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Real-World Risk of Sodium-Associated Negative Clinical Outcomes Among Individuals With Narcolepsy in the United States

Sarah C. Markt, ScD, MPH[1]; Caroleen Drachenberg, PhD, MSPH[1]; Pam R. Taub, MD, FACC, FASPC[2]; Lee A. Surkin, MD, FACC, FCCP, FASNC[3]; Kaitlyn Easson, PhD[4]; Jessica K. Alexander, PhD[1]; Patrick Gagnon-Sanschagrin, MSc[4]; Marisa Whalen, PharmD[5]; Remi Bellefleur, MA[4]; Silky Beaty, PharmD, MSPH[1]; Mohira Levesque-Leroux, MSc[4]; Annie Guérin, MSc[4]; Richard J. Kovacs, MD, FACC[6]

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Introduction

- Narcolepsy is a sleep disorder characterised by symptoms including excessive daytime sleepiness, cataplexy (narcolepsy type 1), and disrupted nighttime sleep[1-3]
- Individuals with narcolepsy have been shown to experience an elevated prevalence of cardiovascular, cardiometabolic, and renal conditions versus individuals without narcolepsy, which may be worsened by excessive sodium exposure[3-5]

Objective

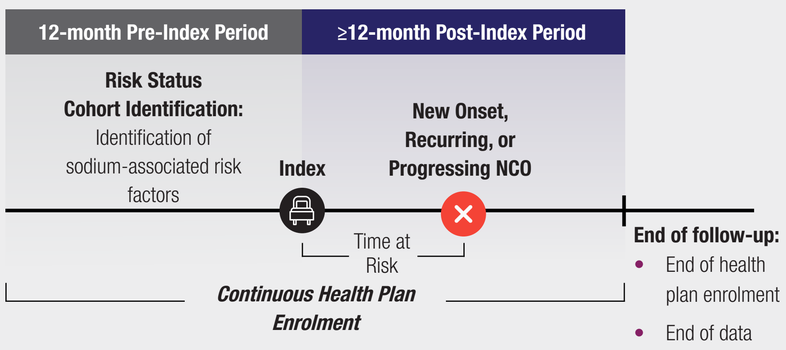
- To characterise the incidence and risk of sodium-associated negative clinical outcomes (NCOs) among individuals with narcolepsy compared with individuals without narcolepsy
- To quantify the incremental elevation in risk for NCOs among individuals with narcolepsy who have pre-existing sodium-associated comorbidities

Methods

Study Design and Population

- **Data Source:** Komodo Research Data (KRD+; 01/01/2016–31/01/2024), an administrative healthcare claims database capturing over 330 million United States individuals
- **Study Design:** Retrospective observational cohort study

Figure 1. Study Design



NCO, negative clinical outcome.

- **Study Population**
  - **Narcolepsy cohort:** Individuals aged ≥7 years with continuous enrolment and ≥2 claims with a diagnosis for narcolepsy (*International Classification of Diseases, Tenth Revision, Clinical Modification* [ICD-10-CM]: G47.411, G47.421, G47.419, G47.429) on distinct dates ≥30 days apart
    - *Index date:* First observed diagnosis of narcolepsy
  - **Non-narcolepsy cohort:** Individuals aged ≥7 years without narcolepsy or idiopathic hypersomnia (ie, no diagnosis code for either condition and no oxybate prescription) at any time in the available data
    - *Index date:* Randomly selected date
- Sodium-associated risk factors, assessed in the 12-months pre-index, comprised cardiovascular, cardiometabolic, and renal conditions; liver cirrhosis; and sleep apnoea
  - The narcolepsy cohort was stratified based on risk factors into *risk subgroups*:
    - **Higher-risk:** Had ≥1 risk factor pre-index
    - **Lower-risk:** Had no risk factors pre-index

Figure 2. Sample Selection for Narcolepsy Cohort

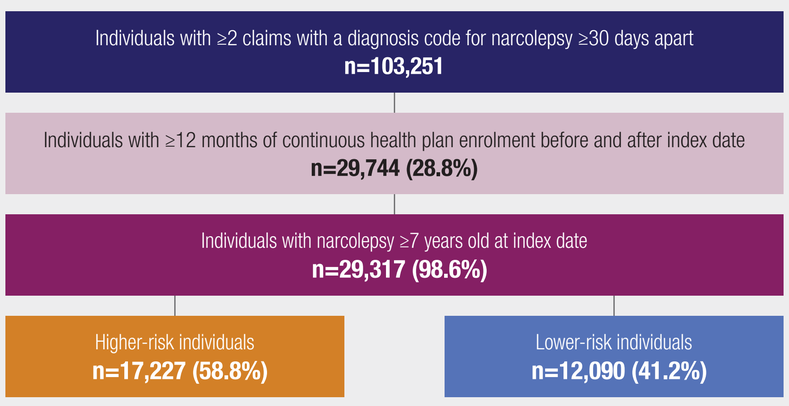
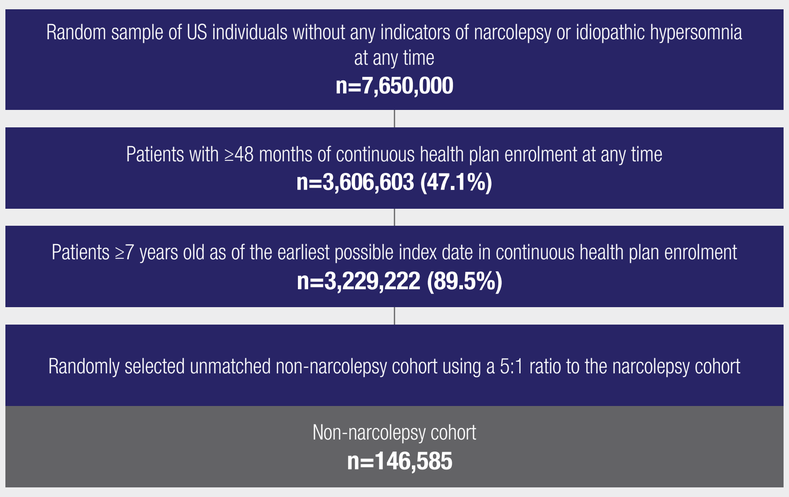


Figure 3. Sample Selection for Non-Narcolepsy Cohort



Outcomes

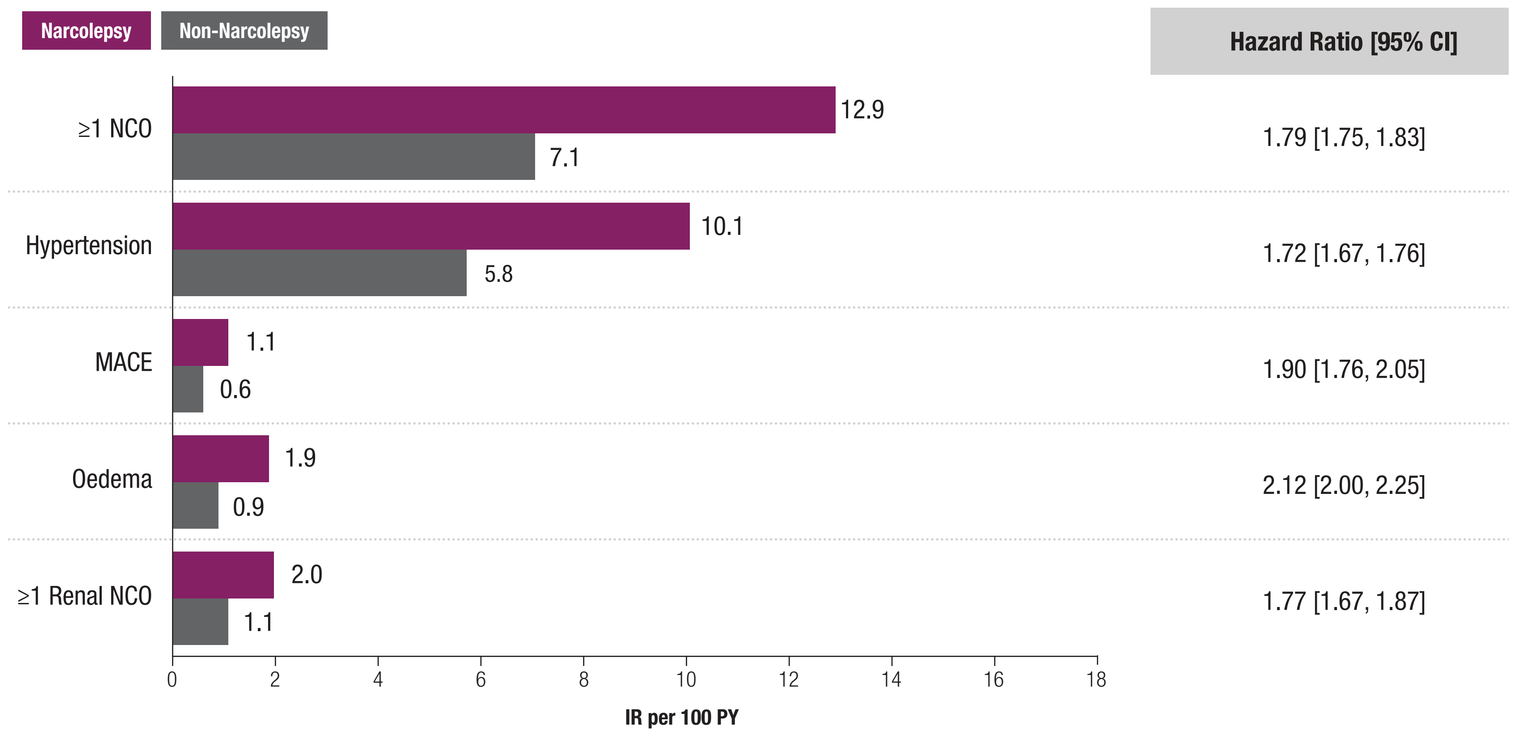
- Primary sodium-associated NCOs, identified through literature review and discussion with clinical experts, included the following conditions or events:
  - **Cardiovascular:** Hypertension, heart failure, stroke, transient ischaemic attack, major adverse cardiovascular event (MACE; defined as heart failure, stroke, myocardial infarction, unstable angina, or coronary revascularisation procedures)
  - **Cardiometabolic:** Oedema
  - **Renal:** Proteinuria, chronic kidney disease, kidney failure
- Additional NCOs included a cardiovascular composite outcome (occurrence of atrial fibrillation, atherosclerosis, myocardial infarction, unstable angina, or cardiac arrest), obesity, type 2 diabetes, metabolic syndrome, or sleep apnoea
- New-onset, recurring, or progressing NCOs were assessed in the post-index period using algorithms developed in collaboration with clinical experts (see **Supplemental Table 1**, accessed via the QR code in the lower right corner of this poster)

