PSYCHOLOGICAL CORRELATES OF OBESITY

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CURRENT/RECENT SUPPORT

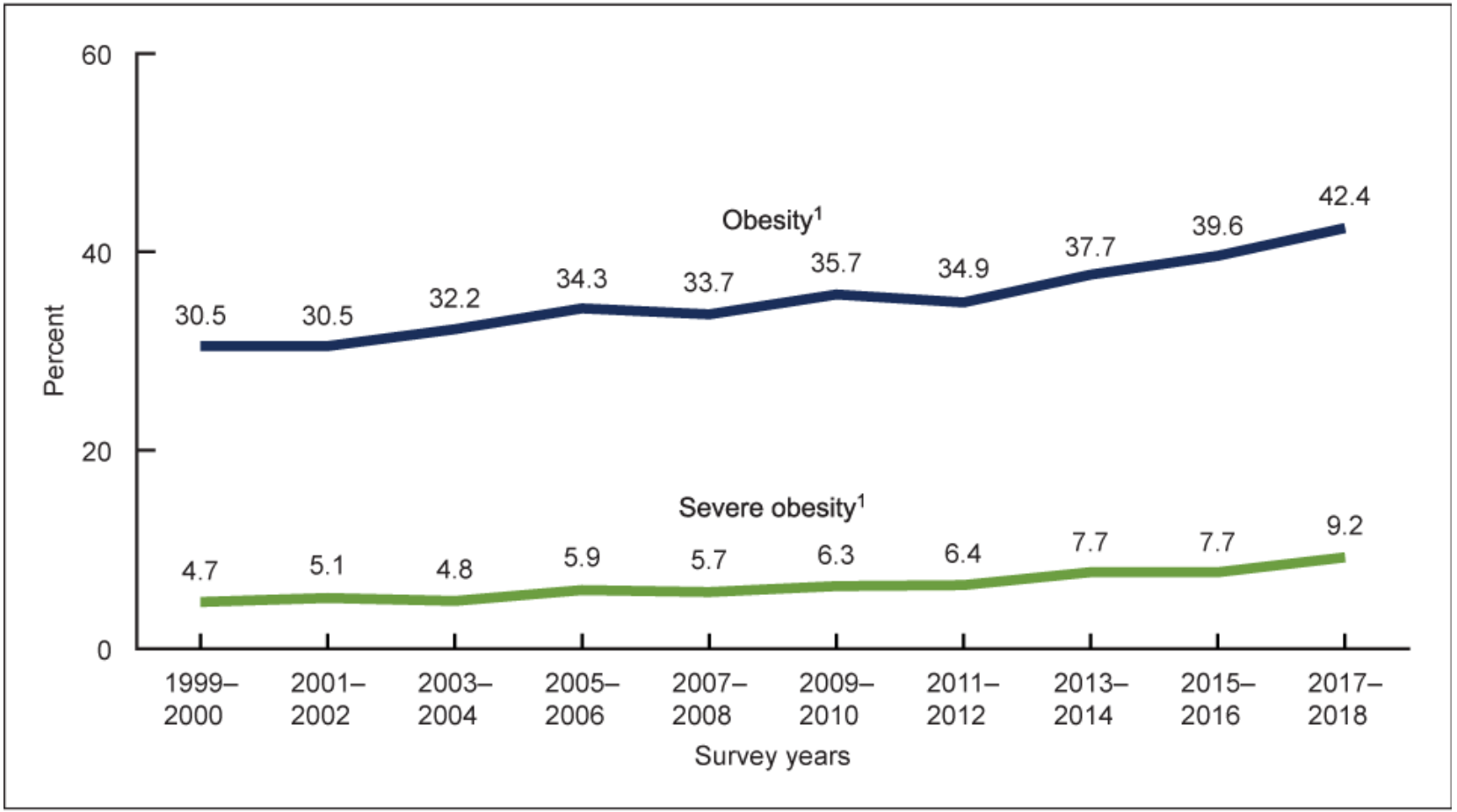
- RESEARCH: NovoNordisk; Eli Lilly, Inc; Epitomee Medical
- HONORARIA: NovoNordisk; Robard

LEARNING OBJECTIVES

- Describe the reciprocal relationship between obesity and depression
- Understand the moderators of risk for psychological disturbance in obesity
- Understand the psychosocial effects of weight loss
- Describe the current evidence regarding the relationship of suicidality to GLP-1 agonists

U.S. PREVALENCE OF ADULT OBESITY: 21st CENTURY

Figure 4. Trends in age-adjusted obesity and severe obesity prevalence among adults aged 20 and over: United States, 1999–2000 through 2017–2018



[1]Significant linear trend.

