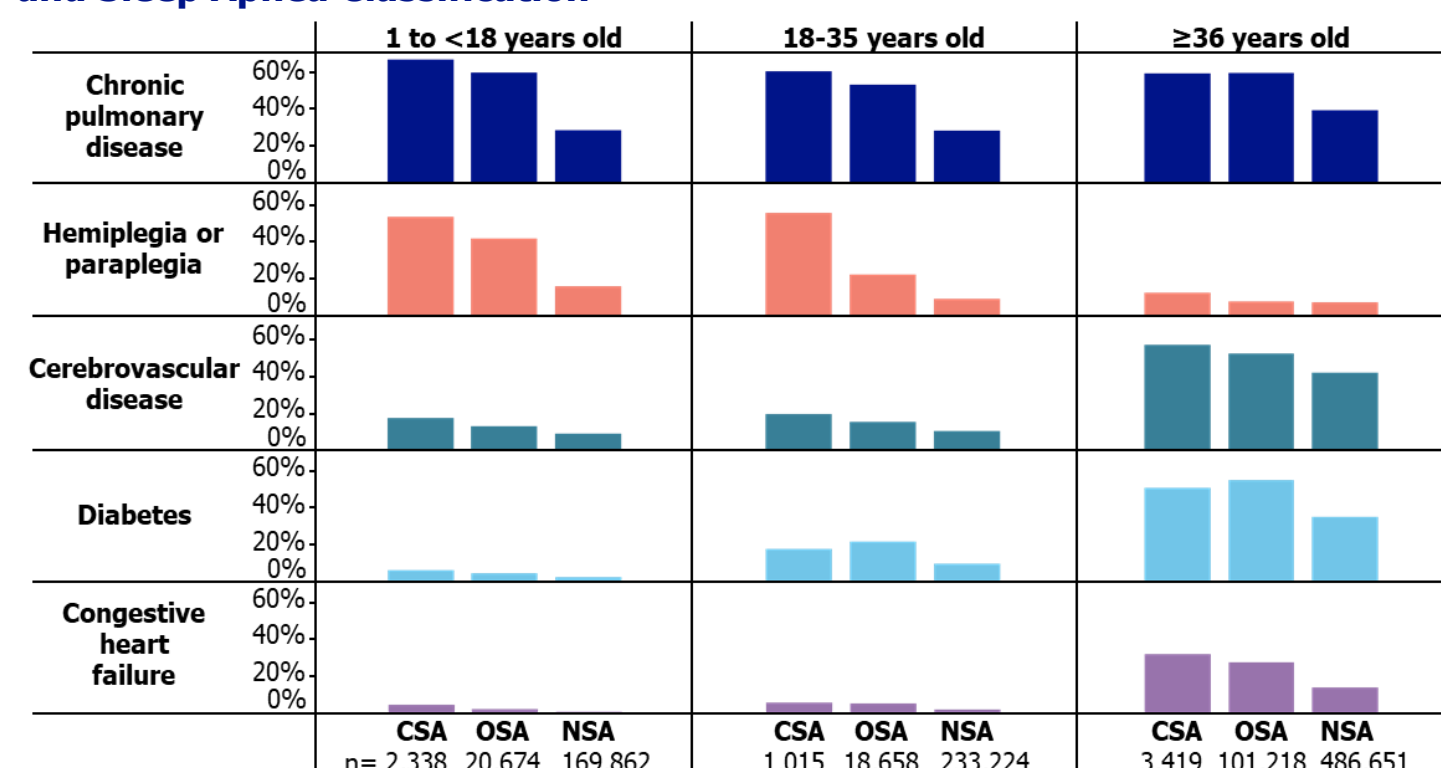


CSA, central sleep apnea; OSA, other sleep apnea.



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Figure 1. Percentage of Patients With Select Comorbidities by Age Group and Sleep Apnea Classification



Patients may have multiple comorbidities. Some patients were observed in multiple age groups; age totals may not match precisely. CSA, central sleep apnea; NSA, no sleep apnea; OSA, other sleep apnea.