Statistical Analyses

- Demographic characteristics were assessed on the index date
- Age, sex, race, health plan type, and index year were balanced between the narcolepsy and non-narcolepsy cohorts using entropy balancing
  - Weights from entropy balancing were applied in all analyses for the non-narcolepsy cohort
- Incidence rates (IRs) for ≥1 NCO, hypertension, MACE, oedema, and ≥1 renal NCO were calculated per 100 person-years (PY) until the first new onset, recurring, or progressing NCO (event) or end of follow-up (censor)
- Hazard ratios and 95% confidence intervals (CIs) were calculated for each reported NCO using weighted and unweighted Cox proportional hazards models to compare the narcolepsy and non-narcolepsy cohorts and the risk subgroups within the narcolepsy cohort
  - A sensitivity analysis was conducted for risk subgroups including age as a covariate in Cox proportional hazards models

Results

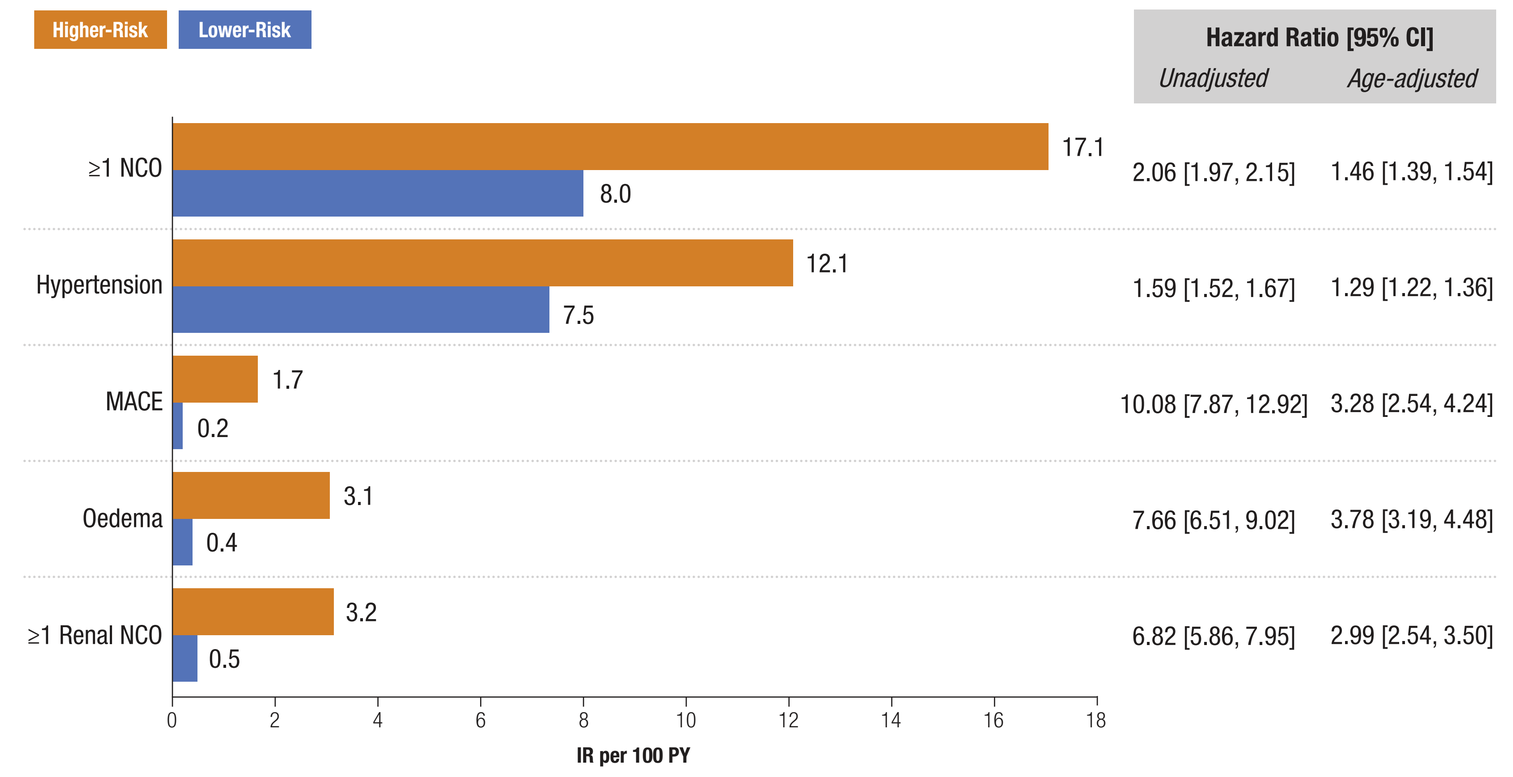
Figure 4. Incidence Rates (per 100 PY) and Hazard Ratios for Primary Negative Clinical Outcomes in Narcolepsy vs Non-Narcolepsy Cohorts



CI, confidence interval; IR, incidence rate; MACE, major adverse cardiovascular event; NCO, negative clinical outcome; PY, person-years.

- Individuals with narcolepsy experienced higher incidence and risk of all assessed NCOs versus individuals without narcolepsy
  - Individuals with narcolepsy had higher incidence rates and higher risk of having at least 1 NCO compared with individuals without narcolepsy
- Among primary NCOs, hazard ratios were highest for oedema and MACE, for which individuals with narcolepsy had a 112% and 90% increased risk, respectively
- Kaplan-Meier curves are presented for primary NCOs in **Supplemental Figures 1–5** and for additional NCOs in **Supplemental Figures 6–10**

Figure 5. Incidence Rates (per 100 PY) and Hazard Ratios for Primary Negative Clinical Outcomes in Higher-Risk vs Lower-Risk Narcolepsy Subgroups



CI, confidence interval, IR, incidence rate; MACE, major adverse cardiovascular event; NCO, negative clinical outcome; PY, person-years.

- Individuals with narcolepsy who had at least 1 sodium-associated risk factor ("higher-risk individuals") had higher rates of experiencing all assessed NCOs, compared with individuals with narcolepsy at lower risk
- The elevation in risk varied across primary NCOs, ranging from 59% increased risk for hypertension to over 900% increased risk for MACE
- Results were attenuated with age adjustment, but risk remained increased for higher-risk individuals
- Kaplan-Meier curves are presented for primary NCOs in **Supplemental Figures 11–15** and for additional NCOs in **Supplemental Figures 16–20**

Table 1. Demographic Characteristics of Narcolepsy and Non-Narcolepsy Cohorts at Baseline

	Narcolepsy Cohort n=29,317	Non-Narcolepsy Cohort n=146,585
Age (years), mean (SD) [median]	**41.4 (17.0) [40.2]**	**41.5 (17.3) [40.4]**
Female, n (%)	**18,199 (62.1)**	**90,994 (62.1)**
Race/ethnicity, n (%)		
Known[a]	21,233 (72.4)	106,165 (72.4)
White	16,523 (77.8)	82,616 (77.8)
Black or African American	2060 (9.7)	10,300 (9.7)
Asian or Pacific Islander	491 (2.3)	2455 (2.3)
Hispanic or Latino	1499 (7.1)	7495 (7.1)
Other	660 (3.1)	3300 (3.1)
Unknown	8084 (27.6)	40,420 (27.6)
Health plan, n (%)		
Commercial	22,126 (75.5)	110,630 (75.5)
Medicare	3771 (12.9)	18,855 (12.9)
Medicaid	3420 (11.7)	17,100 (11.7)

[a]Proportions of patients in each race/ethnicity category were reported among those with known race/ethnicity.
SD, standard deviation.