NOTES: Estimates were age adjusted by the direct method to the 2000 U.S. Census population using the age groups 20–39, 40–59, and 60 and over. Access data table for Figure 4 at: https://www.cdc.gov/nchs/data/databriefs/db360_tables-508.pdf#4.

SOURCE: NCHS, National Health and Nutrition Examination Survey, 1999–2018.

A VERY NUMEROUS AND DIVERSE POPULATION

- >40% OF U.S. ADULTS
- ALL GROUPS REPRESENTED, ALBEIT UNEQUALLY
- AVOID OVERGENERALIZATIONS
  - Differences from non-obese samples in averages or prevalence ≠ universal characteristics

MODERATORS OF RISK FOR PSYCHOLOGICAL DISTURBANCE IN OBESITY

- GENDER
- ETHNICITY
- BINGE EATING
- SEVERITY OF OBESITY
- FAT DISTRIBUTION?

PSYCHOLOGICAL CORRELATES OF OBESITY

- Psychiatric disorders

OBESITY AND DEPRESSION:
A BIDIRECTIONAL RELATIONSHIP

- 3-28 year follow-ups
- Among initially non-depressed subjects, obesity at baseline increases risk of later depression by 55%
- Among initially non-overweight subjects, depression at baseline increases risk of later obesity by 58%
- Adolescents:
  - Obesity at baseline increases risk of later depression by 40%
  - Depression at baseline increases risk of later obesity by 70%

Sources: Luppino et al, *Arch Gen Psychiatry*. 2010;67(3):220-229; Rajan TM and Menon V, *J Postgrad Med* 2017;63:182-190. Mannan M et al, *PLoS ONE*. 2016; 11(6): e0157240. doi:10.1371/journal.pone.0157240. *Simon et al, Arch Gen Psychiatry. 2006;63:824-830*

OBESITY AND DEPRESSION:
MODERATOR VARIABLES

- Reciprocal risks higher for females, especially white females
  - Among young adults, obesity increases depression risk for females (OR = 2.14) but *decreases* risk for males (OR = 0.31)
  - **Depression** predicts **obesity** *for adolescents* and young adults, but only among females
- Among women with BMI > 30, greater severity of obesity increases risk of depression and depression Sx (few data for men)
- Bariatric surgery candidates > others

Sources: McCarty et al,, *Gen Hosp Psychiatry.* 2009; 31, 442-450. Luppino et al, *Arch Gen Psychiatry*. 2010;67(3):220-229; Blaine B, *J Health Psychology. 2008;* 13(8) 1190–1197. Ma J, Xiao L, Obesity. 2010; 18(2):347-53. Rajan TM, Menon V, *J Postgrad Med* 2017;63:182-190.

LIFETIME PREVALENCE OF PSYCHIATRIC DISORDERS BY BMI IN **GENERAL POPULATION**

Table 2. Lifetime Prevalence of Selected Mental Disorders by BMI

Variable	Prevalence If BMI <30, %	Prevalence If BMI ≥30, %	OR (95% CI)
Lifetime			
Mood disorder	18.3	22.0	1.27 (1.15-1.41)
Major depression	16.0	18.6	1.21 (1.09-1.35)
Bipolar disorder	1.9	2.8	1.47 (1.12-1.93)
Anxiety disorder	9.8	12.3	1.28 (1.05-1.57)
Generalized anxiety	5.4	6.5	1.20 (0.99-1.47)
Panic or agoraphobia	5.6	7.1	1.27 (1.01-1.60)
Substance use disorder	15.6	12.8	0.78 (0.65-0.93)
Last 12 months			
Mood disorder	8.1	9.5	1.19 (1.00-1.42)
Major depression	6.6	7.2	1.09 (0.89-1.34)
Bipolar disorder	1.3	2.0	1.61 (1.07-2.43)
Anxiety disorder	5.3	7.0	1.34 (1.07-1.66)
Generalized anxiety	2.6	2.9	1.12 (0.77-1.64)
Panic or agoraphobia	3.1	4.6	1.50 (1.20-1.87)
Substance use disorder	4.3	2.9	0.65 (0.40-1.06)

Simon et al,
Arch Gen Psychiatry.
2006;63:824-830

TABLE 1. Lifetime and Current Axis I Disorders in Candidates for Weight Loss Surgery (N=288)

Disorder	Lifetime (%)	Current (%)
Mood disorders		
Major depressive disorder	42.0	10.4
Dysthymia (current only)		3.8
Bipolar I or bipolar II disorder	3.5	1.7
Any mood disorder	45.5	15.6
Anxiety disorders		
Panic disorder	19.4	5.9
Agoraphobia without panic	3.5	1.0
Social phobia	9.4	9.0
Specific phobia	8.0	7.3
OCD	3.8	2.1
PTSD	11.8	2.8
Generalized anxiety disorder (current only)		6.3
Any anxiety disorder	37.5	24.0
Substance use disorder		
Alcohol abuse	17.7	0.0
Alcohol dependence	13.2	0.7
Drug abuse	6.6	0.0
Drug dependence	9.4	1.0
Any substance disorder	32.6	1.7
Eating disorders		
Anorexia nervosa	0.0	0.0
Bulimia nervosa	3.5	0.3
Binge eating disorder	27.1	16.0
Any eating disorder	29.5	16.3
At least one axis I disorder	66.3	37.8
At least two axis I disorders	42.7	17.0
At least three axis I disorders	25.7	7.6