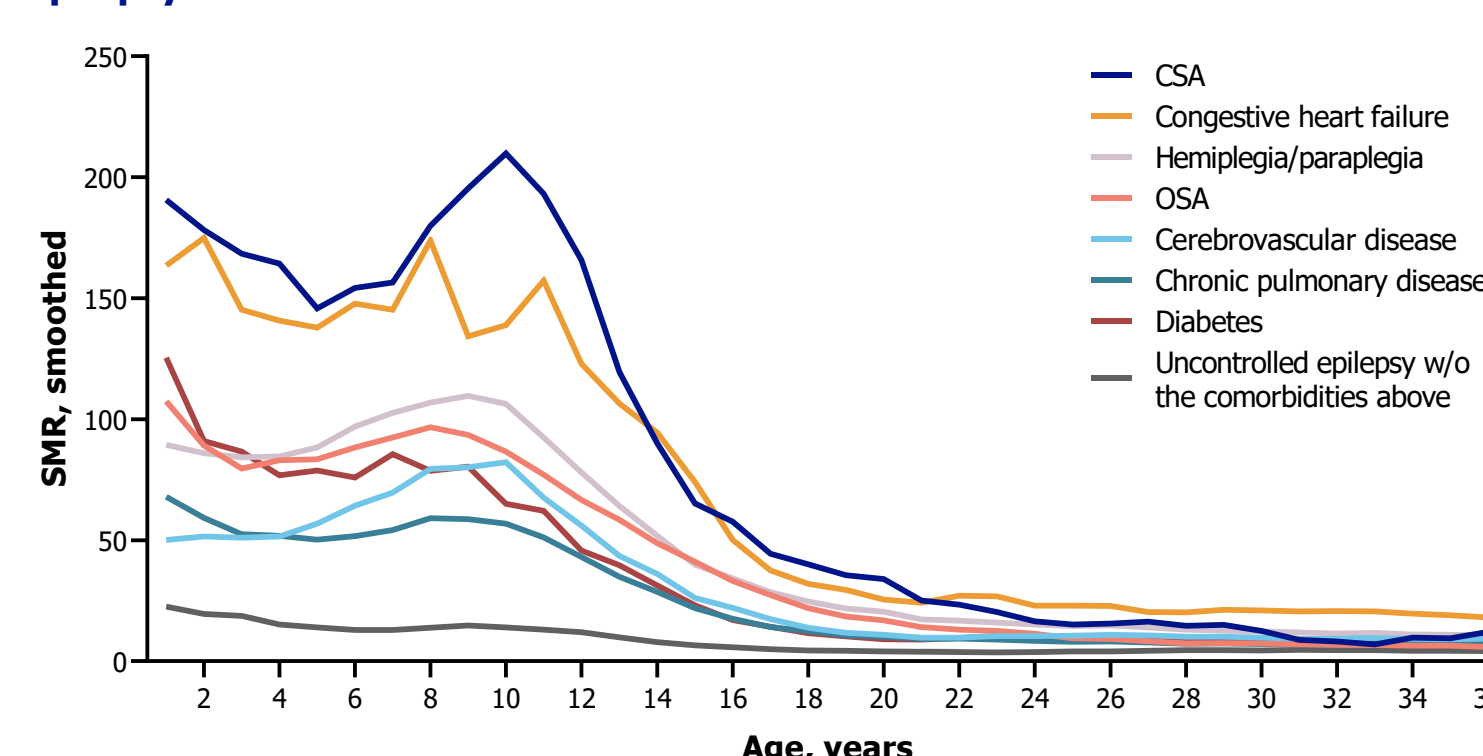
Table 1. SMR and PY in Unique Patients With Uncontrolled Epilepsy

	1 to <18 Years Old			18-35 Years Old			≥36 Years Old		
	SMR	Unique Patients	PY	SMR	Unique Patients	PY	SMR	Unique Patients	PY
CSA	135.9	2,338	5,905	19.5	1,015	2,250	2.8	3,419	7,331
Congestive heart failure	132.3	2,141	4,938	26.3	6,317	12,938	4.3	105,256	216,113
Hemiplegia or paraplegia	74.9	33,840	89,449	17.7	25,131	60,687	5.1	46,319	103,615
OSA	74.2	20,674	50,151	11.3	18,658	40,530	3.1	101,218	222,343
Cerebrovascular disease	55.3	18,685	45,287	12.1	29,818	64,981	3.5	267,747	586,077
Chronic pulmonary disease	44.6	60,038	147,872	9.7	76,959	173,428	3.7	255,626	571,902
All uncontrolled epilepsy patients	27.7	185,458	453,290	7.0	248,215	572,561	3.3	573,545	1,329,559