Conclusions

- In this real-world study, individuals with narcolepsy had an elevated risk of development or progression of sodium-associated cardiovascular, cardiometabolic, and renal negative clinical outcomes (NCOs) relative to those without narcolepsy
- More than half of individuals with narcolepsy (58.8%) had sodium-associated risk factors prior to their narcolepsy diagnosis; these individuals had an increased risk of developing NCOs relative to those with narcolepsy who did not have pre-existing comorbidities
- Due to the unavailability of clinical observations in these data, NCOs were proxied using diagnosis, procedure, and treatment codes, and were not validated or confirmed with chart notes
- Findings highlight the importance of lowering sodium intake to help reduce the clinical burden of NCOs in individuals with narcolepsy, the majority of whom present with pre-existing cardiovascular, cardiometabolic, and renal comorbidities

References: 1. Nishino S. *Sleep Med.* 2007;8(4):373-99. **2.** American Academy of Sleep Medicine. *International Classification of Sleep Disorders – Third Edition, Text Revision.* Darien, IL: American Academy of Sleep Medicine; 2023. **3.** Black J, et al. *Sleep Med.* 2017;33:13-18. **4.** Ohayon MM. *Sleep Med.* 2013;14(6):488-492. **5.** Ben-Joseph RH, et al. *Sleep.* 2023;46(10).

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Disclosures: SC Markt, **C Drachenberg**, **JK Alexander**, **M Whalen**, and **S Beaty** are full-time employees of Jazz Pharmaceuticals who, in the course of this employment, have received stock options exercisable for, and other stock awards of, ordinary shares of Jazz Pharmaceuticals, plc. **PR Taub** is a consultant to Amgen, Bayer, Boehringer Ingelheim, Edwards, Esperion, Jazz Pharmaceuticals, Lilly, Medtronic, Merck, Novartis, Novo Nordisk, and Sanofi. **LA Surkin** is a consultant to Alkermes, Jazz Pharmaceuticals, and Takeda. **K Easson**, **P Gagnon-Sanschagrin**, **R Bellefleur**, **M Levesque-Leroux**, and **A Guérin** are employees of Analysis Group ULC, a consulting company that has provided paid consulting services to Jazz Pharmaceuticals. **RJ Kovacs** is a consultant for Jazz Pharmaceuticals and Lilly, serves on data and safety monitoring boards for Immunovant and Relmada, and is on clinical events committees for Cook and Zydus

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Supplemental Materials

Supplemental Table 1. Operational Definitions for NCOs

NCO	Definition
≥1 NCO	Occurrence of a hypertension, MACE, oedema, or renal NCO, as defined below.
Hypertension	An increase in the number of observed anti-hypertensive treatment classes compared with the 12-month baseline period (eg, from 1 treatment class pre-index to 2 treatment classes post-index), or an inpatient admission with a procedure for renal denervation.
MACE	An inpatient admission with a diagnosis for myocardial infarction, stroke/TIA, heart failure, unstable angina, or a procedure for coronary revascularisation, with no inpatient claims with the same diagnosis and/or procedure within 30 days before admission.
Oedema	An escalation in treatment compared with the 12-month baseline period, as defined by the hierarchy below: 1) No observed diuretics 2) Initiation of first oral diuretic (other than loop diuretic) 3) Increase in the number of observed oral diuretic classes 4) Initiation of first oral loop diuretic or metolazone 5) Initiation of an IV or SC diuretic Individuals with an IV/SC diuretic pre-index could not be observed to progress and were not at risk of an oedema NCO
≥1 renal NCO	An increase in the severity of renal disease compared with the 12-month baseline period, as defined by the hierarchy below: 1) No observed renal disease 2) Proteinuria or CKD stage 1–4 a. Progression to a higher stage of CKD, between stages 1–4, was also considered an NCO if observed 3) CKD stage 5, end-stage renal disease, or dialysis 4) Renal transplant (or repeat renal transplant)
Additional NCOs	**Definition**
CV composite	Occurrence of an atrial fibrillation, atherosclerosis, myocardial infarction, unstable angina, or cardiac arrest NCO. An atrial fibrillation NCO was defined as an interventional procedure with a diagnosis for atrial fibrillation; an increase in the number of treatment classes used for atrial fibrillation compared with the 12-month baseline period; or an inpatient admission with a diagnosis for atrial fibrillation, with no inpatient claims with the same diagnosis within 30 days before admission. An atherosclerosis NCO was defined as an interventional procedure with a diagnosis for atherosclerosis. Myocardial infarction, unstable angina, and cardiac arrest NCOs were defined as an inpatient admission with a diagnosis for myocardial infarction, unstable angina, or cardiac arrest, respectively, with no inpatient claims with the same diagnosis within 30 days before admission.
Obesity	New onset of obesity, defined as ≥2 diagnoses for obesity on distinct dates. Individuals with obesity in the 12-month baseline period were not at risk of an obesity NCO.
Type 2 diabetes	An escalation in treatment compared with the 12-month baseline period, as defined by the hierarchy below: 1) An increase in the number of observed anti-diabetic treatment classes compared with the 12-month baseline period 2) Initiation of insulin Individuals with insulin use pre-index could not be observed to progress and were not at risk of a type 2 diabetes NCO.
Metabolic syndrome	New onset of metabolic syndrome, defined as ≥2 diagnoses for metabolic syndrome on distinct dates. Individuals with metabolic syndrome in the 12-month baseline period were not at risk of a metabolic syndrome NCO.
Sleep apnoea	New onset of sleep apnoea, defined as ≥2 diagnoses for sleep apnoea on distinct dates. Individuals with sleep apnoea in the 12-month baseline period were not at risk of a sleep apnoea NCO.

CKD, chronic kidney disease; CV, cardiovascular; IV, intravenous; MACE, major adverse cardiovascular event; NCO, negative clinical outcome; SC, subcutaneous; TIA, transient ischaemic attack.

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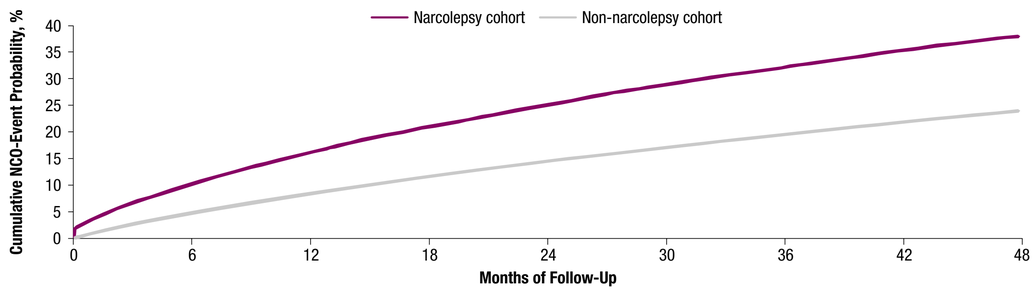
Supplemental Materials

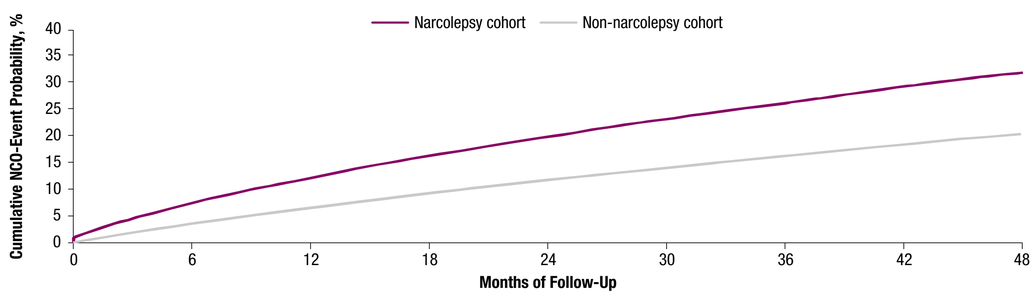
Supplemental Figure 1. Kaplan-Meier Analyses for ≥1 NCO[a]: Narcolepsy vs Non-Narcolepsy Cohorts



≥1 NCO	Total individuals	Individuals with an event, n (%)	Kaplan-Meier results	12 months	24 months	36 months	48 months
Narcolepsy cohort	29,317	9435 (32.2)	Individuals at risk, n (%)	24,585 (83.9)	15,260 (52.1)	9417 (32.1)	5890 (20.1)
			Cumulative number of events, n (%)	4732 (16.1)	6957 (23.7)	8168 (27.9)	8861 (30.2)
			Cumulative probability, % (95% CI)	16.1 (15.7, 16.6)	25.1 (24.5, 25.6)	32.1 (31.5, 32.7)	38.0 (37.3, 38.7)
Non-narcolepsy cohort	146,585	29,564 (20.2)	Individuals at risk, n (%)	134,289 (91.6)	93,676 (63.9)	57,517 (39.2)	33,281 (22.7)
			Cumulative number of events, n (%)	12,296 (8.4)	20,212 (13.8)	24,756 (16.9)	27,298 (18.6)
			Cumulative probability, % (95% CI)	8.4 (8.2, 8.6)	14.5 (14.3, 14.7)	19.5 (19.2, 19.8)	24.0 (23.6, 24.3)

[a]Refer to Supplemental Table 1 for operational definitions of NCOs.
CI, confidence interval; NCO, negative clinical outcome.