Kalarchian et al,
Am J Psychiatry 2007; 164:328–334

OBESITY AND ANXIETY DISORDERS

- Increase in risk of anxiety disorders with obesity
- Generally independent of sex, age, race
  - Inconsistent relation with sex
- GAD, panic disorder, agoraphobia

Sources: Gariepy G et al, International Journal of Obesity. 2010; 34, 407–419. *Simon et al, Arch Gen Psychiatry. 2006;63:824-830*

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Kalarchian et al,
Am J Psychiatry 2007; 164:328–334)

OBESITY AND SUBSTANCE USE DISORDERS

- Obesity ► decreased risk in general population (OR = 0.78)
- Increased prevalence among bariatric surgery applicants

Sources: Gariepy G et al, International Journal of Obesity. 2010; 34, 407–419. *Simon et al, Arch Gen Psychiatry. 2006;63:824-830.* Kalarchian et al, *Am J Psychiatry 2007; 164:328–334)*

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At least two axis I disorders	42.7	17.0
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Kalarchian et al,
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OBESITY AND ADHD

- Increased *prevalence of obesity given ADHD* for children (ORs = 1.13 -1.2) and adults (ORs = 1.37 - 1.55)
  - Effect greater in adults vs. children
- SEX DIFFS?
- DIRECTIONALITY?
  - ADHD precedes obesity in some studies
  - Abnormal and dysfunctional eating patterns more frequent in ADHD
  - “Food addiction” reported more prevalent in ADHD

Source: Cortese S, *Brain Sci.* **2019**, *9*, 256; doi:10.3390/brainsci9100256

BINGE EATING DISORDER (BED)

- Recurrent episodes of binge eating
  - Eating unusually large quantities of food
  - Subjective sense of loss-of-control
- Marked distress regarding the binge eating
- Episodes associated with ≥ 3 of:
  - Eating much more rapidly than normal
  - Eating until feeling uncomfortably full
  - Eating large amounts of food when not feeling physically hungry
  - Eating alone because of being embarrassed by how much one is eating
  - Feeling disgusted with oneself, depressed, or very guilty after overeating
- ≥ 1/week X 3 months
- Absence of extreme compensatory or purging behaviors that define bulimia nervosa

https://www.ncbi.nlm.nih.gov/books/NBK338301/table/introduction.t1/. Accessed 5-20-23

