

Risk of New-Onset Cardiovascular and Cardiometabolic Conditions in Narcolepsy: An Analysis of the *All of Us* Research Program

Sarah C. Markt, ScD, MPH¹; Anan Zhou, MPH²; Katarina Irwin, MS³; Caroleen Drachenberg, PhD, MSPH¹; Silky Beaty, PharmD, MSPH¹; Jon Michael Stroh³; Martin Zagari, MD³; Jessica K. Alexander, PhD¹; Marisa Whalen, PharmD¹; Junko Saber, MBA³; Christina L. Wassel, PhD¹; Barbara Hutchinson, MD, PhD⁴

¹Jazz Pharmaceuticals, Palo Alto, CA, USA; ²Genesis Research Group, Hoboken, NJ, USA; ³Innopihany, Irvine, CA, USA; ⁴Chesapeake Cardiac Care, Bowie, MD, USA

Introduction

- Narcolepsy is a central disorder of hypersomnolence primarily characterised by excessive daytime sleepiness; people with narcolepsy may also experience disrupted nighttime sleep, cataplexy, sleep paralysis, or hypnagogic/hypnopompic hallucinations^{1,2}
 - The prevalence of cardiovascular and cardiometabolic conditions is higher in people with narcolepsy than in those without narcolepsy³⁻⁵
- The literature describing differences in developing new-onset cardiovascular or cardiometabolic conditions in people with and without narcolepsy is limited^{3,6}
- The *All of Us* Research Program, launched by the National Institutes of Health, is a nationwide initiative in the United States to create a database that reflects its increasingly diverse population⁷

