

# **SUPPLEMENTAL MATERIAL**

**Table S1. Cross-Tabulation of Obesity with BMI Variability and Metabolic Health with Metabolic Health Variability.**

	Stable BMI (BMI VIM in quintile 1-4)	Variable BMI (BMI VIM in quintile 5)
Non-obese (BMI < 30 kg/m <sup>2</sup> )	Stable BMI, non-obese <b>(SNO)</b>	Variable BMI, non-obese <b>(VNO)</b>
Obese (BMI ≥ 30 kg/m <sup>2</sup> )	Stable BMI, obese <b>(SO)</b>	Variable BMI, obese <b>(VO)</b>
	Stable Metabolic Health (<2 metabolic health conditions with VIM in quintile 5)	Variable Metabolic Health (≥2 metabolic health conditions with VIM in quintile 5)
Metabolically healthy (<2 metabolic health conditions)	Stable metabolic health, metabolically healthy <b>(SMH)</b>	Variable metabolic health, metabolically healthy <b>(VMH)</b>
Metabolically unhealthy (≥2 metabolic health conditions)	Stable metabolic health, metabolically unhealthy <b>(SMU)</b>	Variable metabolic health, metabolically unhealthy <b>(VMU)</b>

**Table S2. Baseline Characteristics of Offspring Cohort Participants Included In and Excluded From the Analysis.**

	Included	Excluded
n	3,632	1,492
Men*	1,669 (46.0)	814 (54.6)
Age, years†	34.8 (9.9)	40.0 (10.9)
BMI, kg/m <sup>2</sup> †	25.1 (4.3)	26.1 (4.7)
With obesity*	428 (11.8)	258 (17.3)
Serum triglycerides, mg/dL†	91.9 (62.8)	119.0 (117.9)
High triglycerides*	430 (12.0)	306 (21.0)
Serum HDL, mg/dL†	51.3 (14.6)	48.5 (14.7)
Low HDL*	1,196 (33.6)	597 (41.0)
Systolic blood pressure, mm Hg†	120.0 (14.7)	126.6 (19.4)
Diastolic blood pressure, mm Hg†	77.6 (10.1)	81.1 (12.2)
High blood pressure*	1,782 (49.2)	929 (62.6)
Blood glucose, mg/dL†	100.8 (10.6)	105.9 (23.7)
High glucose*	50 (1.4)	97 (6.8)
Education, years†	14.1 (2.6)	13.2 (2.6)
Smoking*		
Never	1,236 (35.2)	344 (23.4)
Former	749 (21.3)	220 (15.0)
Current	1,527 (43.5)	904 (61.7)
Death prior to examination 4†	0 (0.0)	239 (16.0)

\*Presented as n (%)

†Presented as mean (S.D)

**Table S3. Associations of Obesity, Metabolic Health Status, and Coefficient of Variability-Defined Variability of Body Mass Index and Metabolic Health with Risk of Incident Obesity and Metabolically Unhealthy State, Framingham Offspring Examination 4-Examination 9.**

	Incident Obesity					Incident Metabolically Unhealthy State				
	Cases	Rate*	HR†	95% CI	$P_{\text{difference}}‡$	Cases	Rate*	HR†	95% CI	$P_{\text{difference}}§$
Obesity										
SNO	397	498.5	1.00	Reference	<0.0001	505	1,290.6	1.00	Reference	<0.0001
VNO	170	1,882.6	3.47	2.67, 4.53		95	2,004.2	1.75	1.32, 2.32	
SO						80	2,564.1	1.84	1.37, 2.48	0.30
VO						79	2,668.9	2.27	1.69, 3.05	
Metabolic health										
SMH	247	511.1	1.00	Reference	0.45	599	1,484.9	1.00	Reference	0.60
VMH	69	552.0	1.12	0.84, 1.48		160	1664.9	1.06	0.86, 1.29	
SMU	152	883.7	1.64	1.27, 2.13	0.21					
VMU	89	963.2	2.00	1.53, 2.60						

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CI, confidence interval; HR, hazard ratio; SMH, stable metabolic health, metabolically healthy; SMU, stable metabolic health, metabolically unhealthy; SNO, stable BMI, without obesity; SO, stable BMI, with obesity; VMH, variable metabolic health, metabolically healthy; VMU, variable metabolic health, metabolically unhealthy; VNO, variable BMI, without obesity; VO, variable BMI, with obesity.

\*Crude rate per 10,000 person-periods.

†Adjusted for age, sex, examination, education, smoking status, physical activity index, and BMI.

‡P-value comparing association of stability with diabetes to that of variability within a given obesity/metabolic health status

§Adjusted for age, sex, examination, education, smoking status, physical activity index, systolic blood pressure, diastolic blood pressure, current antihypertensive medication use, HDL, triglycerides, blood glucose, current use of antidiabetic medication.