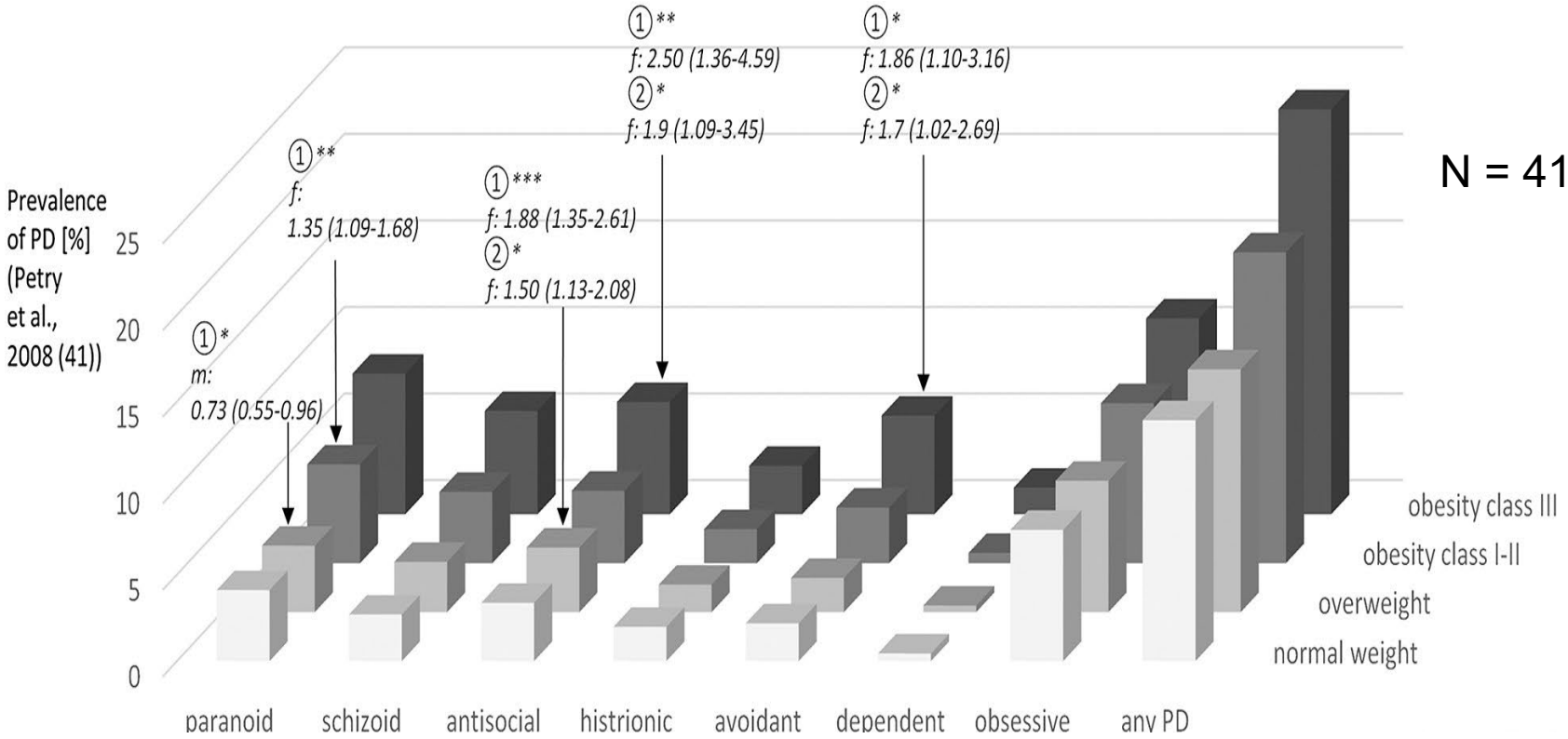
OBESITY AND BINGE EATING DISORDER

- Lifetime prevalence, general population (US):
  - Males: 0.42%
  - Females 1.25%
  - Prevalence estimates from questionnaires > vs. structured interview
- Prevalence higher with BMI > 30, more so with BMI > 40:
  - <30: 0.5%
  - 30-40: 1.4%
  - >40: 2.8%
- BED does not contraindicate obesity treatment
  - Patients with BED may lose less weight than those without, but lose significant weight

Sources: Udo T and Grilo CM, *Biol Psychiatry.* 2018;84:345-354. Peat CM, *European Eating Disorders Review*. 2017: https://doi.org/10.1002/erv.2517

OBESITY AND PERSONALITY DISORDERS:

National Epidemiologic Survey on Alcohol and Related Conditions



N = 41,654

Gerlach G et al, *Obesity Reviews. 2016;* 17: 691-723, based on Petry NM et al, *Psychosomatic Medicine. 2008;* 70: 288-297.