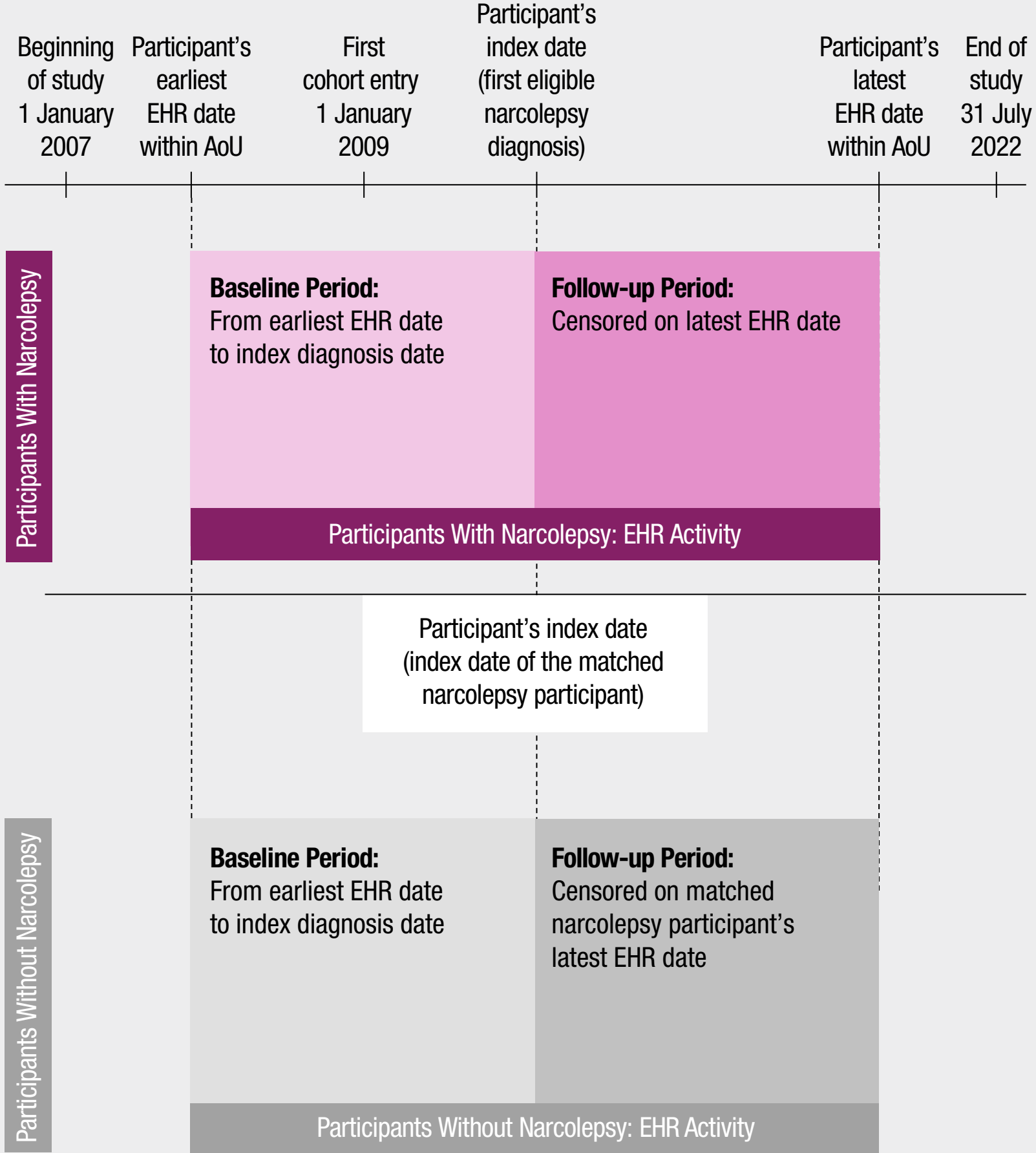
Objective

- To compare the incidence of hypertension, obesity, hyperlipidaemia, and coronary arteriosclerosis in people with and without narcolepsy in the *All of Us* Research Program

Methods

- A retrospective, observational cohort study was conducted using electronic health record (EHR) and survey data (study period: 1 January 2007 to 31 July 2022) from the *All of Us* Research Program database
 - The *All of Us* database includes deidentified data from EHRs and participant surveys, including surveys assessing demographics, overall health, lifestyle, and social determinants of health

Figure 1. Study Design



AoU, *All of Us*; EHR, electronic health record.

- US participants with narcolepsy were required to have completed the core *All of Us* Research Program surveys (The Basics, Overall Health, and Lifestyle) and to have 1 Systematized Nomenclature of Medicine (SNOMED) code for narcolepsy (participant identification period: 1 January 2009 to 31 January 2022)
 - For participants with narcolepsy, the index date was defined as the earliest confirmed diagnosis date within the participant identification period
- Participants without narcolepsy were matched in a 3:1 ratio to participants with narcolepsy on age, sex, year and month of their earliest EHR date, time in EHR, and social determinants of health survey completion
 - The index date for participants without narcolepsy was the index date for their matched participants with narcolepsy
- Demographic characteristics were assessed at baseline
- Hypertension, hyperlipidaemia, obesity, and coronary arteriosclerosis were defined using SNOMED codes; use of antihypertensive medication also defined hypertension
- Unadjusted incidence rates (IRs) per 100 person-years were calculated for the total follow-up period, as well as for the 1-year, 3-year, and 5-year periods after index
- Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated using Cox proportional hazards models

References: **1.** American Academy of Sleep Medicine. *International Classification of Sleep Disorders – Third Edition, Text Revision*. Darien, IL: American Academy of Sleep Medicine; 2023. **2.** Morse AM, et al. *CNS Drugs*. 2025;39 (Suppl 1):9-22. **3.** Ben-Joseph RH, et al. *Sleep*. 2023;46(10):zsad161. **4.** Black J, et al. *Sleep Med*. 2017;33:13-18. **5.** Ohayon MM. *Sleep Med*. 2013;14(6):488-492. **6.** Kaufmann CN, et al. *J Am Heart Assoc*. 2025:e039899. **7.** Denny JC, et al. *N Engl J Med*. 2019;381(7):668-676.