SMR data are not mutually exclusive. Patients may have multiple comorbidities. Some patients were observed in multiple age groups; age totals may not match precisely. CSA, central sleep apnea; OSA, other sleep apnea; PY, patient-years; SMR, standardized mortality ratio.

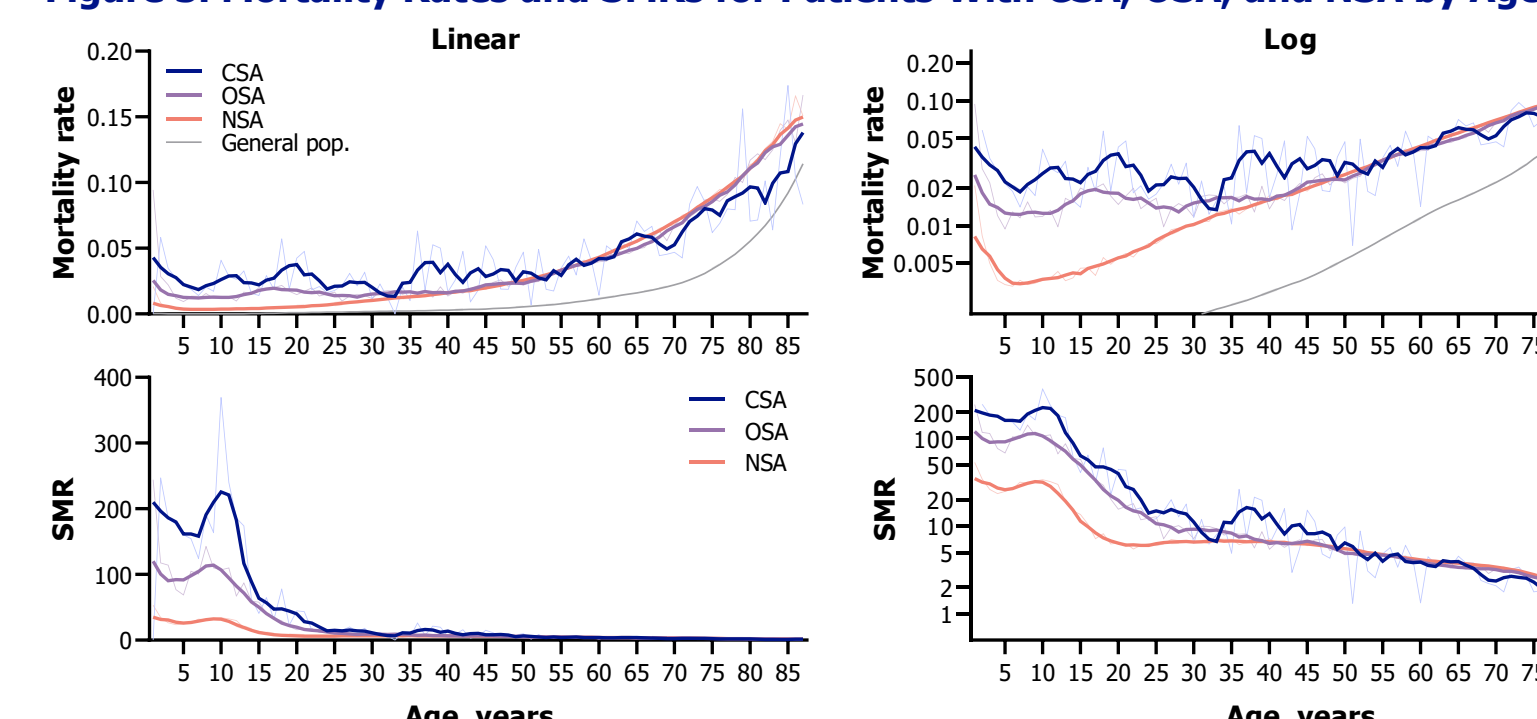
- Mortality tends to be more strongly associated with comorbidities in younger patients (Figure 2)
- While high SMR spikes are largely denominator-driven (due to very low general-population death rates in children), a young child with uncontrolled epilepsy and comorbid CSA has a mortality risk comparable to a 50-year-old patient with uncontrolled epilepsy, and a young child with uncontrolled epilepsy and comorbid OSA has a mortality risk comparable to a 40-year-old patient with uncontrolled epilepsy (Figure 3)
- SMR is higher in children and young adults with sleep apnea, peaking around age 10 for both CSA and OSA at ~200-fold and ~100-fold higher mortality than the general population, respectively (Figure 3)
- 46% of patients with CSA/OSA and uncontrolled epilepsy were on positive airway pressure treatments such as continuous positive airway pressure (CPAP) and bilevel positive airway pressure (Bi-PAP)
- CPAP/Bi-PAP is associated with higher mortality in young patients and lower mortality in older patients with sleep apnea and epilepsy (Figure 4)
 - However, this should be interpreted with caution, as other clinical characteristics that are not controlled for may contribute to the effect

