

Changes in Cardiovascular and Cardiometabolic Biomarkers Following Low-Sodium Oxybate Initiation for Narcolepsy or Idiopathic Hypersomnia

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Objective

- This study was conducted to understand real-world changes in cardiovascular (CV) and cardiometabolic (CM) biomarkers among individuals initiating low-sodium oxybate (LXB), overall and among those switching from high-sodium oxybate (SXB)

Conclusions

- The study provides novel observations of reductions in non-high-density lipoprotein (HDL) cholesterol and triglycerides and an increase in HDL cholesterol after LXB initiation
 - Changes in these biomarkers appeared more pronounced in females than in males, although no direct comparisons were conducted
- In those with baseline SXB use, a decrease in office-based systolic blood pressure and increase in HDL cholesterol were observed following initiation of LXB
- This observational study was not designed to establish causality, and small sample sizes may have limited the ability to detect significant changes
- Since individuals with narcolepsy and idiopathic hypersomnia are at heightened risk for CV, CM, and renal comorbidities,¹⁻⁵ these findings merit additional evaluation for potential risk mitigation with LXB

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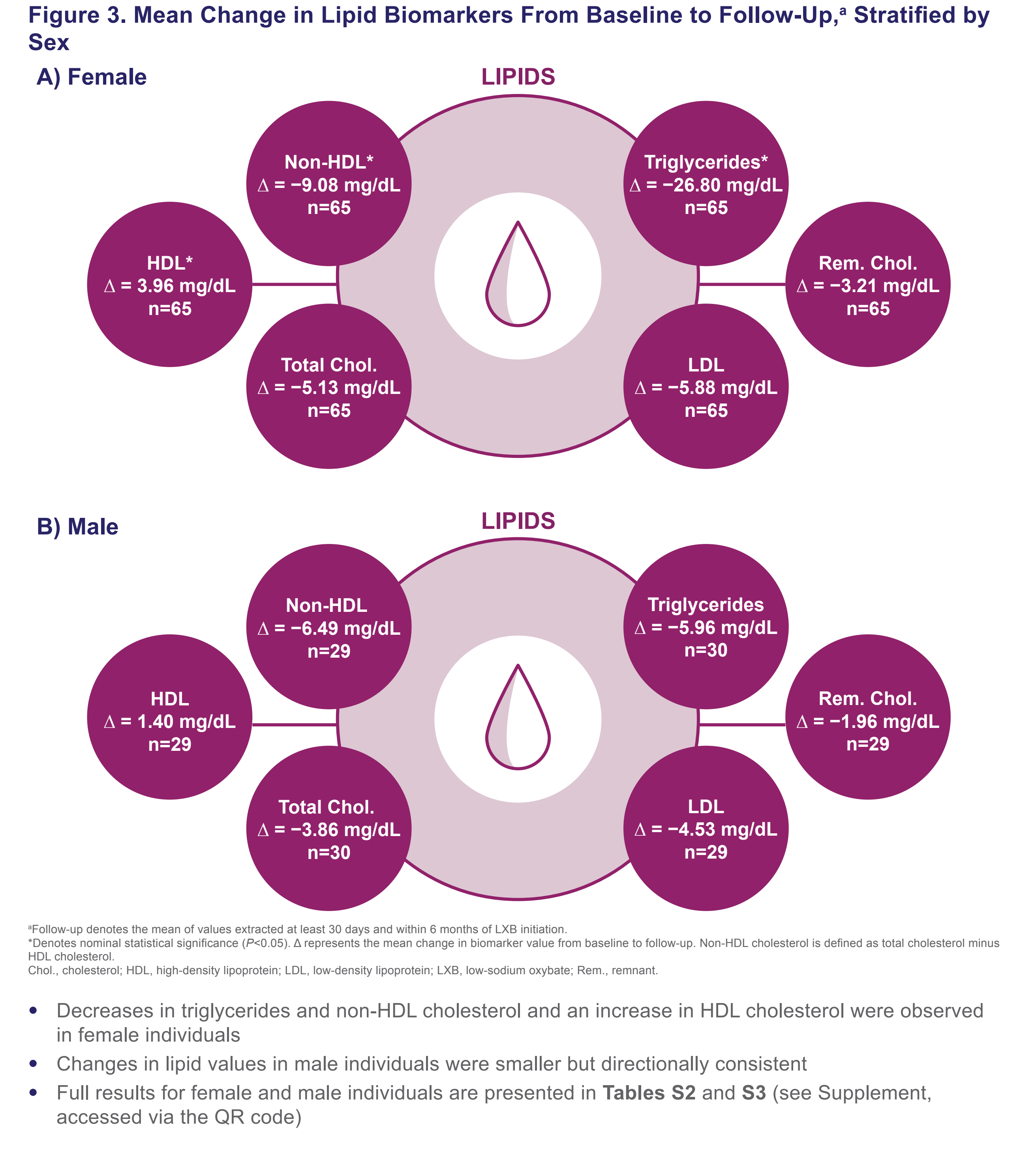
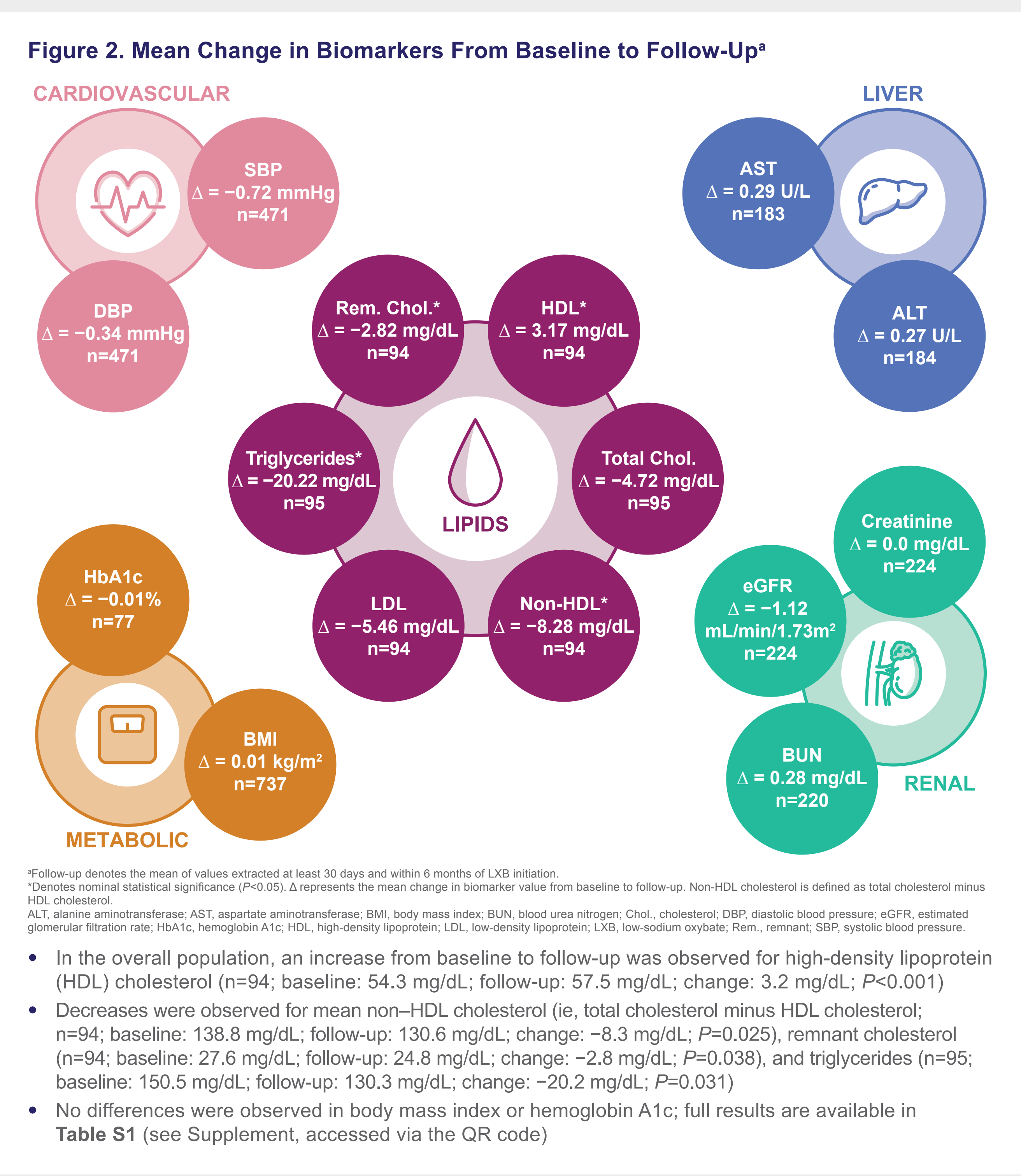
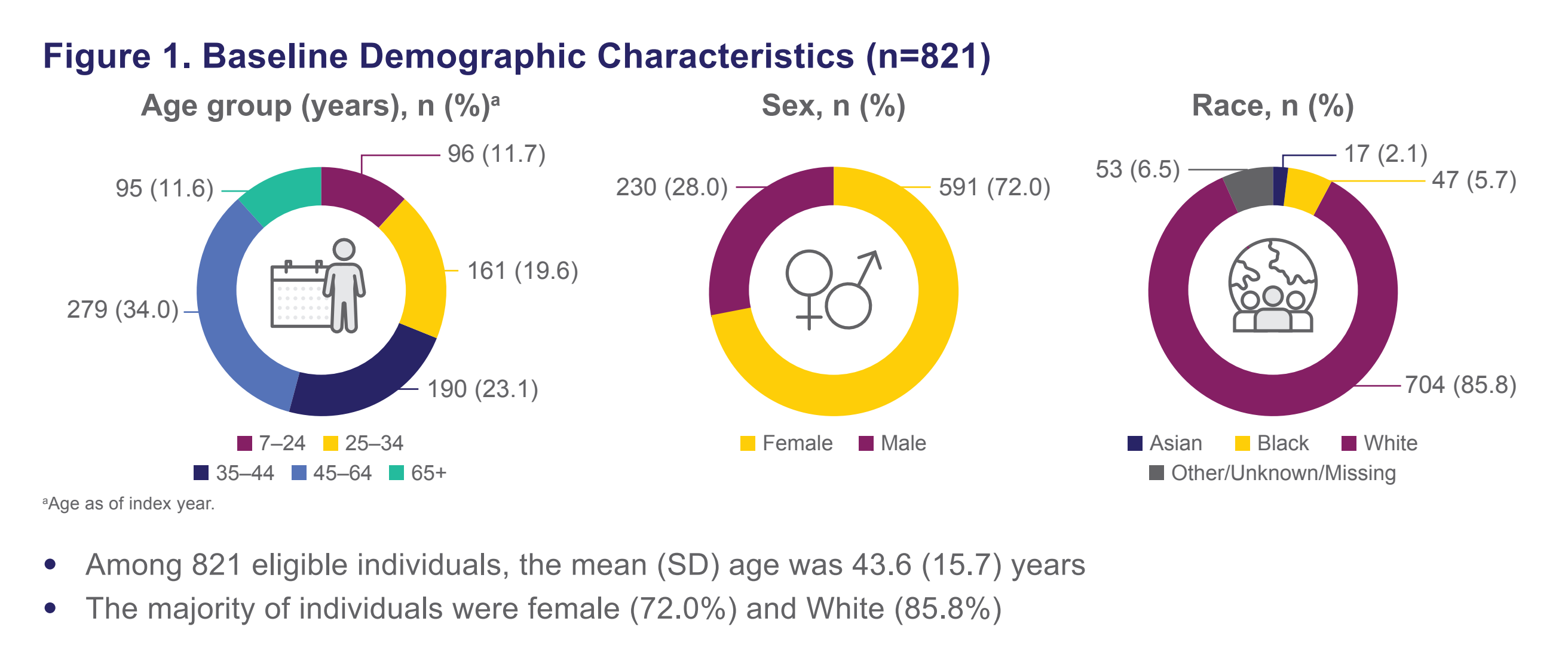
Introduction