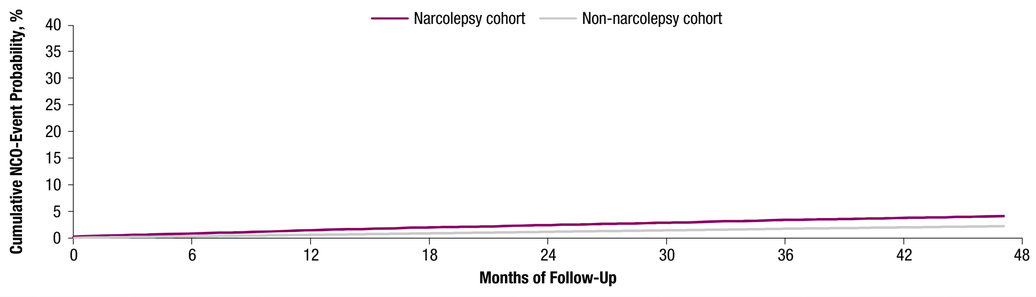
Supplemental Figure 2. Kaplan-Meier Analyses for Hypertension[a]: Narcolepsy vs Non-Narcolepsy Cohorts



Hypertension	Total individuals	Individuals with an event, n (%)	Kaplan-Meier results	12 months	24 months	36 months	48 months
Narcolepsy cohort	29,317	7794 (26.6)	Individuals at risk, n (%)	25,773 (87.9)	16,315 (55.7)	10,219 (34.9)	6407 (21.9)
			Cumulative number of events, n (%)	3544 (12.1)	5478 (18.7)	6555 (22.4)	7226 (24.6)
			Cumulative probability, % (95% CI)	12.1 (11.7, 12.5)	19.8 (19.4, 20.3)	26.1 (25.5, 26.7)	31.9 (31.2, 32.5)
Non-narcolepsy cohort	146,585	24,884 (17.0)	Individuals at risk, n (%)	137,055 (93.5)	96,580 (65.9)	59,748 (40.8)	34,733 (23.7)
			Cumulative number of events, n (%)	9530 (6.5)	16,344 (11.1)	20,402 (13.9)	22,762 (15.5)
			Cumulative probability, % (95% CI)	6.5 (6.4, 6.7)	11.8 (11.6, 12.0)	16.2 (16.0, 16.5)	20.4 (20.1, 20.7)

[a]Refer to Supplemental Table 1 for operational definitions of NCOs.
CI, confidence interval; NCO, negative clinical outcome.

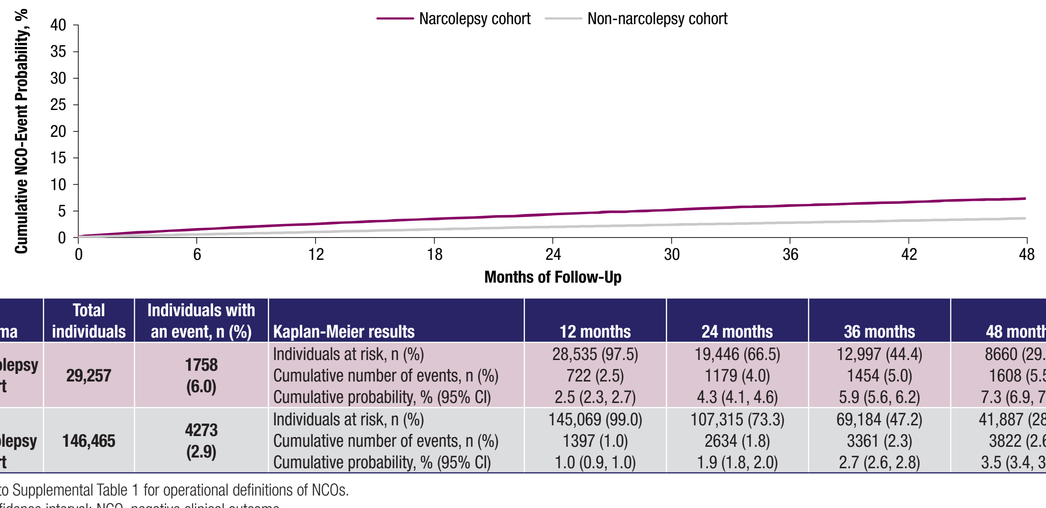
Supplemental Figure 3. Kaplan-Meier Analyses for MACE[a]: Narcolepsy vs Non-Narcolepsy Cohorts



MACE	Total individuals	Individuals with an event, n (%)	Kaplan-Meier results	12 months	24 months	36 months	48 months
Narcolepsy cohort	29,317	983 (3.4)	Individuals at risk, n (%)	28,898 (98.6)	19,912 (67.9)	13,418 (45.8)	8991 (30.7)
			Cumulative number of events, n (%)	419 (1.4)	656 (2.2)	814 (2.8)	903 (3.1)
			Cumulative probability, % (95% CI)	1.4 (1.3, 1.6)	2.4 (2.2, 2.6)	3.3 (3.1, 3.6)	4.1 (3.8, 4.4)
Non-narcolepsy cohort	146,585	2640 (1.8)	Individuals at risk, n (%)	145,773 (99.4)	108,310 (73.9)	70,007 (47.8)	42,556 (29.0)
			Cumulative number of events, n (%)	812 (0.6)	1534 (1.0)	2043 (1.4)	2351 (1.6)
			Cumulative probability, % (95% CI)	0.6 (0.5, 0.6)	1.1 (1.0, 1.2)	1.7 (1.6, 1.8)	2.2 (2.1, 2.3)

[a]Refer to Supplemental Table 1 for operational definitions of NCOs.
CI, confidence interval; MACE, major adverse cardiovascular event; NCO, negative clinical outcome.

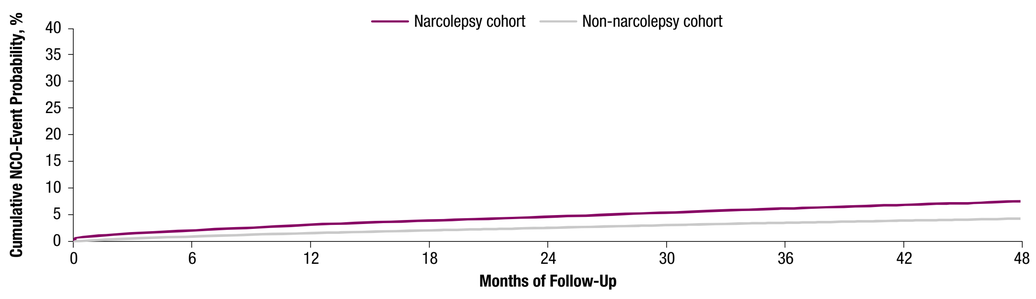
Supplemental Figure 4. Kaplan-Meier Analyses for Oedema[a]: Narcolepsy vs Non-Narcolepsy Cohorts



Oedema	Total individuals	Individuals with an event, n (%)	Kaplan-Meier results	12 months	24 months	36 months	48 months
Narcolepsy cohort	29,257	1758 (6.0)	Individuals at risk, n (%)	28,535 (97.5)	19,446 (66.5)	12,997 (44.4)	8660 (29.6)
			Cumulative number of events, n (%)	722 (2.5)	1179 (4.0)	1454 (5.0)	1608 (5.5)
			Cumulative probability, % (95% CI)	2.5 (2.3, 2.7)	4.3 (4.1, 4.6)	5.9 (5.6, 6.2)	7.3 (6.9, 7.6)
Non-narcolepsy cohort	146,465	4273 (2.9)	Individuals at risk, n (%)	145,069 (99.0)	107,315 (73.3)	69,184 (47.2)	41,887 (28.6)
			Cumulative number of events, n (%)	1397 (1.0)	2634 (1.8)	3361 (2.3)	3822 (2.6)
			Cumulative probability, % (95% CI)	1.0 (0.9, 1.0)	1.9 (1.8, 2.0)	2.7 (2.6, 2.8)	3.5 (3.4, 3.7)

[a]Refer to Supplemental Table 1 for operational definitions of NCOs.
CI, confidence interval; NCO, negative clinical outcome.

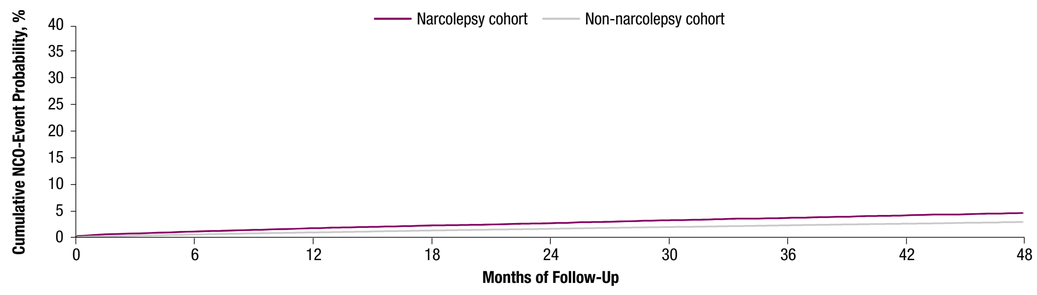
Supplemental Figure 5. Kaplan-Meier Analyses for ≥1 Renal NCO[a]: Narcolepsy vs Non-Narcolepsy Cohorts



≥1 renal NCO	Total individuals	Individuals with an event, n (%)	Kaplan-Meier results	12 months	24 months	36 months	48 months
Narcolepsy cohort	29,317	1832 (6.2)	Individuals at risk, n (%)	28,387 (96.8)	19,392 (66.1)	12,933 (44.1)	8596 (29.3)
			Cumulative number of events, n (%)	930 (3.2)	1299 (4.4)	1563 (5.3)	1715 (5.8)
			Cumulative probability, % (95% CI)	3.2 (3.0, 3.4)	4.7 (4.4, 4.9)	6.2 (5.9, 6.5)	7.5 (7.2, 7.9)
Non-narcolepsy cohort	146,585	5330 (3.6)	Individuals at risk, n (%)	144,265 (98.4)	106,590 (72.7)	68,578 (46.8)	41,507 (28.3)
			Cumulative number of events, n (%)	2320 (1.6)	3615 (2.5)	4472 (3.1)	4922 (3.4)
			Cumulative probability, % (95% CI)	1.6 (1.5, 1.7)	2.6 (2.5, 2.7)	3.5 (3.4, 3.7)	4.3 (4.2, 4.5)

[a]Refer to Supplemental Table 1 for operational definitions of NCOs.
CI, confidence interval; NCO, negative clinical outcome.