Figure 2. Age-Related SMRs by Comorbidities in Patients With Uncontrolled Epilepsy



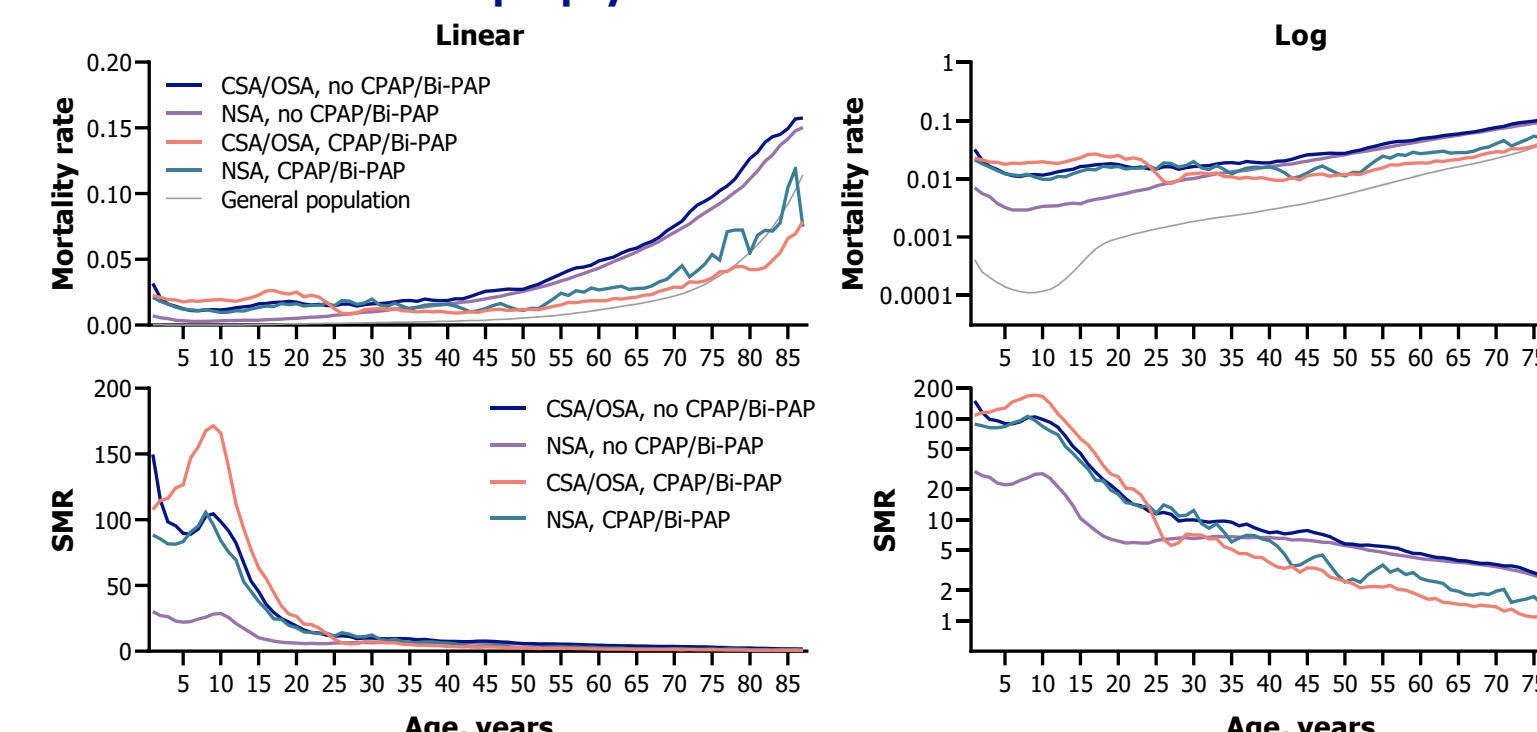
SMR data are not mutually exclusive. Patients may have multiple comorbidities. CSA, central sleep apnea; OSA, other sleep apnea; SMR, standardized mortality ratio; w/o, without.