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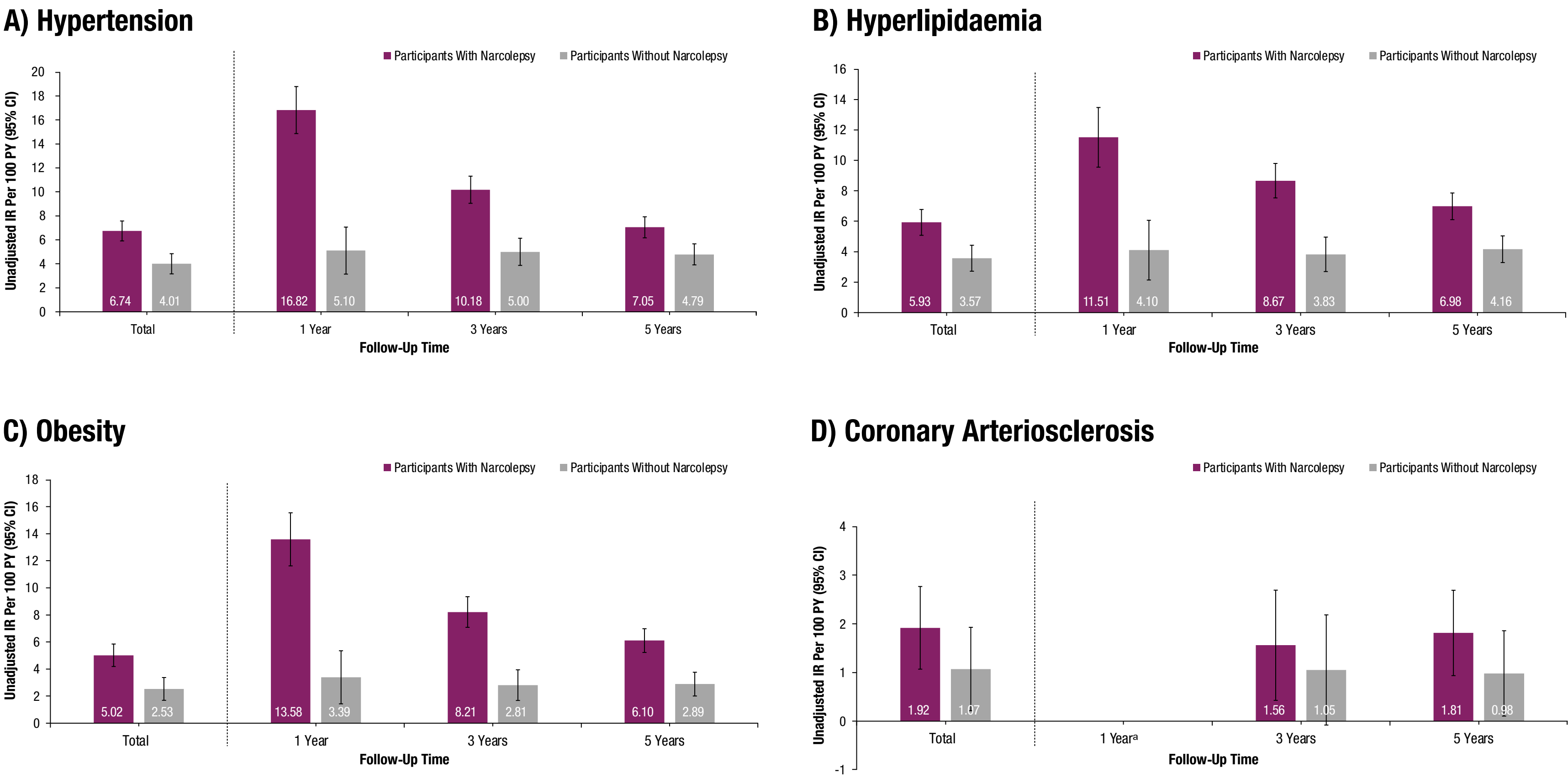
Disclosures: **SC Markt, C Drachenberg, S Beaty, JK Alexander, and M Whalen** are full-time employees of Jazz Pharmaceuticals who, in the course of this employment, have received stock options exercisable for and other stock awards of ordinary shares of Jazz Pharmaceuticals, plc. **A Zhou** is a full-time employee of Genesis Research Group and has received consulting fees from Jazz Pharmaceuticals, plc. **K Irwin, JM Stroh, M Zagari, and J Saber** are employees of Innopihany, which has received consulting fees from Jazz Pharmaceuticals, plc. **CL Wassel** has received consulting fees from Jazz Pharmaceuticals plc as a contract worker. **B Hutchinson** is a consultant for Jazz Pharmaceuticals, plc.