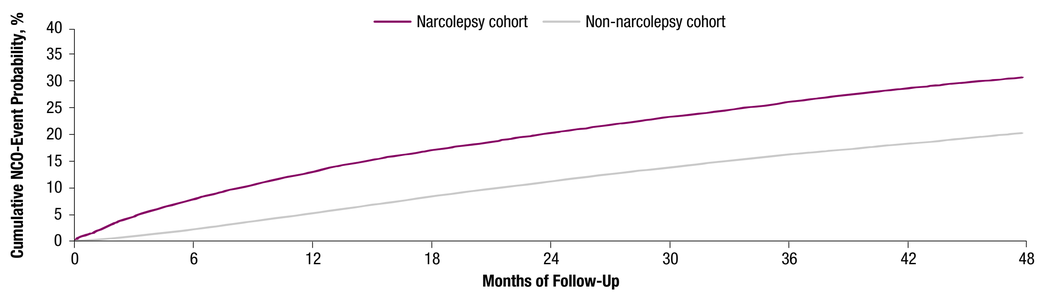
Supplemental Figure 6. Kaplan-Meier Analyses for CV Composite NCO[a]: Narcolepsy vs Non-Narcolepsy Cohorts



CV composite NCO	Total individuals	Individuals with an event, n (%)	Kaplan-Meier results	12 months	24 months	36 months	48 months
Narcolepsy cohort	29,317	1169 (4.0)	Individuals at risk, n (%)	28,807 (98.3)	19,837 (67.7)	13,347 (45.5)	8932 (30.5)
			Cumulative number of events, n (%)	510 (1.7)	756 (2.6)	937 (3.2)	1049 (3.6)
			Cumulative NCO-event probability, % (95% CI)	1.7 (1.6, 1.9)	2.7 (2.5, 2.9)	3.8 (3.5, 4.0)	4.7 (4.4 , 5.1)
Non-narcolepsy cohort	146,585	3622 (2.5)	Individuals at risk, n (%)	145,251 (99.1)	107,734 (73.5)	69,572 (47.5)	42,284 (28.8)
			Cumulative number of events, n (%)	1334 (0.9)	2261 (1.5)	2878 (2.0)	3252 (2.2)
			Cumulative NCO-event probability, % (95% CI)	0.9 (0.9, 1.0)	1.6 (1.5, 1.7)	2.3 (2.2, 2.4)	3.0 (2.8, 3.1)

[a]Refer to Supplemental Table 1 for operational definitions of NCOs.
CI, confidence interval; CV, cardiovascular; NCO, negative clinical outcome.

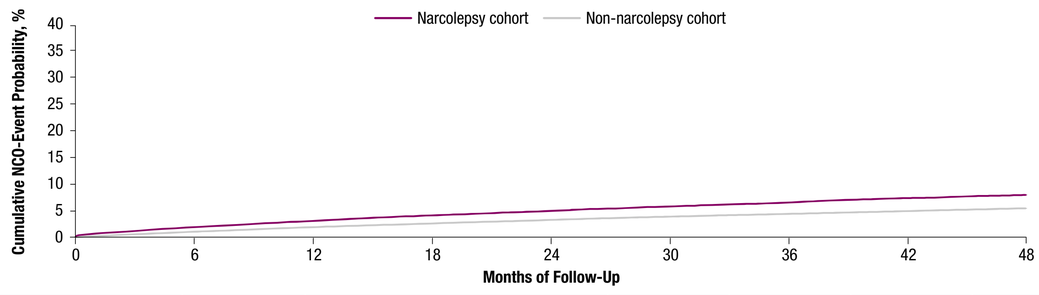
Supplemental Figure 7. Kaplan-Meier Analyses for Obesity[a]: Narcolepsy vs Non-Narcolepsy Cohorts



Obesity	Total individuals	Individuals with an event, n (%)	Kaplan-Meier results	12 months	24 months	36 months	48 months
Narcolepsy cohort	24,007	6296 (26.2)	Individuals at risk, n (%)	20,932 (87.2)	13,397 (55.8)	8522 (35.5)	5374 (22.4)
			Cumulative number of events, n (%)	3075 (12.8)	4584 (19.1)	5411 (22.5)	5866 (24.4)
			Cumulative NCO-event probability, % (95% CI)	12.8 (12.4, 13.2)	20.1 (19.6, 20.7)	26.0 (25.4, 26.6)	30.7 (30.0, 31.4)
Non-narcolepsy cohort	133,998	22,178 (16.5)	Individuals at risk, n (%)	127,132 (94.9)	89,554 (66.8)	55,156 (41.2)	32,193 (24.0)
			Cumulative number of events, n (%)	6865 (5.1)	13,882 (10.4)	18,089 (13.5)	20,198 (15.1)
			Cumulative NCO-event probability, % (95% CI)	5.1 (5.0, 5.3)	11.0 (10.8, 11.2)	16.1 (15.8, 16.3)	20.1 (19.8, 20.5)

[a]Refer to Supplemental Table 1 for operational definitions of NCOs.
CI, confidence interval; NCO, negative clinical outcome.

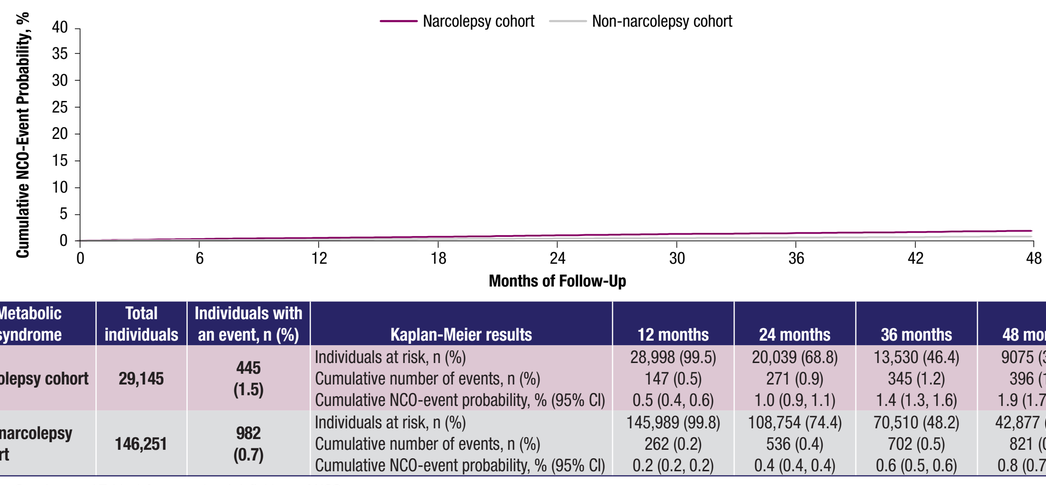
Supplemental Figure 8. Kaplan-Meier Analyses for Type 2 Diabetes[a]: Narcolepsy vs Non-Narcolepsy Cohorts



Type 2 diabetes	Total individuals	Individuals with an event, n (%)	Kaplan-Meier results	12 months	24 months	36 months	48 months
Narcolepsy cohort	28,568	1940 (6.8)	Individuals at risk, n (%)	27,700 (97.0)	18,866 (66.0)	12,622 (44.2)	8420 (29.5)
			Cumulative number of events, n (%)	868 (3.0)	1325 (4.6)	1588 (5.6)	1751 (6.1)
			Cumulative NCO-event probability, % (95% CI)	3.0 (2.8, 3.2))	4.9 (4.7, 5.2)	6.5 (6.2, 6.8)	7.9 (7.5, 8.3)
Non-narcolepsy cohort	144,674	6610 (4.6)	Individuals at risk, n (%)	141,957 (98.1)	104,610 (72.3)	67,215 (46.5)	40,572 (28.0)
			Cumulative number of events, n (%)	2717 (1.9)	4449 (3.1)	5461 (3.8)	6039 (4.2)
			Cumulative NCO-event probability, % (95% CI)	1.9 (1.8, 2.0)	3.2 (3.1, 3.4)	4.4 (4.2, 4.5)	5.4 (5.2, 5.6)

[a]Refer to Supplemental Table 1 for operational definitions of NCOs.
CI, confidence interval; MACE, major adverse cardiovascular event; NCO, negative clinical outcome.