- Compared with the general population, individuals with narcolepsy and idiopathic hypersomnia have an increased cardiovascular (CV), cardiometabolic (CM), and renal burden and an elevated risk of developing CV and CM comorbidities¹⁻⁵
- Low-sodium oxybate (LXB; Xywav®) is approved by the US Food and Drug Administration for the treatment of cataplexy or excessive daytime sleepiness in patients aged ≥7 years with narcolepsy and for the treatment of idiopathic hypersomnia in adults⁶
 - High-sodium oxybate (SXB) is also approved for the treatment of cataplexy or excessive daytime sleepiness in patients aged ≥7 years with narcolepsy⁷
- Health authorities, including the American College of Cardiology/American Heart Association, recommend a maximum daily sodium intake of 2300 mg, with an ideal limit of no more than 1500 mg per day for most adults, to protect CV health^{8,9}
 - Containing 92% less sodium than SXB, LXB contributes 131 mg of sodium at a 9 g dosage, compared with 1640 mg of sodium contributed by an equivalent dosage of SXB¹⁰
 - An open-label, phase 4 switch study in narcolepsy showed that switching from SXB to LXB was associated with clinically meaningful reductions in ambulatory systolic blood pressure (SBP)¹¹

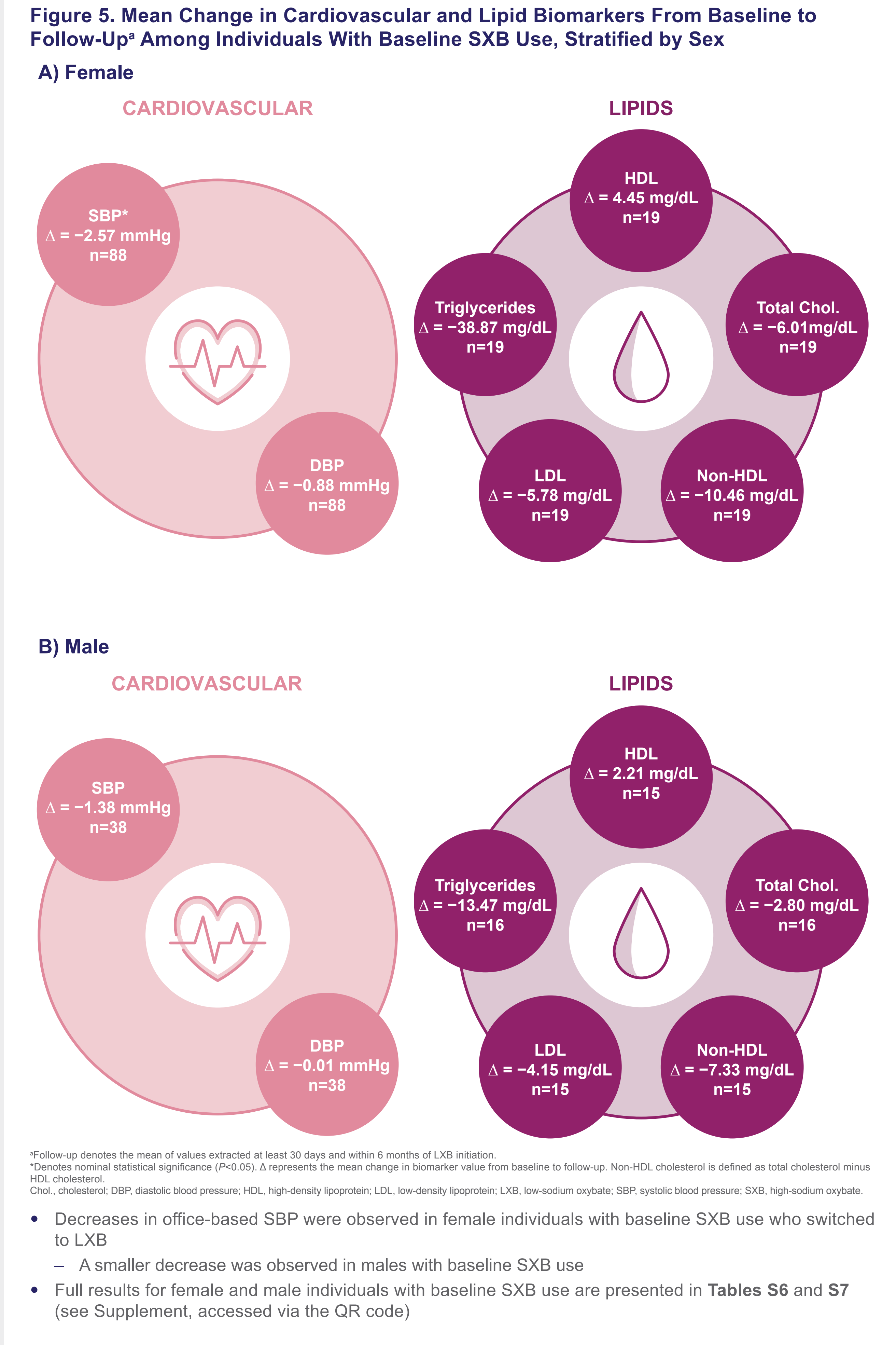
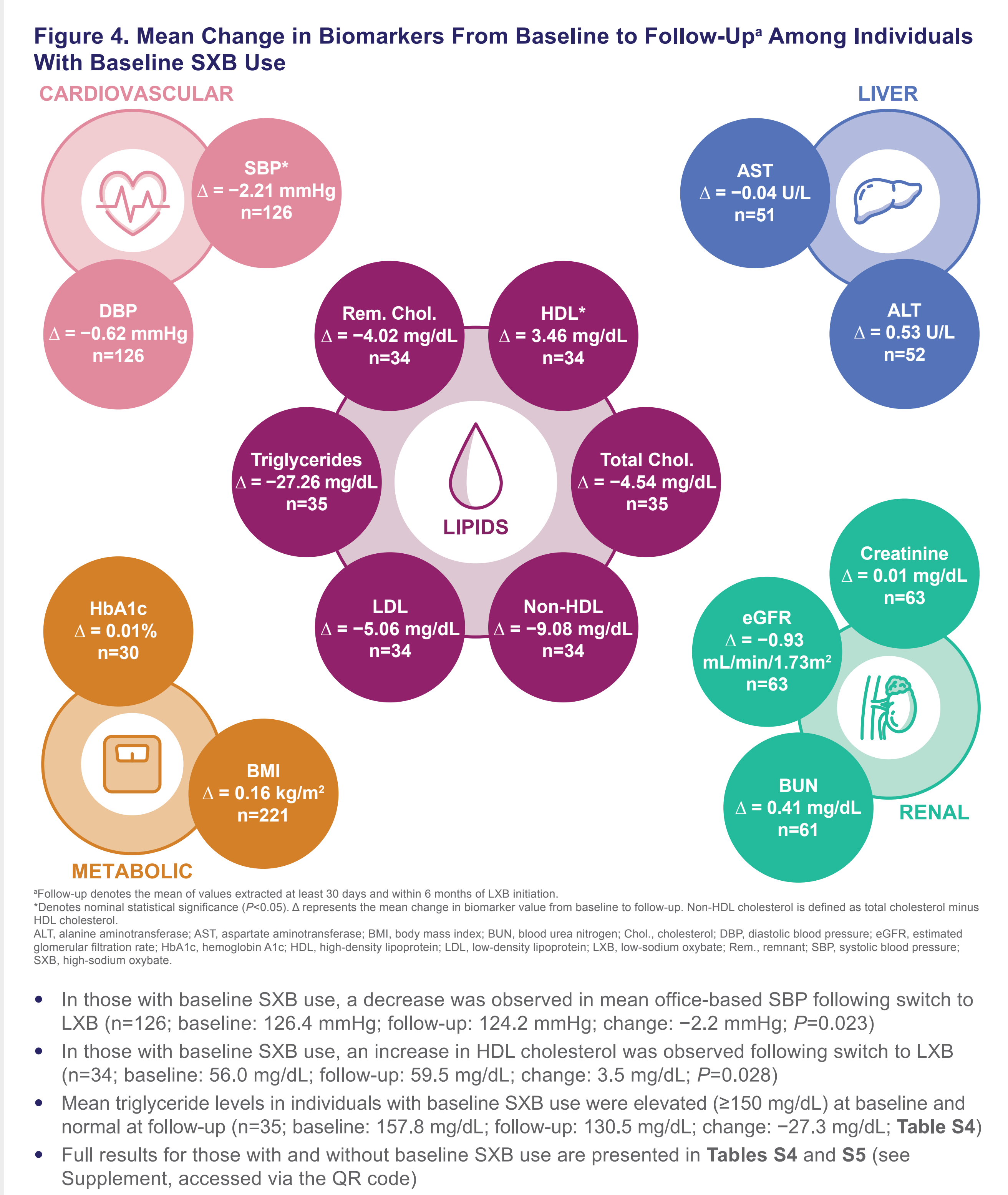
Methods