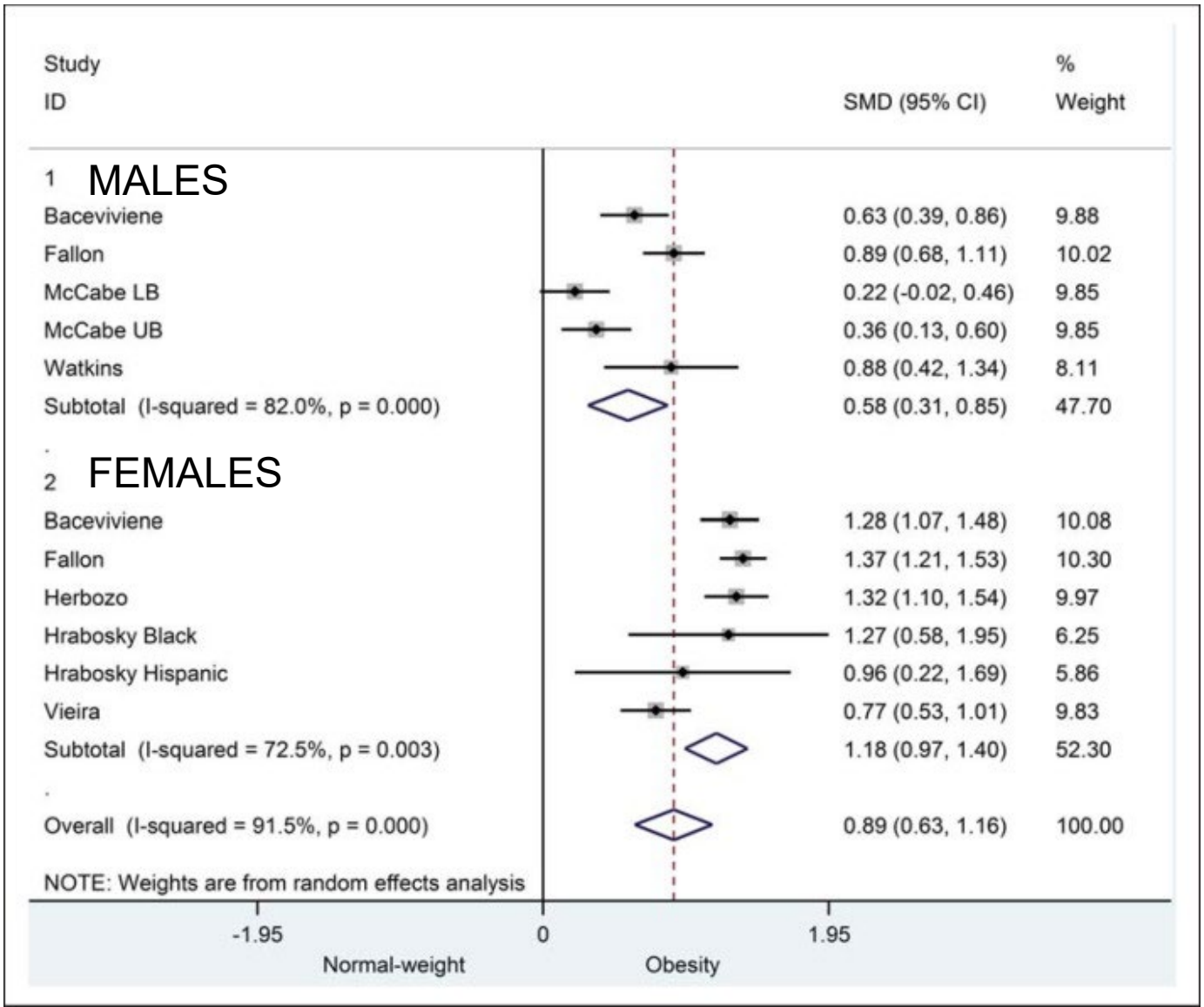
OBESITY AND *BORDERLINE* PERSONALITY DISORDER

FIRST AUTHOR	RECRUITMENT SITE	N	MEASURES	BPD%
Grana et al[18] 1989	Gastric surgery setting	150	CATI	2.2
Black et al[19] 1989	Gastric surgery setting	38	PDQ	18.4
Black et al[20] 1992	Gastric surgery setting	46	SIDP	30.4
Berman et al[21] 1992	Weight management program	56	SCID-II	7.1
			PDQ-R	25
Sansone et al[22] 1995	Primary care setting	61	DIB	7
			PDQ-R	25
Sansone et al[23] 1996	Eating disorder program	17	PDQ-R/DIB	62.5/41.2
	Primary care setting	60	PDQ-R/DIB	36.7/6.7
Sansone et al[24] 2001	Primary care setting	36	PDQ-4/SHI	27.8/27.8
	Outpatient mental health clinic	17	PDQ-4/SHI	94.1/58.8
Van Hanswijck de Jonge et al[16] 2003	Gastric surgery setting	37	IPDE	5.4
Sansone et al[25] 2008	Gastric surgery setting	121	SHI/PDQ-4/ MSI-BPD	14.0/14.0/7.4

Sansone RA and Sansone LA, Innov Clin Neurosci. 2013 Apr; 10(4): 36–40.

OBESITY AND BODY DISSATISFACTION:

Differences vs. non-obese subjects



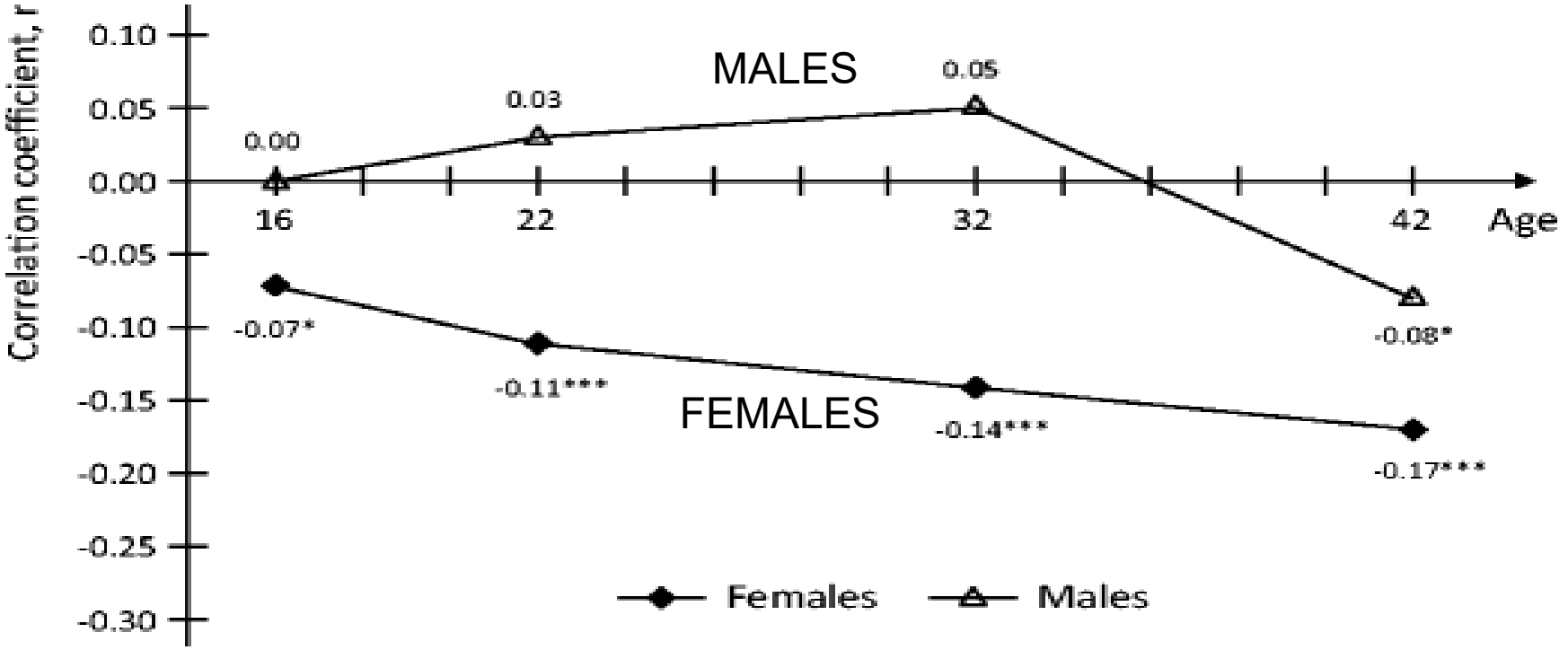
N = 13,508; multinational

Source: Weinberger N et al, *Obes Facts.* 2017; 9: 424–441.

SELF-ESTEEM AND OBESITY

- IMPAIRED SELF-ESTEEM AMONG ADULT TREATMENT-SEEKERS
- LOWER OVERALL SELF-ESTEEM AMONG OBESE ADOLESCENTS AND YOUNG ADULTS
- INCONSISTENT EFFECTS AMONG PRE-TEENS
- IMPAIRED SELF-ESTEEM MAY PREDICT WEIGHT GAIN

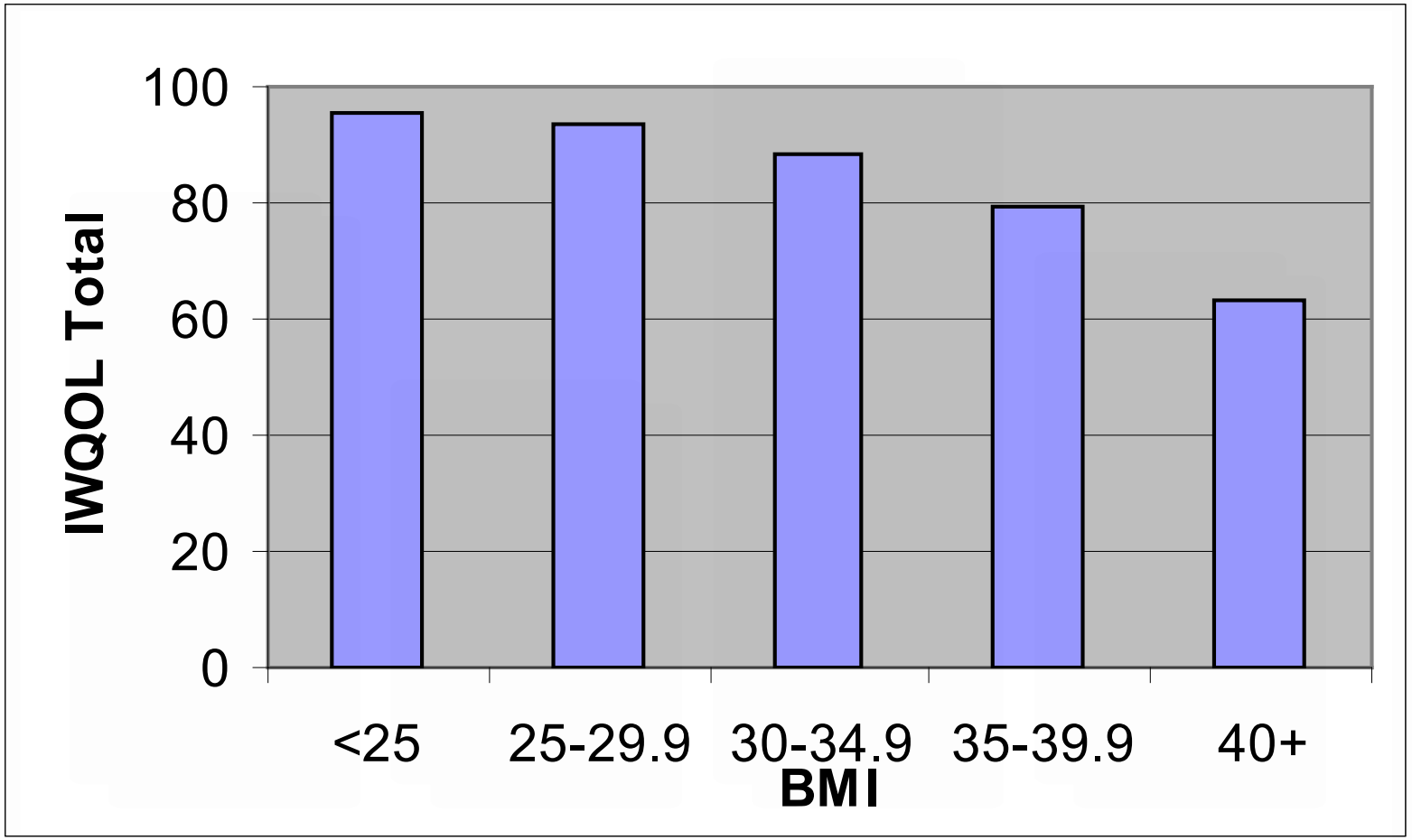
SELF-ESTEEM AND BMI: Relation depends on gender and age 26-year Finnish cohort study 1983-2009