**Table S4. Associations of Obesity, Metabolic Health Status, and Coefficient of Variability-Defined Variability of Body Mass Index and Metabolic Health with Risk of Incident Diabetes and Hypertension, Framingham Offspring Examination 4-Examination 9.**

	Incident Diabetes					Incident Hypertension				
	Cases	Rate*	HR†	95% CI	<i>P</i> <sub>difference‡</sub>	Cases	Rate*	HR†	95% CI	<i>P</i> <sub>difference‡</sub>
<b>Obesity</b>										
SNO	113	135.0	1.00	Reference	0.009	324	1,682.2	1.00	Reference	0.002
VNO	25	211.1	1.92	1.18, 3.14		85	2,698.4	1.67	1.21, 2.31	
SO	92	555.6	3.05	2.24, 4.15	0.87	33	4,177.2	2.46	1.39, 4.37	0.70
VO	42	361.4	2.94	1.94, 4.46		61	4,326.2	2.15	1.41, 3.28	
<b>Metabolic health</b>										
SMH	68	101.9	1.00	Reference	0.93	350	1,909.4	1.00	Reference	0.35
VMH	13	104.0	0.97	0.53, 1.79		75	1,879.7	0.87	0.65, 1.17	
SMU	147	477.7	3.33	2.41, 4.60	0.21	50	3,546.1	1.74	1.19, 2.54	0.46
VMU	41	344.8	2.62	1.71, 4.01		21	3,962.3	1.30	0.64, 2.65	

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CI, confidence interval; HR, hazard ratio; SMH, stable metabolic health, metabolically healthy; SMU, stable metabolic health, metabolically unhealthy; SNO, stable BMI, without obesity; SO, stable BMI, with obesity; VMH, variable metabolic health, metabolically healthy; VMU, variable metabolic health, metabolically unhealthy; VNO, variable BMI, without obesity; VO, variable BMI, with obesity.

\*Crude rate per 10,000 person-periods

†Adjusted for age, sex, examination, education, smoking status, and physical activity index

‡P-value comparing association of stability with diabetes to that of variability within a given obesity/metabolic health status

**Table S5. Associations of Obesity, Metabolic Health Status, and Coefficient of Variability-Defined Variability of Body Mass Index and Metabolic Health with Risk of Incident Cardiovascular Disease and Chronic Kidney Disease, Framingham Offspring Examination 4-Examination 9.**

	Incident Cardiovascular Disease					Incident Chronic Kidney Disease				
	Cases	Rate*	HR†	95% CI	<i>P</i> <sub>difference‡</sub>	Cases	Rate*	HR†	95% CI	<i>P</i> <sub>difference‡</sub>
<b>Obesity</b>										
SNO	351	90.7	1.00	Reference	0.38	114	184.3	1.00	Reference	0.87
VNO	30	51.3	0.84	0.57, 1.34		9	90.0	0.94	0.44, 2.00	
SO	143	156.0	1.25	1.03, 1.53	0.98	52	344.8	1.47	1.00, 2.15	0.95
VO	64	98.8	1.25	0.94, 1.65		20	174.1	1.44	0.84, 2.47	
<b>Metabolic health</b>										
SMH	180	59.6	1.00	Reference	0.44	55	122.6	1.00	Reference	0.57
VMH	40	70.3	1.14	0.81, 1.61		16	114.4	0.85	0.48, 1.50	
SMU	220	138.3	1.68	1.37, 2.06	0.0006	58	256.0	1.26	0.84, 1.91	0.01
VMU	145	190.4	2.44	1.94, 3.06		65	398.3	2.11	1.39, 3.21	

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CI, confidence interval; CKD, chronic kidney disease; CVD, cardiovascular disease; HR, hazard ratio; SMH, stable metabolic health, metabolically healthy; SMU, stable metabolic health, metabolically unhealthy; SNO, stable BMI, without obesity; SO, stable BMI, with obesity; VMH, variable metabolic health, metabolically healthy; VMU, variable metabolic health, metabolically unhealthy; VNO, variable BMI, without obesity; VO, variable BMI, with obesity.