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Results

Figure 2. Unadjusted Incidence Rates in Participants With and Without Narcolepsy for (A) Hypertension, (B) Hyperlipidaemia, (C) Obesity, and (D) Coronary Arteriosclerosis



*Unadjusted incidence rates for coronary arteriosclerosis during the 1-year follow-up period are not shown due to sample size <20 in the narcolepsy cohort; the minimum output bin size for the *All of Us* database is 20 participants to mitigate the risk of identifying respondents. CI, confidence interval; IR, incidence rate; PY, person-years.

- Participants with narcolepsy had higher incidence rates of hypertension, hyperlipidaemia, obesity, and coronary arteriosclerosis, compared to those without narcolepsy

Figure 3. Hazard Ratios for the Association Between Narcolepsy and Hypertension, Hyperlipidaemia, Obesity, and Coronary Arteriosclerosis

	Participants With Narcolepsy			Participants Without Narcolepsy			HR (95% CI)*	
	Participants at Risk, n	Events, n	Person-Time in Years	Participants at Risk, n	Events, n	Person-Time in Years		
Hypertension								
Total	356	134	1988	1321	287	7166	2.02 (1.53, 2.67)	Total
1 Year	327	55	327	1215	62	1215	3.84 (2.37, 6.22)	1Y
3 Year	262	80	786	953	143	2859	2.67 (1.89, 3.77)	3Y
5 Year	176	62	880	639	153	3195	2.25 (1.66, 3.06)	5Y
Hyperlipidaemia								
Total	462	146	2464	1529	289	8090	1.96 (1.52, 2.54)	Total
1 Year	417	48	417	1390	57	1390	3.63 (2.45, 5.37)	1Y
3 Year	327	85	981	1080	124	3240	2.89 (2.22, 3.78)	3Y
5 Year	212	74	1060	711	148	3555	2.42 (1.92, 3.05)	5Y
Obesity								
Total	471	132	2630	1659	228	9008	2.42 (1.93, 3.05)	Total
1 Year	427	58	427	1504	51	1504	4.98 (3.32, 7.47)	1Y
3 Year	349	86	1047	1186	100	3558	3.17 (2.38, 4.23)	3Y
5 Year	236	72	1180	797	115	3985	2.75 (2.13, 3.55)	5Y
Coronary arteriosclerosis								
Total	636	65	3391	1963	110	10,275	1.75 (1.27, 2.42)	Total
1 Year ^b	—	—	—	—	—	—	—	1Y ^b
3 Year	449	21	1347	1363	43	4089	1.61 (1.00, 2.61)	3Y
5 Year	298	27	1490	897	44	4485	1.93 (1.31, 2.83)	5Y

*HRs were adjusted for age, time in EHR, sex, race/ethnicity, education level, household income, employment status, health insurance, and disability status. ^bResults for coronary arteriosclerosis during the 1-year follow-up period are not shown due to sample sizes <20 in the narcolepsy cohort; the minimum output bin size for the *All of Us* database is 20 participants to mitigate the risk of identifying respondents. 1Y, 1-year follow-up period; 3Y, 3-year follow-up period; 5Y, 5-year follow-up period; CI, confidence interval; EHR, electronic health record; HR, hazard ratio.