- This retrospective pre–post study used electronic health records (EHRs) in the Optum® Market Clarity database
- Individuals with ≥1 pharmacy claim for LXB from July 21, 2020–December 31, 2023 (index date) and ≥1 laboratory value for ≥1 of the biomarkers of interest during the baseline (12 months pre-index) and follow-up (6 months post-index) periods were included
- Baseline values of common CV, metabolic, lipid, and liver biomarkers were calculated as the mean of all values observed for each individual during the baseline period
 - Blood pressure measurements reflect office-based assessments recorded in the EHR

Results



- Follow-up biomarker values were extracted ≥30 days, but within 6 months, after the index date and calculated as the mean of all values observed within each outcome for each individual during the follow-up period
- Analyses (mean change from baseline to follow-up) were conducted overall and stratified by sex and baseline SXB (Xyrem) use
 - Paired t-tests were used to compare differences between baseline and follow-up periods; P values are nominal



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Supplemental Results

Supplemental Table S1. Biomarker Changes, Overall Population

	n	Baseline, mean (SD)	Follow-up, mean (SD)	Raw change, mean	P value
DBP, mmHg	471	76.7 (7.9)	76.4 (8.8)	−0.34	0.334
SBP, mmHg	471	123.6 (12.8)	122.9 (13.1)	−0.72	0.152
BMI, kg/m²	737	29.4 (7.8)	29.4 (7.9)	0.01	0.898
HbA1c, %	77	6.3 (1.3)	6.3 (1.2)	−0.01	0.886
LDL cholesterol, mg/dL	94	111.2 (37.1)	105.8 (31.0)	−5.46	0.089
HDL cholesterol, mg/dL	94	54.3 (14.5)	57.5 (16.2)	3.17	<0.001
Non-HDL cholesterol, mg/dL	94	138.8 (42.4)	130.6 (35.6)	−8.28	0.025
Total cholesterol, mg/dL	95	192.9 (42.4)	188.2 (36.6)	−4.72	0.221
Remnant cholesterol, mg/dL	94	27.6 (21.1)	24.8 (16.0)	−2.82	0.038
Triglycerides, mg/dL	95	150.5 (165.4)	130.3 (104.0)	−20.22	0.031
eGFR, mL/min/1.73m²	224	90.1 (15.1)	89.0 (16.2)	−1.12	0.054
Creatinine, mg/dL	224	0.9 (0.3)	0.9 (0.3)	0.00	0.925
BUN, mg/dL	220	14.7 (6.4)	15.0 (6.1)	0.28	0.306
AST, U/L	183	22.6 (9.4)	22.9 (11.4)	0.29	0.744
ALT, U/L	184	24.7 (13.5)	24.9 (17.1)	0.27	0.828

Statistically significant changes (P<0.05) are indicated in bold. Non-HDL cholesterol is defined as total cholesterol minus HDL cholesterol.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; BUN, blood urea nitrogen; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HbA1C, hemoglobin A1c; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SBP, systolic blood pressure; SD, standard deviation.

Supplemental Table S2. Biomarker Changes, Female Individuals

	n	Baseline, mean (SD)	Follow-up, mean (SD)	Raw change, mean	P value
DBP, mmHg	335	76.13 (7.74)	75.74 (8.56)	−0.38	0.345
SBP, mmHg	335	122.02 (12.71)	121.06 (12.63)	−0.96	0.107
BMI, kg/m²	532	29.39 (7.72)	29.33 (7.83)	−0.06	0.573
HbA1c, %	52	6.28 (1.37)	6.22 (1.37)	−0.06	0.625
LDL cholesterol, mg/dL	65	110.00 (34.43)	104.12 (28.57)	−5.88	0.124
HDL cholesterol, mg/dL	65	56.22 (14.00)	60.18 (16.47)	3.96	0.002
Non-HDL cholesterol, mg/dL	65	138.42 (41.79)	129.34 (34.91)	−9.08	0.036
Total cholesterol, mg/dL	65	194.64 (38.40)	189.52 (34.49)	−5.13	0.255
Remnant cholesterol, mg/dL	65	28.43 (23.96)	25.22 (17.77)	−3.21	0.057
Triglycerides, mg/dL	65	160.59 (195.16)	133.79 (119.82)	−26.80	0.034
eGFR, mL/min/1.73m²	166	90.82 (13.04)	89.17 (14.3)	−1.65	0.005
Creatinine, mg/dL	166	0.83 (0.23)	0.83 (0.22)	0.01	0.586
BUN, mg/dL	163	13.49 (5.19)	13.80 (5.38)	0.31	0.298
AST, U/L	137	22.09 (9.99)	21.79 (9.64)	−0.30	0.758
ALT, U/L	137	23.30 (13.24)	23.22 (15.60)	−0.08	0.951

Statistically significant changes (P<0.05) are indicated in bold. Non-HDL cholesterol is defined as total cholesterol minus HDL cholesterol.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; BUN, blood urea nitrogen; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HbA1C, hemoglobin A1c; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SBP, systolic blood pressure; SD, standard deviation.

Supplemental Table S3. Biomarker Changes, Male Individuals

	n	Baseline, mean (SD)	Follow-up, mean (SD)	Raw change, mean	P value
DBP, mmHg	136	78.13 (8.19)	77.92 (9.09)	−0.22	0.747
SBP, mmHg	136	127.55 (12.14)	127.42 (13.03)	−0.12	0.896
BMI, kg/m²	205	29.55 (7.85)	29.74 (7.92)	0.19	0.156
HbA1c, %	25	6.32 (1.00)	6.41 (0.89)	0.09	0.561
LDL cholesterol, mg/dL	29	114.03 (43.03)	109.50 (36.19)	−4.53	0.456
HDL cholesterol, mg/dL	29	50.09 (15.03)	51.49 (13.89)	1.40	0.296
Non-HDL cholesterol, mg/dL	29	139.74 (44.48)	133.26 (37.51)	−6.49	0.369
Total cholesterol, mg/dL	30	189.07 (50.36)	185.22 (41.23)	−3.86	0.609
Remnant cholesterol, mg/dL	29	25.72 (12.45)	23.76 (11.13)	−1.96	0.401
Triglycerides, mg/dL	30	128.72 (62.17)	122.77 (57.30)	−5.96	0.617
eGFR, mL/min/1.73m²	58	88.09 (19.70)	88.49 (20.73)	0.40	0.786
Creatinine, mg/dL	58	1.11 (0.43)	1.09 (0.34)	−0.02	0.407
BUN, mg/dL	57	18.13 (8.09)	18.34 (6.77)	0.21	0.747
AST, U/L	46	24.15 (7.29)	26.20 (15.07)	2.05	0.322
ALT, U/L	47	28.67 (13.51)	29.95 (20.10)	1.28	0.628