Ns= 2,194-1,334

Source: Kiviruusu O et al. *Int.J. Behav. Med.* 2016: **23**, 355–363

OBESITY AND QUALITY OF LIFE



Kolotkin & Crosby. *Qual Life Research. 2002;* 11: 157-171

PSYCHOSOCIAL EFFECTS OF WEIGHT LOSS

- Improved mood
- Increased dietary restraint
- Improved eating behaviors
- Improved body image
- Improved quality of life

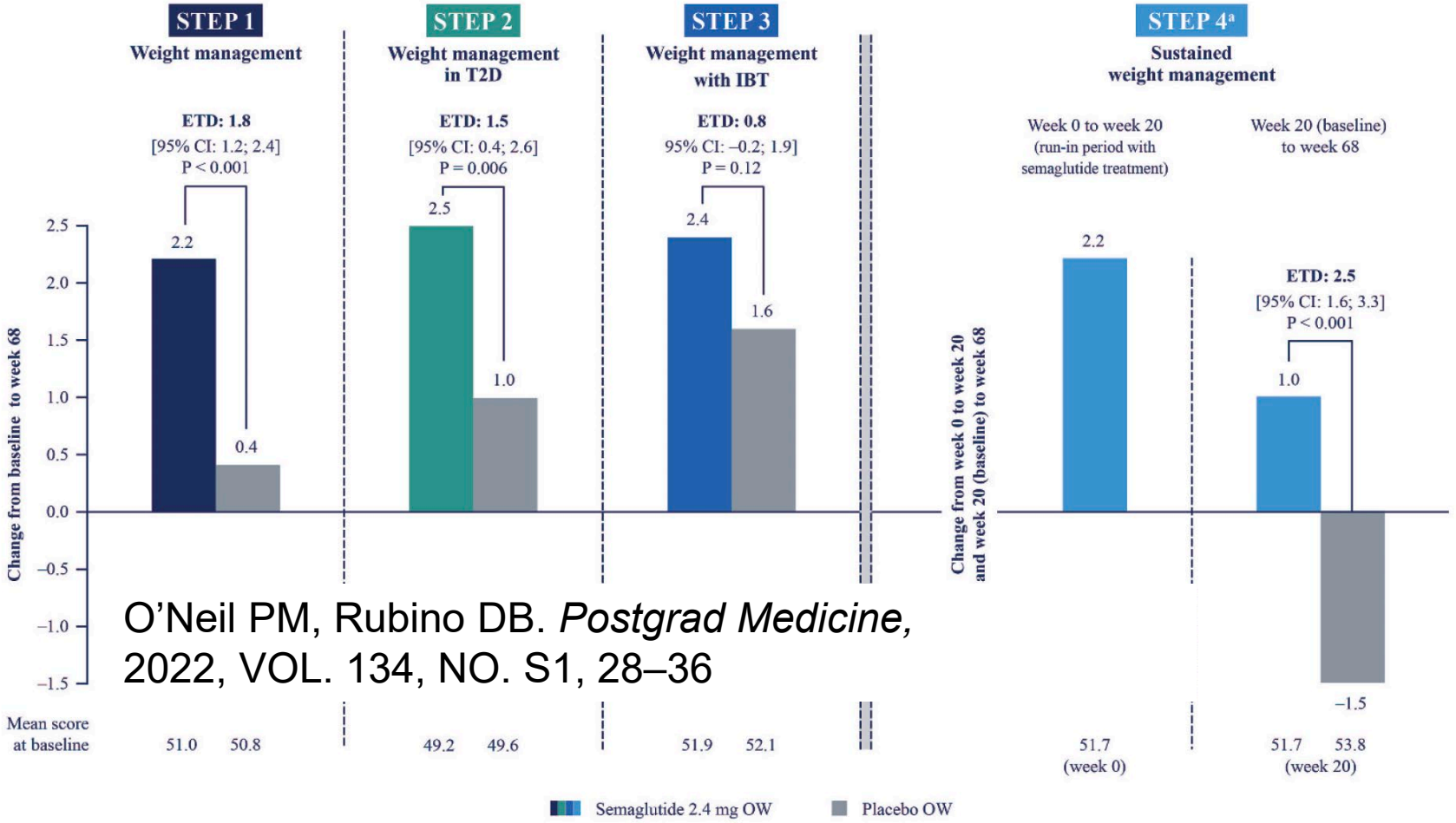
WEIGHT LOSS AND QUALITY OF LIFE: Meta-analysis of 5 RCTs, N = 10,884