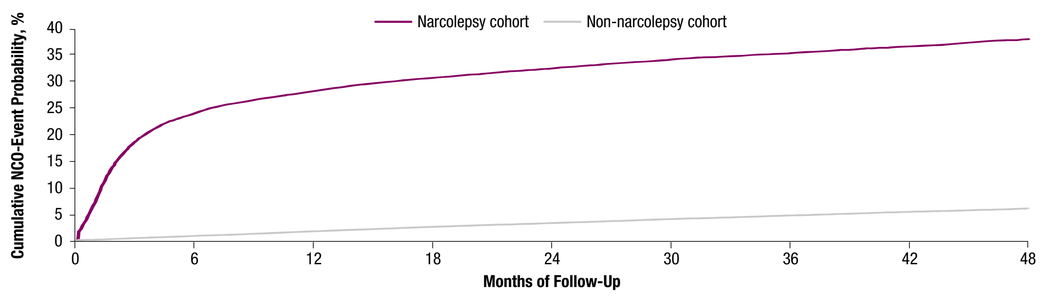
Supplemental Figure 9. Kaplan-Meier Analyses for Metabolic Syndrome[a]: Narcolepsy vs Non-Narcolepsy Cohorts



Metabolic syndrome	Total individuals	Individuals with an event, n (%)	Kaplan-Meier results	12 months	24 months	36 months	48 months
Narcolepsy cohort	29,145	445 (1.5)	Individuals at risk, n (%)	28,998 (99.5)	20,039 (68.8)	13,530 (46.4)	9075 (31.1)
			Cumulative number of events, n (%)	147 (0.5)	271 (0.9)	345 (1.2)	396 (1.4)
			Cumulative NCO-event probability, % (95% CI)	0.5 (0.4, 0.6)	1.0 (0.9, 1.1)	1.4 (1.3, 1.6)	1.9 (1.7, 2.1)
Non-narcolepsy cohort	146,251	982 (0.7)	Individuals at risk, n (%)	145,989 (99.8)	108,754 (74.4)	70,510 (48.2)	42,877 (29.3)
			Cumulative number of events, n (%)	262 (0.2)	536 (0.4)	702 (0.5)	821 (0.6)
			Cumulative NCO-event probability, % (95% CI)	0.2 (0.2, 0.2)	0.4 (0.4, 0.4)	0.6 (0.5, 0.6)	0.8 (0.7, 0.9)

[a]Refer to Supplemental Table 1 for operational definitions of NCOs.
CI, confidence interval; NCO, negative clinical outcome.

Supplemental Figure 10. Kaplan-Meier Analyses for Sleep Apnoea[a]: Narcolepsy vs Non-Narcolepsy Cohorts



Sleep apnoea	Total individuals	Individuals with an event, n (%)	Kaplan-Meier results	12 months	24 months	36 months	48 months
Narcolepsy cohort	21,868	7820 (35.8)	Individuals at risk, n (%)	15,685 (71.7)	10,211 (46.7)	6725 (30.8)	4364 (20.0)
			Cumulative number of events, n (%)	6183 (28.3)	6992 (32.0)	7368 (33.7)	7596 (34.7)
			Cumulative NCO-event probability, % (95% CI)	28.3 (27.7, 28.9)	32.6 (31.9, 33.2)	35.5 (34.8, 36.1)	38.1 (37.4, 38.8)
Non-narcolepsy cohort	141,245	7020 (5.0)	Individuals at risk, n (%)	138,911 (98.3)	102,255 (72.4)	65,495 (46.4)	39,453 (27.9)
			Cumulative number of events, n (%)	2334 (1.7)	4297 (3.0)	5553 (3.9)	6283 (4.4)
			Cumulative NCO-event probability, % (95% CI)	1.7 (1.6, 1.7)	3.2 (3.1, 3.3)	4.7 (4.5, 4.8)	6.0 (5.8, 6.2)

[a]Refer to Supplemental Table 1 for operational definitions of NCOs.
CI, confidence interval; NCO, negative clinical outcome.

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Real-World Risk of Sodium-Associated Negative Clinical Outcomes Among Individuals With Narcolepsy in the United States

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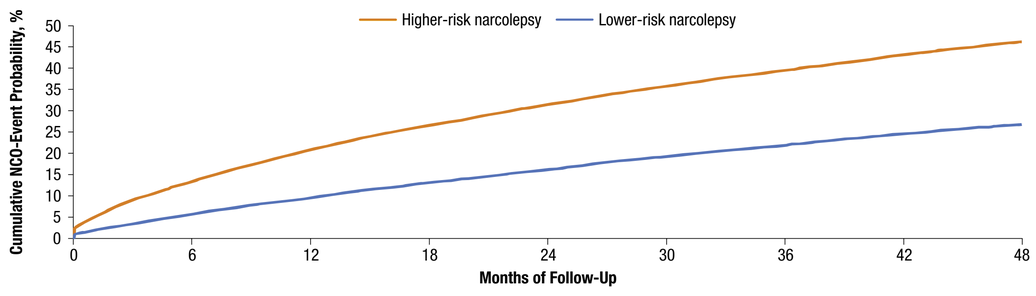
Supplemental Materials

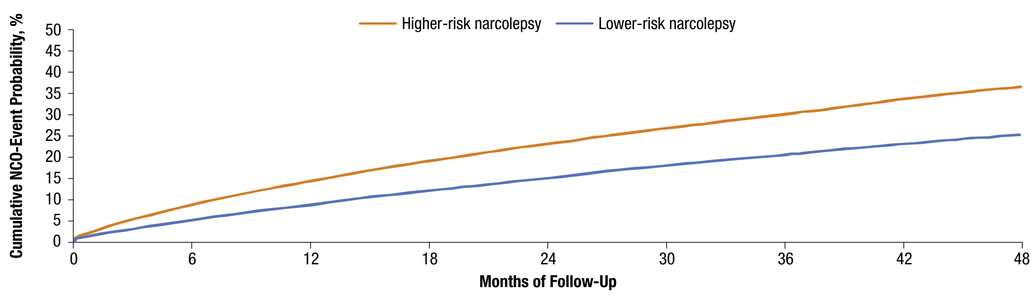
Supplemental Figure 11. Kaplan-Meier Analyses for ≥1 NCO[a]: Risk Subgroups Within the Narcolepsy Cohort



≥1 NCO	Total individuals	Individuals with an event, n (%)	Kaplan-Meier results	12 months	24 months	36 months	48 months
Higher-risk	**17,227**	**6730 (39.1)**	Individuals at risk, n (%)	13,642 (79.2)	8105 (47.0)	4825 (28.0)	2893 (16.8)
			Cumulative number of events, n (%)	3585 (20.8)	5122 (29.7)	5921 (34.4)	6368 (37.0)
			Cumulative probability, % (95% CI)	20.8 (20.2, 21.4)	31.4 (30.6, 32.1)	39.4 (38.6, 40.2)	46.1 (45.1, 47.0)
Lower-risk	**12,090**	**2705 (22.4)**	Individuals at risk, n (%)	10,943 (90.5)	7155 (59.2)	4592 (38.0)	2997 (24.8)
			Cumulative number of events, n (%)	1147 (9.5)	1835 (15.2)	2247 (18.6)	2493 (20.6)
			Cumulative probability, % (95% CI)	9.5 (9.0, 10.0)	16.1 (15.4, 16.8)	21.8 (21.0, 22.6)	26.7 (25.7, 27.7)

[a]Refer to Supplemental Table 1 for operational definitions of NCOs.
CI, confidence interval; NCO, negative clinical outcome.

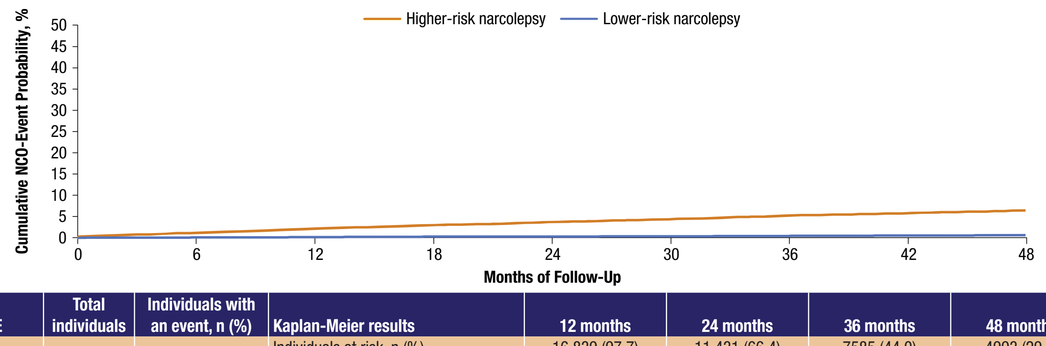
Supplemental Figure 12. Kaplan-Meier Analyses for Hypertension[a]: Risk Subgroups Within the Narcolepsy Cohort



Hypertension	Total individuals	Individuals with an event, n (%)	Kaplan-Meier results	12 months	24 months	36 months	48 months
Higher-risk	**17,227**	**5235 (30.4)**	Individuals at risk, n (%)	14,742 (85.6)	9072 (52.7)	5549 (32.2)	3354 (19.5)
			Cumulative number of events, n (%)	2485 (14.4)	3760 (21.8)	4444 (25.8)	4875 (28.3)
			Cumulative probability, % (95% CI)	14.4 (13.9, 15.0)	23.2 (22.5, 23.8)	30.1 (29.3, 30.9)	36.6 (35.7, 37.5)
Lower-risk	**12,090**	**2559 (21.2)**	Individuals at risk, n (%)	11,031 (91.2)	7243 (59.9)	4670 (38.6)	3053 (25.3)
			Cumulative number of events, n (%)	1059 (8.8)	1718 (14.2)	2111 (17.5)	2351 (19.4)
			Cumulative probability, % (95% CI)	8.8 (8.3, 9.3)	15.1 (14.5, 15.8)	20.5 (19.7, 21.3)	25.3 (24.4, 26.3)

[a]Refer to Supplemental Table 1 for operational definitions of NCOs.
CI, confidence interval; NCO, negative clinical outcome.