Non-HDL cholesterol is defined as total cholesterol minus HDL cholesterol.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; BUN, blood urea nitrogen; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HbA1C, hemoglobin A1c; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SBP, systolic blood pressure; SD, standard deviation.

Supplemental Table S4. Biomarker Changes, Individuals With Baseline SXB Use

	n	Baseline, mean (SD)	Follow-up, mean (SD)	Raw change, mean	P value
DBP, mmHg	126	77.59 (8.29)	76.97 (7.96)	−0.62	0.280
SBP, mmHg	126	126.44 (12.43)	124.23 (12.22)	−2.21	0.023
BMI, kg/m²	221	29.21 (7.73)	29.38 (7.83)	0.16	0.270
HbA1c, %	30	6.21 (1.08)	6.32 (1.32)	0.10	0.389
LDL cholesterol, mg/dL	34	104.96 (30.41)	99.90 (31.93)	−5.06	0.310
HDL cholesterol, mg/dL	34	56.03 (16.20)	59.49 (18.73)	3.46	0.028
Non-HDL cholesterol, mg/dL	34	132.96 (37.96)	123.88 (35.60)	−9.08	0.151
Total cholesterol, mg/dL	35	188.36 (36.09)	183.81 (37.43)	−4.54	0.487
Remnant cholesterol, mg/dL	34	28.00 (28.10)	23.98 (19.09)	−4.02	0.143
Triglycerides, mg/dL	35	157.76 (239.23)	130.50 (141.07)	−27.26	0.183
eGFR, mL/min/1.73m²	63	88.19 (13.56)	87.26 (15.88)	−0.93	0.418
Creatinine, mg/dL	63	0.91 (0.22)	0.92 (0.26)	0.01	0.635
BUN, mg/dL	61	15.73 (5.08)	16.14 (6.08)	0.41	0.434
AST, U/L	51	23.87 (9.01)	23.83 (10.58)	−0.04	0.977
ALT, U/L	52	27.05 (14.06)	27.58 (18.25)	0.53	0.800

Statistically significant changes (P<0.05) are indicated in bold. Non-HDL cholesterol is defined as total cholesterol minus HDL cholesterol.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; BUN, blood urea nitrogen; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HbA1C, hemoglobin A1c; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SBP, systolic blood pressure; SD, standard deviation; SXB, high-sodium oxybate.

Supplemental Table S5. Biomarker Changes, Individuals Without Baseline SXB Use

	n	Baseline, mean (SD)	Follow-up, mean (SD)	Raw change, mean	P value
DBP, mmHg	154	76.16 (7.91)	76.40 (8.72)	0.23	0.703
SBP, mmHg	154	121.29 (12.64)	121.11 (11.92)	−0.18	0.810
BMI, kg/m²	224	29.32 (7.17)	29.16 (7.41)	−0.16	0.265
HbA1c, %	23	6.24 (1.41)	6.26 (1.40)	0.02	0.936
LDL cholesterol, mg/dL	28	108.08 (29.25)	103.04 (29.67)	−5.04	0.265
HDL cholesterol, mg/dL	28	52.57 (14.49)	55.07 (13.66)	2.51	0.127
Non-HDL cholesterol, mg/dL	28	136.43 (33.78)	126.45 (32.32)	−9.99	0.041
Total cholesterol, mg/dL	28	189.00 (37.23)	181.52 (36.67)	−7.48	0.150
Remnant cholesterol, mg/dL	28	28.35 (16.21)	23.41 (10.40)	−4.95	0.043
Triglycerides, mg/dL	28	149.12 (93.12)	119.73 (55.98)	−29.39	0.025
eGFR, mL/min/1.73m²	71	91.17 (14.56)	89.62 (15.43)	−1.55	0.103
Creatinine, mg/dL	71	0.89 (0.22)	0.90 (0.24)	0.01	0.510
BUN, mg/dL	70	13.04 (4.80)	13.26 (4.45)	0.23	0.595
AST, U/L	58	23.27 (12.09)	22.99 (14.75)	−0.28	0.902
ALT, U/L	58	24.69 (14.57)	25.52 (22.02)	0.83	0.784

Statistically significant changes (P<0.05) are indicated in bold. Non-HDL cholesterol is defined as total cholesterol minus HDL cholesterol.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; BUN, blood urea nitrogen; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HbA1C, hemoglobin A1c; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SBP, systolic blood pressure; SD, standard deviation; SXB, high-sodium oxybate.