\*Crude rate per 10,000 person-years

†Adjusted for age, sex, examination, education, smoking status, and physical activity index

‡P-value comparing association of stability with diabetes to that of variability within a given obesity/metabolic health status

§Crude rate per 10,000 person-periods

**Table S6. Inverse Probability of Censoring-Weighted Associations of Obesity Sub-phenotypes with Risk of Obesity and Becoming Metabolically Unhealthy, Framingham Offspring Examination 4- Examination 9.**

Obesity Subphenotypes	Cases	Rate*	HR†	95% CI	$P_{\text{Interaction}\ddagger}$	Cases	Rate*	HR†	95% CI	$P_{\text{Interaction}\S}$
	Incident Obesity					Incident Metabolically Unhealthy State				
MHNO	316	519.5	1.00	Reference		605	1,378.8	1.00	Reference	
MUNO	241	911.5	1.98	1.63, 2.39						
MHO						166	2,707.9	2.02	1.64, 2.50	
MUO										
	Incident Diabetes					Incident Hypertension				
MHNO	49	73.7	1.00	Reference		358	1,737.0	1.00	Reference	
MUNO	88	320.2	4.94	3.27, 7.45		45	2,125.0	1.89	1.35, 2.65	
MHO	32	253.2	4.45	2.71, 7.29		67	4,012.0	2.19	1.66, 2.89	
MUO	100	664.9	10.49	7.07, 15.55		25	5,102.0	2.31	1.47, 3.62	
Obesity x MU			0.48	0.27, 0.86	0.01			0.56	0.31, 1.01	0.05
Obesity+MU			1.73	-0.80, 4.27	0.18			-0.77	-1.77, 0.22	0.13

	Cases	Rate*	HR†	95% CI	$P_{\text{interaction}}‡$	Cases	Rate*	HR†	95% CI	$P_{\text{interaction}}§$
	Incident Cardiovascular Disease					Incident Chronic Kidney Disease				
MHNO	170	29,717	1.00	Reference		53	4811	1.00	Reference	
MUNO	207	14,158	1.74	1.38, 2.20		69	2317	1.75	1.18, 2.59	
MHO	50	6,113	1.33	0.93, 1.91		18	1065	1.60	0.87, 2.93	
MUO	157	9,304	2.45	1.90, 3.16		54	1570	2.97	1.94, 4.56	
Obesity x MU			1.06	0.79, 1.42	0.71			1.06	0.51, 2.21	0.87
Obeisty+MU			0.06	-0.35, 0.47	0.79			0.62	0.10, 1.15	0.02

CI, confidence interval; HR, hazard ratio; SMH, stable metabolic health, metabolically healthy; SMU, stable metabolic health, metabolically unhealthy; RERI, relative excess risk due to interaction; SNO, stable BMI, without obesity; SO, stable BMI, with obesity; VMH, variable metabolic health, metabolically healthy; VMU, variable metabolic health, metabolically unhealthy; VNO, variable BMI, without obesity; VO, variable BMI, with obesity.

\*Crude rate per 10,000 person-periods.

†Adjusted for age, sex, exam, education, smoking status, physical activity index, and BMI.

‡P-value for the multiplicative interaction between obesity and the metabolically unhealthy state

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§Adjusted for age, sex, exam, education, smoking status, physical activity index, systolic blood pressure, diastolic blood pressure, current antihypertensive medication use, HDL, triglycerides, blood glucose, current use of antidiabetic medication.

**Table S7. Inverse Probability of Censoring-Weighted Associations of Obesity, Metabolic Health Status, and Variability of Body Mass Index and Metabolic Health with Risk of Incident Obesity and Metabolically Unhealthy State, Framingham Offspring Examination 4- Examination 9.**

	Incident Obesity					Incident Metabolically Unhealthy State				
	Cases	Rate*	HR†	95% CI	$P_{\text{difference}}‡$	Cases	Rate*	HR§	95% CI	$P_{\text{difference}}§$
Obesity										
SNO	390	510.3	1.00	Reference	0.04	483	1,291.4	1.00	Reference	<0.0001
VNO	177	1,444.9	1.26	1.01, 1.59		122	1,882.7	1.65	1.29, 2.11	
SO						97	2,607.5	1.15	0.87, 1.51	0.02
VO						69	2,863.1	1.89	1.35, 2.65	
Metabolic health										
SMH	247	501.9	1.00	Reference	0.12	629	1534.9	1.00	Reference	0.71
VMH	69	593.8	1.25	0.94, 1.67		142	1572.5	1.08	0.83, 1.31	
SMU	160	808.5	0.92	0.74, 1.13	0.49					
VMU	81	1,218.0	1.02	0.77, 1.33						

CI, confidence interval; HR, hazard ratio; SMH, stable metabolic health, metabolically healthy; SMU, stable metabolic health, metabolically unhealthy; SNO, stable BMI, without obesity; SO, stable BMI, with obesity; VMH, variable metabolic health,

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metabolically healthy; VMU, variable metabolic health, metabolically unhealthy; VNO, variable BMI, without obesity; VO, variable BMI, with obesity.