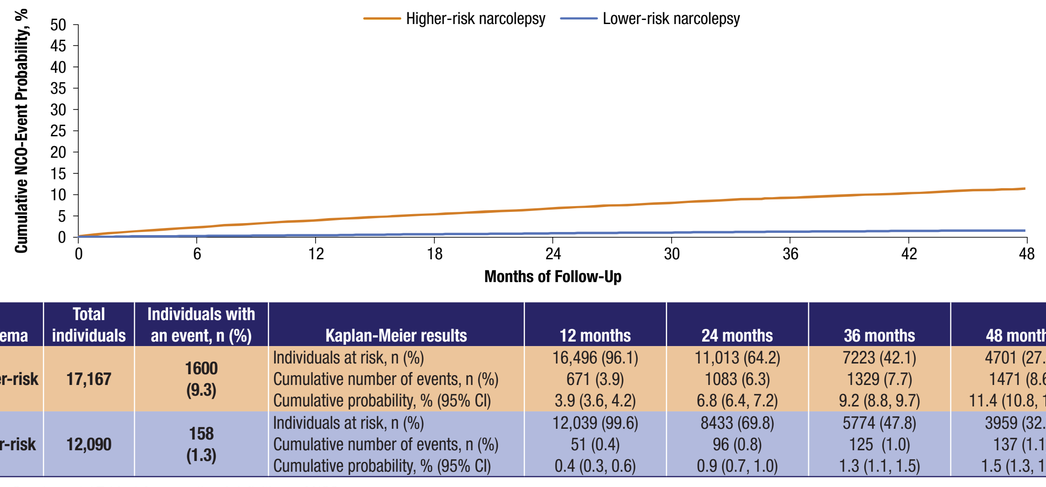
Supplemental Figure 13. Kaplan-Meier Analyses for MACE[a]: Risk Subgroups Within the Narcolepsy Cohort



MACE	Total individuals	Individuals with an event, n (%)	Kaplan-Meier results	12 months	24 months	36 months	48 months
Higher-risk	**17,167**	**916 (5.3)**	Individuals at risk, n (%)	16,839 (97.7)	11,431 (66.4)	7585 (44.0)	4993 (29.0)
			Cumulative number of events, n (%)	388 (2.3)	612 (3.6)	760 (4.4)	840 (4.9)
			Cumulative probability, % (95% CI)	2.3 (2.0, 2.5)	3.8 (3.5, 4.1)	5.3 (4.9, 5.7)	6.5 (6.1, 7.0)
Lower-risk	**12,090**	**67 (0.6)**	Individuals at risk, n (%)	12,059 (99.7)	8481 (70.1)	5833 (48.2)	3998 (33.1)
			Cumulative number of events, n (%)	31 (0.3)	44 (0.4)	54 (0.4)	63 (0.5)
			Cumulative probability, % (95% CI)	0.3 (0.2, 0.4)	0.4 (0.3, 0.5)	0.5 (0.4, 0.7)	0.7 (0.5, 0.9)

[a]Refer to Supplemental Table 1 for operational definitions of NCOs.
CI, confidence interval; MACE, major adverse cardiovascular event; NCO, negative clinical outcome.

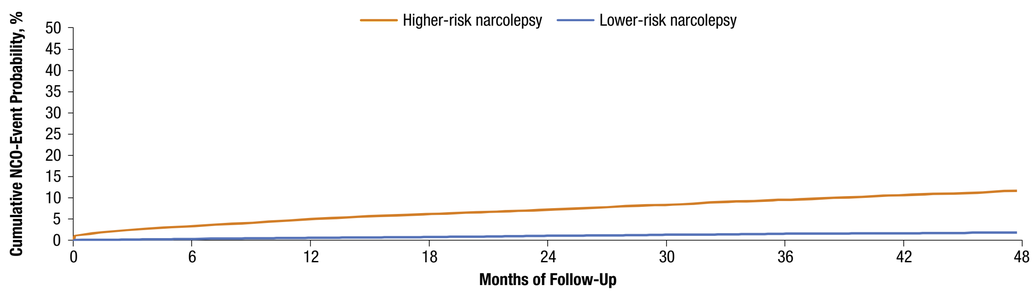
Supplemental Figure 14. Kaplan-Meier Analyses for Oedema[a]: Risk Subgroups Within the Narcolepsy Cohort



Oedema	Total individuals	Individuals with an event, n (%)	Kaplan-Meier results	12 months	24 months	36 months	48 months
Higher-risk	**17,167**	**1600 (9.3)**	Individuals at risk, n (%)	16,496 (96.1)	11,013 (64.2)	7223 (42.1)	4701 (27.4)
			Cumulative number of events, n (%)	671 (3.9)	1083 (6.3)	1329 (7.7)	1471 (8.6)
			Cumulative probability, % (95% CI)	3.9 (3.6, 4.2)	6.8 (6.4, 7.2)	9.2 (8.8, 9.7)	11.4 (10.8, 12.0)
Lower-risk	**12,090**	**158 (1.3)**	Individuals at risk, n (%)	12,039 (99.6)	8433 (69.8)	5774 (47.8)	3959 (32.7)
			Cumulative number of events, n (%)	51 (0.4)	96 (0.8)	125 (1.0)	137 (1.1)
			Cumulative probability, % (95% CI)	0.4 (0.3, 0.6)	0.9 (0.7, 1.0)	1.3 (1.1, 1.5)	1.5 (1.3, 1.8)

[a]Refer to Supplemental Table 1 for operational definitions of NCOs.
CI, confidence interval; NCO, negative clinical outcome.

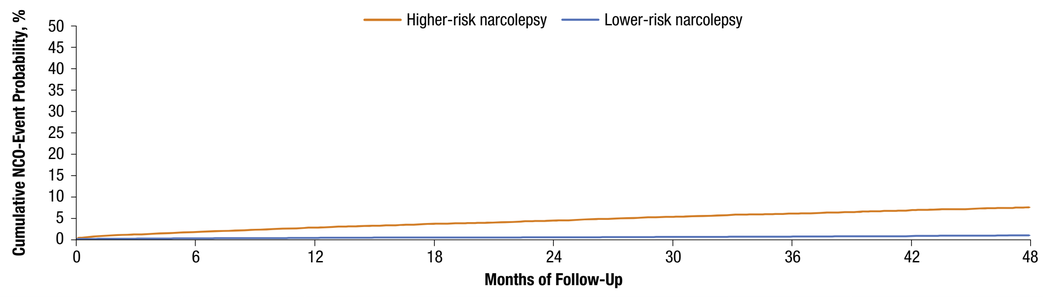
Supplemental Figure 15. Kaplan-Meier Analyses for ≥1 Renal NCO[a]: Risk Subgroups Within the Narcolepsy Cohort



≥1 renal NCO	Total individuals	Individuals with an event, n (%)	Kaplan-Meier results	12 months	24 months	36 months	48 months
Higher-risk	**17,227**	**1650 (9.6)**	Individuals at risk, n (%)	16,368 (95.0)	10,975 (63.7)	7174 (41.6)	4650 (27.0)
			Cumulative number of events, n (%)	859 (5.0)	1181 (6.9)	1411 (8.2)	1549 (9.0)
			Cumulative probability, % (95% CI)	5.0 (4.7, 5.3)	7.2 (6.8, 7.6)	9.5 (9.1, 10.0)	11.6 (11.1, 12.3)
Lower-risk	**12,090**	**182 (1.5)**	Individuals at risk, n (%)	12,019 (99.4)	8417 (69.6)	5759 (47.6)	3946 (32.6)
			Cumulative number of events, n (%)	71 (0.6)	118 (1.0)	152 (1.3)	166 (1.4)
			Cumulative probability, % (95% CI)	0.6 (0.5, 0.7)	1.1 (0.9, 1.3)	1.5 (1.3, 1.8)	1.8 (1.6, 2.1)

[a]Refer to Supplemental Table 1 for operational definitions of NCOs.
CI, confidence interval; NCO, negative clinical outcome.

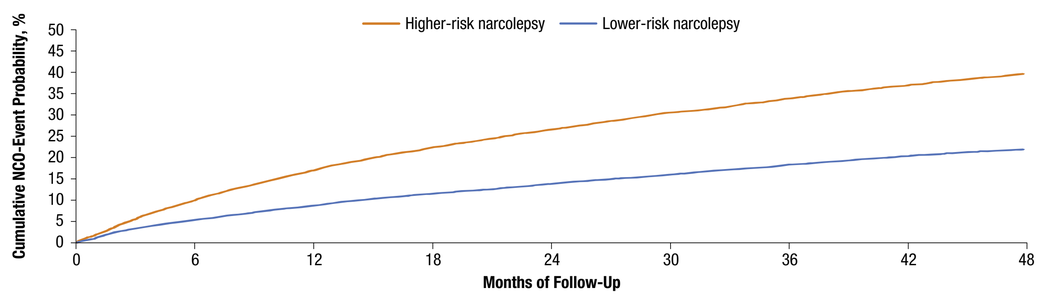
Supplemental Figure 16. Kaplan-Meier Analyses for CV Composite NCO[a]: Risk Subgroups Within the Narcolepsy Cohort



CV composite NCO	Total individuals	Individuals with an event, n (%)	Kaplan-Meier results	12 months	24 months	36 months	48 months
Higher-risk	**17,227**	**1081 (6.3)**	Individuals at risk, n (%)	16,755 (97.3)	11,358 (65.9)	7524 (43.7)	4944 (28.7)
			Cumulative number of events, n (%)	472 (2.7)	707 (4.1)	874 (5.1)	972 (5.6)
			Cumulative NCO-event probability, % (95% CI)	2.7 (2.5, 3.0)	4.4 (4.1, 4.7)	6.0 (5.6, 6.4)	7.5 (7.0, 8.0)
Lower-risk	**12,090**	**88 (0.7)**	Individuals at risk, n (%)	12,052 (99.7)	8479 (70.1)	5823 (48.2)	3988 (33.0)
			Cumulative number of events, n (%)	38 (0.3)	49 (0.4)	63 (0.5)	77 (0.6)
			Cumulative NCO-event probability, % (95% CI)	0.3 (0.2, 0.4)	0.4 (0.3, 0.6)	0.6 (0.5, 0.8)	0.9 (0.7, 1.1)

[a]Refer to Supplemental Table 1 for operational definitions of NCOs.
CI, confidence interval; NCO, negative clinical outcome.