Supplemental Table S6. Biomarker Changes, Females With Baseline SXB Use

	n	Baseline, mean (SD)	Follow-up, mean (SD)	Raw change, mean	P value
DBP, mmHg	88	77.04 (7.73)	76.17 (8.02)	−0.88	0.176
SBP, mmHg	88	124.89 (12.40)	122.32 (12.55)	−2.57	0.027
BMI, kg/m²	156	29.40 (8.21)	29.48 (8.30)	0.08	0.667
HbA1c, %	21	6.27 (1.22)	6.38 (1.49)	0.11	0.501
LDL cholesterol, mg/dL	19	94.62 (23.42)	88.84 (24.99)	−5.78	0.366
HDL cholesterol, mg/dL	19	59.08 (15.73)	63.53 (19.31)	4.45	0.076
Non-HDL cholesterol, mg/dL	19	125.98 (37.41)	115.53 (33.57)	−10.46	0.244
Total cholesterol, mg/dL	19	185.06 (30.96)	179.05 (34.22)	−6.01	0.543
Triglycerides, mg/dL	19	191.61 (320.68)	152.74 (187.44)	−38.87	0.287
eGFR, mL/min/1.73m²	41	88.86 (8.47)	87.15 (9.15)	−1.71	0.101
Creatinine, mg/dL	41	0.80 (0.14)	0.81 (0.17)	0.01	0.593
BUN, mg/dL	39	14.20 (3.96)	14.06 (4.56)	−0.14	0.769
AST, U/L	31	24.55 (10.26)	23.97 (12.06)	−0.58	0.759
ALT, U/L	31	27.99 (16.17)	28.55 (19.67)	0.56	0.839

Statistically significant changes (P<0.05) are indicated in bold. Non-HDL cholesterol is defined as total cholesterol minus HDL cholesterol.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; BUN, blood urea nitrogen; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HbA1C, hemoglobin A1c; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SBP, systolic blood pressure; SD, standard deviation; SXB, high-sodium oxybate.

Supplemental Table S7. Biomarker Changes, Males With Baseline SXB Use

	n	Baseline, mean (SD)	Follow-up, mean (SD)	Raw change, mean	P value
DBP, mmHg	38	78.85 (9.46)	78.85 (7.59)	−0.01	0.996
SBP, mmHg	38	130.01 (11.89)	128.64 (10.27)	−1.38	0.442
BMI, kg/m²	65	28.76 (6.48)	29.12 (6.64)	0.36	0.092
HbA1c, %	9	6.08 (0.69)	6.18 (0.87)	0.09	0.575
LDL cholesterol, mg/dL	15	118.05 (33.84)	113.90 (34.98)	−4.15	0.615
HDL cholesterol, mg/dL	15	52.16 (16.49)	54.37 (17.24)	2.21	0.207
Non-HDL cholesterol, mg/dL	15	141.79 (38.06)	134.46 (36.39)	−7.33	0.427
Total cholesterol, mg/dL	16	192.27 (42.10)	189.47 (41.33)	−2.80	0.749
Triglycerides, mg/dL	16	117.56 (56.07)	104.09 (39.67)	−13.47	0.337
eGFR, mL/min/1.73m²	22	86.94 (20.10)	87.47 (24.19)	0.52	0.847
Creatinine, mg/dL	22	1.10 (0.20)	1.11 (0.29)	0.01	0.869
BUN, mg/dL	22	18.45 (5.77)	19.83 (6.77)	1.38	0.252
AST, U/L	20	22.80 (6.75)	23.62 (8.06)	0.81	0.511
ALT, U/L	21	25.65 (10.41)	26.14 (16.30)	0.49	0.883

Non-HDL cholesterol is defined as total cholesterol minus HDL cholesterol.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; BUN, blood urea nitrogen; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HbA1C, hemoglobin A1c; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SBP, systolic blood pressure; SD, standard deviation; SXB, high-sodium oxybate.