\*Crude rate per 10,000 person-periods.

†Adjusted for age, sex, examination, education, smoking status, physical activity index, and BMI.

‡P-value comparing association of stability with diabetes to that of variability within a given obesity/metabolic health status

§Adjusted for age, sex, examination, education, smoking status, physical activity index, systolic blood pressure, diastolic blood pressure, current antihypertensive medication use, HDL, triglycerides, blood glucose, current use of antidiabetic medication.

**Table S8. Inverse Probability of Censoring-Weighted Associations of Obesity, Metabolic Health Status, and Variability of Body Mass Index and Metabolic Health with Risk of Incident Diabetes and Hypertension, Framingham Offspring Examination 4-Examination 9.**

	Incident Diabetes					Incident Hypertension				
	Cases	Rate*	HR†	95% CI	$P_{\text{difference}}‡$	Cases	Rate*	HR†	95% CI	$P_{\text{difference}}§$
<b>Obesity</b>										
SNO	109	121.1	1.00	Reference	0.004	301	1,659.3	1.00	Reference	<0.0001
VNO	29	171.3	2.00	1.24, 3.21		108	2,529.3	1.67	1.31, 2.13	
SO	103	482.2	3.30	2.39, 4.55	0.62	41	3,831.8	1.86	1.29, 2.68	0.15
VO	31	282.1	2.86	1.76, 4.67		53	4,690.3	2.60	1.88, 3.59	
<b>Metabolic health</b>										
SMH	70	109.9	1.00	Reference	0.09	338	1,860.2	1.00	Reference	0.28
VMH	11	70.8	0.55	0.28, 1.10		87	2,096.4	1.16	0.90, 1.50	
SMU	152	476.3	3.47	2.46, 4.90	0.49	50	3,448.3	1.50	1.04, 2.19	0.46
VMU	36	334.9	3.01	1.91, 4.75		21	4,285.7	1.84	1.21, 2.80	

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CI, confidence interval; HR, hazard ratio; SMH, stable metabolic health, metabolically healthy; SMU, stable metabolic health, metabolically unhealthy; SNO, stable BMI, without obesity; SO, stable BMI, with obesity; VMH, variable metabolic health, metabolically healthy; VMU, variable metabolic health, metabolically unhealthy; VNO, variable BMI, without obesity; VO, variable BMI, with obesity.

\*Crude rate per 10,000 person-periods

†Adjusted for age, sex, examination, education, smoking status, and physical activity index

‡P-value comparing association of stability with diabetes to that of variability within a given obesity/metabolic health status

**Table S9. Inverse Probability of Censoring-Weighted Associations of Obesity, Metabolic Health Status, and Variability of Body Mass Index and Metabolic Health with Risk of Incident Cardiovascular Disease and Chronic Kidney Disease, Framingham Offspring Examination 4-Examination 9.**

	Incident Cardiovascular Disease					Incident Chronic Kidney Disease				
	Cases	Rate*	HR†	95% CI	<i>P</i> <sub>difference‡</sub>	Cases	Rate*	HR†	95% CI	<i>P</i> <sub>difference‡</sub>
<b>Obesity</b>										
SNO	344	92.2	1.00	Reference	0.41	113	190.1	1.00	Reference	0.75
VNO	37	51.2	0.84	0.57, 1.25		10	80.5	0.88	0.41, 1.88	
SO	157	149.3	1.31	1.04, 1.63	0.55	61	350.2	1.71	1.20, 2.45	0.70
VO	50	97.4	1.47	1.03, 2.12		11	63.1	1.47	0.71, 3.04	
<b>Metabolic health</b>										
SMH	179	61.9	1.00	Reference	0.69	60	125.5	1.00	Reference	0.84
VMH	41	58.8	1.08	0.73, 1.59		11	99.7	0.93	0.44, 1.97	
SMU	252	149.4	1.72	1.37, 2.15	0.24	80	288.9	1.66	1.14, 2.42	0.31
VMU	113	169.8	2.01	1.53, 2.65		43	380.9	2.07	1.31, 3.28	

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CI, confidence interval; HR, hazard ratio; SMH, stable metabolic health, metabolically healthy; SMU, stable metabolic health, metabolically unhealthy; SNO, stable BMI, without obesity; SO, stable BMI, with obesity; VMH, variable metabolic health, metabolically healthy; VMU, variable metabolic health, metabolically unhealthy; VNO, variable BMI, without obesity; VO, variable BMI, with obesity.

\*Crude rate per 10,000 person-periods

†Adjusted for age, sex, examination, education, smoking status, and physical activity index

‡P-value comparing association of stability with diabetes to that of variability within a given obesity/metabolic health status

§Crude rate per 10,000 person-periods