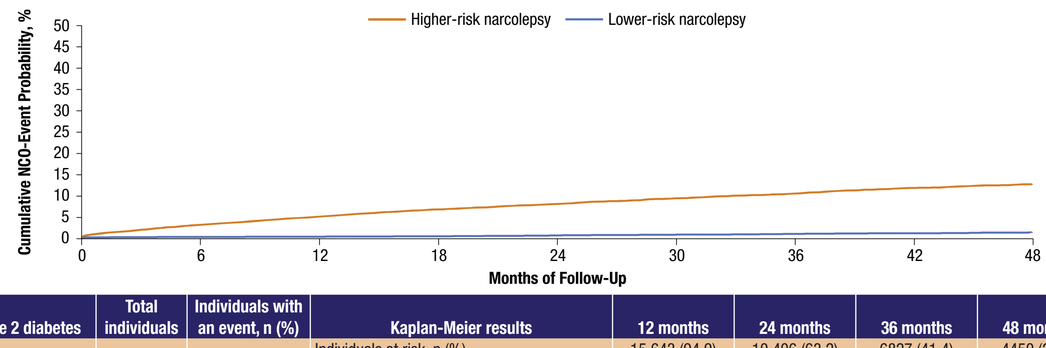
Supplemental Figure 17. Kaplan-Meier Analyses for Obesity[a]: Risk Subgroups Within the Narcolepsy Cohort



Obesity	Total individuals	Individuals with an event, n (%)	Kaplan-Meier results	12 months	24 months	36 months	48 months
Higher-risk	**11,917**	**3999 (33.6)**	Individuals at risk, n (%)	9894 (83.0)	6068 (50.9)	3737 (31.4)	2222 (18.6)
			Cumulative number of events, n (%)	2023 (17.0)	3001 (25.2)	3510 (29.5)	3783 (31.7)
			Cumulative NCO-event probability, % (95% CI)	17.0 (16.3, 17.7)	26.6 (25.8, 27.4)	33.9 (32.9, 34.8)	39.7 (38.6, 40.8)
Lower-risk	**12,090**	**2297 (19.0)**	Individuals at risk, n (%)	11,038 (91.3)	7329 (60.6)	4785 (39.6)	3152 (26.1)
			Cumulative number of events, n (%)	1052 (8.7)	1583 (13.1)	1901 (15.7)	2083 (17.2)
			Cumulative NCO-event probability, % (95% CI)	8.7 (8.2, 9.2)	13.8 (13.2, 14.5)	18.3 (17.5, 19.1)	21.9 (21.0, 22.8)

[a]Refer to Supplemental Table 1 for operational definitions of NCOs.
CI, confidence interval; NCO, negative clinical outcome.

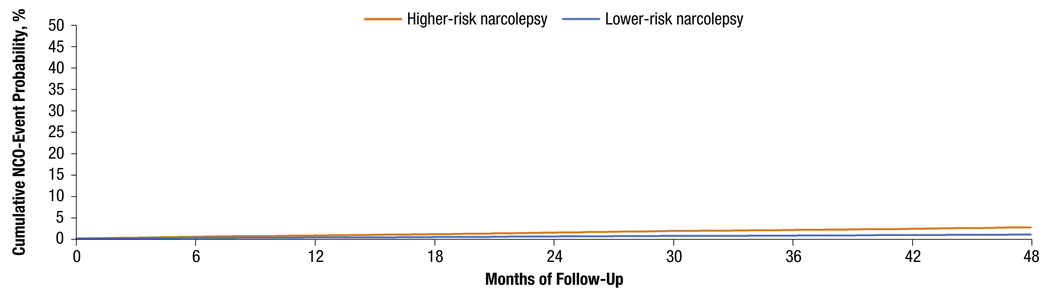
Supplemental Figure 18. Kaplan-Meier Analyses for Type 2 Diabetes[a]: Risk Subgroups Within the Narcolepsy Cohort



Type 2 diabetes	Total individuals	Individuals with an event, n (%)	Kaplan-Meier results	12 months	24 months	36 months	48 months
Higher-risk	**16,478**	**1807 (11.0)**	Individuals at risk, n (%)	15,643 (94.9)	10,406 (63.2)	6827 (41.4)	4450 (27.0)
			Cumulative number of events, n (%)	835 (5.1)	1264 (7.7)	1501 (9.1)	1646 (10.0)
			Cumulative NCO-event probability, % (95% CI)	5.1 (4.7, 5.4)	8.1 (7.7, 8.6)	10.6 (10.1, 11.1)	12.8 (12.2, 13.5)
Lower-risk	**12,090**	**133 (1.1)**	Individuals at risk, n (%)	12,057 (99.7)	8460 (70.0)	5795 (47.9)	3970 (32.8)
			Cumulative number of events, n (%)	33 (0.3)	61 (0.5)	87 (0.7)	105 (0.9)
			Cumulative NCO-event probability, % (95% CI)	0.3 (0.2, 0.4)	0.6 (0.4, 0.7)	0.9 (0.7, 1.1)	1.3 (1.0, 1.6)

[a]Refer to Supplemental Table 1 for operational definitions of NCOs.
CI, confidence interval; MACE, major adverse cardiovascular event; NCO, negative clinical outcome.

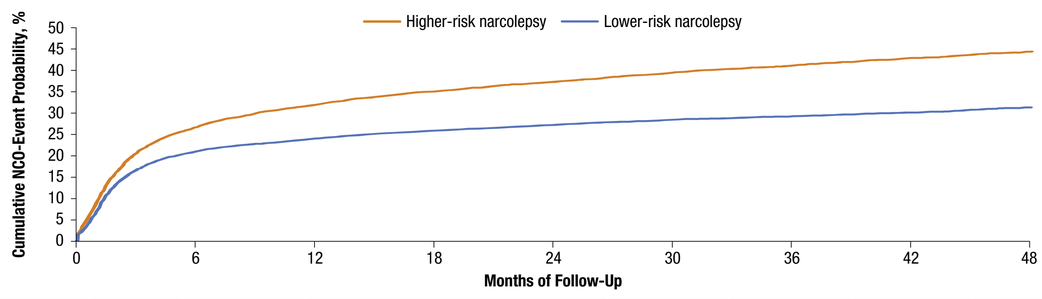
Supplemental Figure 19. Kaplan-Meier Analyses for Metabolic Syndrome[a]: Risk Subgroups Within the Narcolepsy Cohort



Metabolic syndrome	Total individuals	Individuals with an event, n (%)	Kaplan-Meier results	12 months	24 months	36 months	48 months
Higher-risk	**17,055**	**352 (2.1)**	Individuals at risk, n (%)	16,937 (99.3)	11,571 (67.8)	7712 (45.2)	5081 (29.8)
			Cumulative number of events, n (%)	118 (0.7)	218 (1.3)	277 (1.6)	316 (1.9)
			Cumulative NCO-event probability, % (95% CI)	0.7 (0.6, 0.8)	1.4 (1.2, 1.6)	2.0 (1.8, 2.2)	2.6 (2.3, 2.9)
Lower-risk	**12,090**	**93 (0.8)**	Individuals at risk, n (%)	12,061 (99.8)	8468 (70.0)	5818 (48.1)	3994 (33.0)
			Cumulative number of events, n (%)	29 (0.2)	53 (0.4)	68 (0.6)	80 (0.7)
			Cumulative NCO-event probability, % (95% CI)	0.2 (0.2, 0.3)	0.5 (0.4, 0.6)	0.7 (0.5, 0.9)	0.9 (0.7, 1.2)

[a]Refer to Supplemental Table 1 for operational definitions of NCOs.
CI, confidence interval; NCO, negative clinical outcome.

Supplemental Figure 20. Kaplan-Meier Analyses for Sleep Apnoea[a]: Risk Subgroups Within the Narcolepsy Cohort



Sleep apnoea	Total individuals	Individuals with an event, n (%)	Kaplan-Meier results	12 months	24 months	36 months	48 months
Higher-risk	**9778**	**4127 (42.2)**	Individuals at risk, n (%)	6575 (67.2)	4083 (41.8)	2587 (26.5)	1594 (16.3)
			Cumulative number of events, n (%)	3203 (32.8)	3668 (37.5)	3892 (39.8)	4016 (41.1)
			Cumulative NCO-event probability, % (95% CI)	32.8 (31.8, 33.7)	38.3 (37.3, 39.3)	42.3 (41.2, 43.3)	45.6 (44.5, 46.8)
Lower-risk	**12,090**	**3693 (30.5)**	Individuals at risk, n (%)	9110 (75.4)	6128 (50.7)	4138 (34.2)	2770 (22.9)
			Cumulative number of events, n (%)	2980 (24.6)	3324 (27.5)	3476 (28.8)	3580 (29.6)
			Cumulative NCO-event probability, % (95% CI)	24.6 (23.9, 25.4)	27.9 (27.1, 28.8)	30.0 (29.2, 30.9)	32.1 (31.2, 33.1)

[a]Refer to Supplemental Table 1 for operational definitions of NCOs.
CI, confidence interval; NCO, negative clinical outcome.