- Participants with narcolepsy had a greater risk of each assessed cardiovascular and cardiometabolic comorbidity during the total follow-up period and in each follow-up period (1-year, 3-years, and 5-years)

Table 1. Demographic Characteristics for Participants With Narcolepsy and Matched Participants Without Narcolepsy

Characteristics	Participants With Narcolepsy (n=694)	Participants Without Narcolepsy (n=2072)
Age at time of core survey completion, years, mean (SD)	48.0 (16.8)	49.2 (16.4)
Age at index, years, mean (SD)	45.5 (16.3)	46.7 (16.0)
Sex, n (%)		
Female	496 (71.5)	1449 (69.9)
Race/ethnicity, n (%)		
Non-Hispanic Asian/Native Hawaiian or Pacific Islander	22 (3.2)	47 (2.3)
Non-Hispanic Black	82 (11.8)	383 (18.5)
Hispanic	58 (8.4)	391 (18.9)
Non-Hispanic White	466 (67.1)	1115 (53.8)
Other	36 (5.2)	77 (3.7)
Missing/prefer not to answer	30 (4.3)	59 (2.8)
Education level, n (%)		
No high school diploma	25 (3.6)	170 (8.2)
High school diploma or GED	94 (13.5)	389 (18.8)
Some college	226 (32.6)	536 (25.9)
College graduate	329 (47.4)	909 (43.9)
Missing/prefer not to answer	20 (2.9)	68 (3.3)
Income, USD, n (%)		
<\$25,000	190 (27.4)	479 (23.1)
\$25,000–\$49,999	134 (19.3)	354 (17.1)
\$50,000–\$99,999	138 (19.9)	387 (18.7)
≥\$100,000	118 (17.0)	444 (21.4)
Missing/prefer not to answer	114 (16.4)	408 (19.7)
Characteristics	Participants With Narcolepsy (n=694)	Participants Without Narcolepsy (n=2072)
Duration of follow-up, years, mean (SD)	5.2 (3.5)	5.2 (3.5)
Employment status, n (%)		
Employed	270 (38.9)	1020 (49.2)
Not in the workforce	206 (29.7)	430 (20.8)
Out of work	61 (8.8)	174 (8.4)
Retired	131 (18.9)	367 (17.7)
Missing/prefer not to answer	26 (3.7)	81 (3.9)
Insurance type, n (%)		
Private	260 (37.5)	872 (42.1)
Medicare	226 (32.6)	480 (23.2)
Medicaid	126 (18.2)	435 (21.0)
Missing/prefer not to answer/uninsured	28 (4.0)	163 (7.9)
Disability status, n (%)		
Yes	128 (18.4)	215 (10.4)
No	117 (16.9)	468 (22.6)
Missing/prefer not to answer	449 (64.7)	1389 (67.0)
Clinical conditions,^a n (%)		
Coronary arteriosclerosis	58 (8.4)	109 (5.3)
Hypertension	338 (48.7)	751 (36.2)
Hyperlipidaemia	232 (33.4)	543 (26.2)
Obesity	223 (32.1)	413 (19.9)

^aParticipants could report more than 1 comorbidity; therefore, the sum of percentages may exceed 100. GED, General Educational Development; SD, standard deviation; USD, US dollar.

- In total, 2766 participants (with narcolepsy, n=694; without narcolepsy, n=2072) were eligible for analysis; participants had a mean (standard deviation [SD]) follow-up time of 5.2 (3.5) years
- At survey completion, participants with narcolepsy had a mean (SD) age of 48.0 (16.8) years; 71.5% were female, and 67.1% were non-Hispanic White; participants without narcolepsy had a mean (SD) age of 49.2 (16.4) years; 69.9% were female, and 53.8% were non-Hispanic White
- Despite high education levels, more participants with versus without narcolepsy were out of work/not in the workforce (38.5% vs 29.2%)
- At baseline, participants with narcolepsy had a higher prevalence of hypertension, hyperlipidaemia, obesity, and coronary arteriosclerosis

Conclusions

- Participants with narcolepsy experienced higher rates of hypertension, hyperlipidaemia, obesity, and coronary arteriosclerosis compared with those without narcolepsy during the total follow-up period, as well as in the 1-year, 3-year, and 5-year periods following narcolepsy diagnosis
- Limitations of the study include potential misclassification of diagnosis date, thus introducing bias in estimating early new-onset cardiovascular and cardiometabolic outcomes, use of EHR data to classify diagnoses, and small sample size for some of the outcomes assessed
- Early identification and comprehensive management are warranted to address whole-person health, including comorbidities and social determinants of health factors, that may influence access to care and health outcomes