Figure 3. Mortality Rates and SMRs for Patients With CSA, OSA, and NSA by Age



Thick lines represent smoothed mortality rates and SMRs. Thin lines represent single-year mortality rates and SMRs. SMR for the United States general population equals 1.0. CSA, central sleep apnea; NSA, no sleep apnea; OSA, other sleep apnea; pop, population; SMR, standardized mortality ratio.

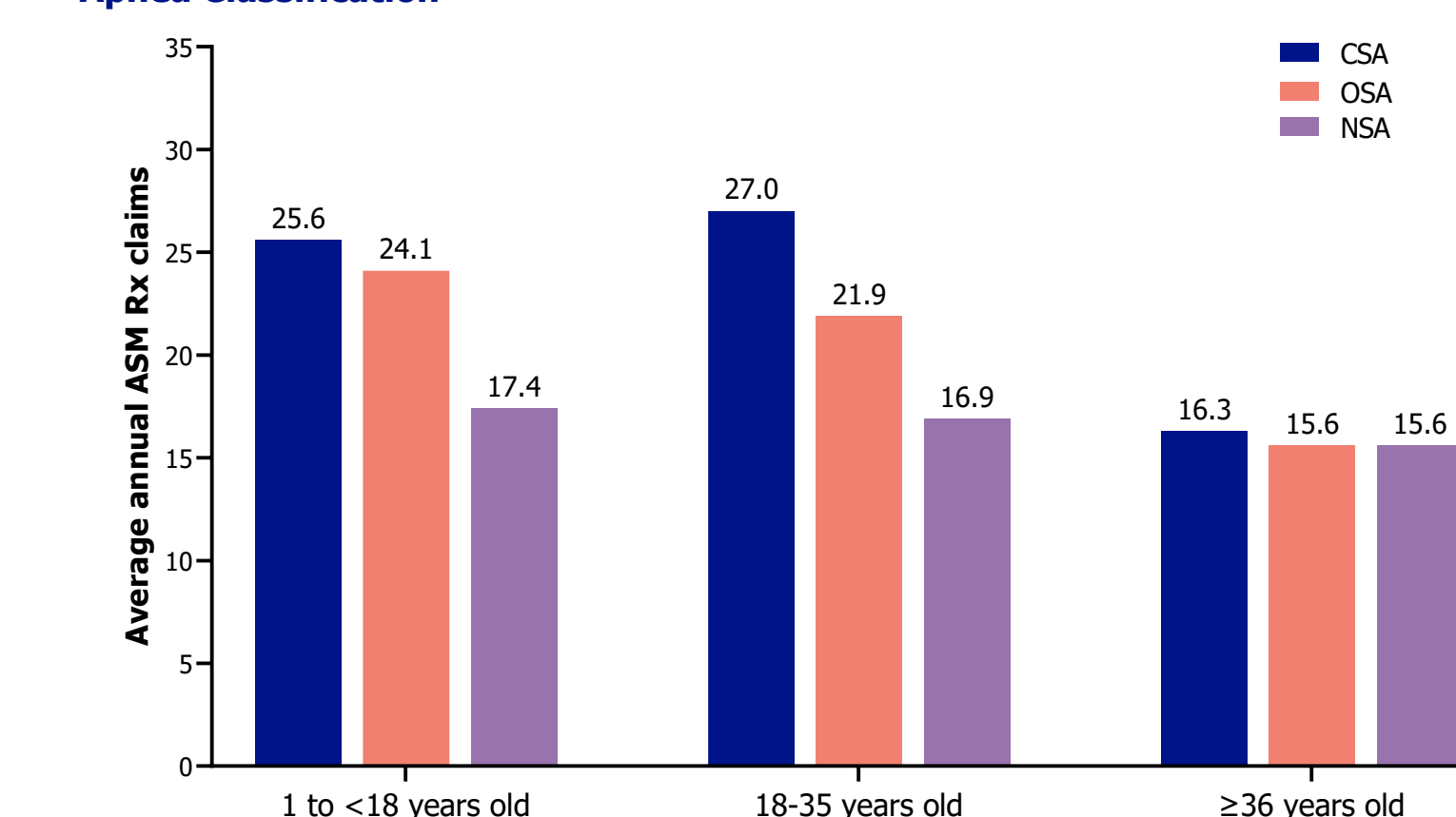
Figure 4. Association of CPAP/Bi-PAP and Mortality in Patients With CSA, OSA, and NSA and Uncontrolled Epilepsy



Bi-PAP, bilevel positive airway pressure; CPAP, continuous positive airway pressure; CSA, central sleep apnea; NSA, no sleep apnea; OSA, other sleep apnea; SMR, standardized mortality ratio.

- CSA and OSA were associated with more ASM prescriptions in patients 1 to <18 years old and 18-35 years old, but not in patients ≥36 years old (Figure 5)

Figure 5. Average Annual Prescription Claims for ASMs by Age Group and Sleep Apnea Classification



ASM, antiseizure medication; CSA, central sleep apnea; NSA, no sleep apnea; OSA, other sleep apnea; Rx, prescription.

Conclusions

- Results from this real-world study using administrative claims data show that pediatric and adult patients with uncontrolled epilepsy experience increased mortality relative to the US general population
- Patients with any sleep apnea comorbidity experience increased mortality compared to the US general population
 - Therefore, sleep apnea is an important and potentially actionable comorbidity numerically associated with increased mortality in children and young adults with uncontrolled epilepsy
- Mortality tends to be more strongly associated with comorbidities in younger patients vs age as the key driver in older patients, which presents an opportunity for increased awareness and intervention in younger patients
- This study is limited by the nature of administrative claims data, which does not fully capture mortality; the mortality rates and SMRs observed here should be regarded as conservative estimates
 - Identification of comorbidities relied on claims data, and thus were not confirmed clinically
 - This study did not control for confounding variables, such as socioeconomic status, treatment status, and other comorbidities or congenital conditions
- These observations suggest a particularly vulnerable age group and, as such, warrant further research to inform clinical practice, while also emphasizing the need to raise awareness of the elevated risk associated with sleep apnea comorbidities in pediatric patients with epilepsy

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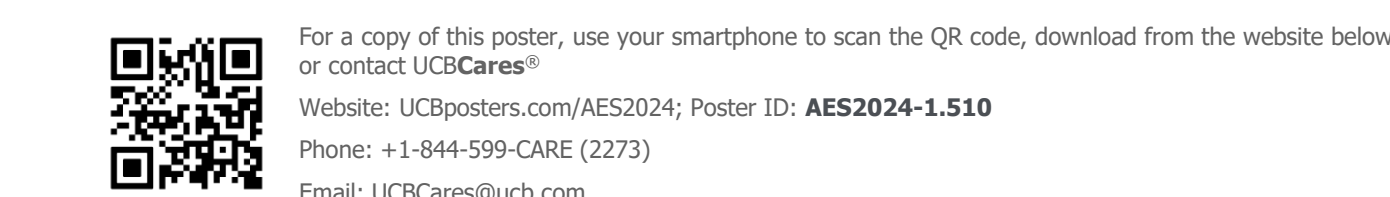
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Disclosures

SD, DL, AD, JVZ, AL, CC: Employees of UCB. MM: Employee of mck2x.



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