	Delta model			Delta spline regression		
	Est	95% CI	*p* value	Est	95% CI	*p* value
Change in BMI	−0.087848	(−0.099 to −0.075)	<0.01			
Change in BMI: 18.5–24.9				0.00		
Change in BMI: 25–29.9				−0.08522	(−0.131 to −0.039)	<0.01
Change in BMI: 30–34.9				−0.1048	(−0.162 to −0.046)	<0.01
Change in BMI: 35–39.9				−0.12335	(−0.193 to −0.052)	<0.01
Change in BMI: ≥40				−0.1524	(−0.231 to −0.073)	<0.01

Source: Buckell J et al, *Obesity Reviews*. 2021;22:e13317.

PSYCHOLOGICAL CORRELATES OF NEWER ANTI-OBESITY MEDICATIONS

SEMAGLUTIDE AND WEIGHT LOSS AND QUALITY OF LIFE:
SF-36 V2 Physical Functioning score



O'Neil PM, Rubino DB. *Postgrad Medicine,* 2022, VOL. 134, NO. S1, 28–36

NEUROPSYCHIATRIC SAFETY OF GLP-1 OBESITY MEDICATIONS: SUICIDAL IDEATION AND BEHAVIOR: Pharmacovigilance reports of adverse drug reactions

- FDA database:
  - Metformin >>semaglutide ~ tirzepatide ~ liraglutide > orlistat
- European Medicines Agency database:
  - 31,444 ADRs for people on liraglutide, semaglutide, tirzepatide
  - 1.18% psychiatric; 0.2% suicidal ideation/behavior
  - 8/9 deaths were males
- "Disproportionality analysis" of 269 reported suicidal and self-injurious adverse drug reactions (WHO database)
  - Liraglutide: No signal
  - Semaglutide: Signal for suicidal ideation; no signal for self-injurious events

Guirguis A et al. European Neuropsychopharmacology 82 (2024) 82–91.
Tobaiqy, M., Elkout, H. *Int J Clin Pharm* **46**, 488–495 (2024).
Schoretsanitis M et al. *JAMA Network Open*. 2024;7(8):e2423385.

SUICIDAL IDEATION IN LIRAGLUTIDE TRIALS

TABLE 4 C-SSRS results post-baseline

Pooled phase 3a trials[a]	Liraglutide 3.0 mg N = 3291	Placebo N = 1843
Number of participants completing C-SSRS	3270	1832
N (%) with suicidal ideation on the C-SSRS	34 (1.03)	19 (1.03)
1. Wish to be dead	30 (0.91)	18 (0.98)
2. Active suicidal ideation, non-specific thoughts	15 (0.46)	8 (0.43)
3. Active suicidal ideation, any method (no plan) without intent	11 (0.33)	3 (0.16)
4. Active suicidal ideation, some intent to act, without specific plan	2 (0.06)	1 (0.05)
5. Active suicidal ideation, specific plan and intent	1 (0.03)	2 (0.11)

Abbreviations: C-SSRS, Columbia-Suicide Severity Rating Scale; N (%), number and percentage of individuals; SCALE, Satiety and Clinical Adiposity – Liraglutide Evidence.

Suicidal ideation or behavior ***AE***s : Liraglutide 0.3%; Placebo 0.1%)

O'Neil PM et al. *Diabetes Obes Metab*. 2017;19:1529–1536.

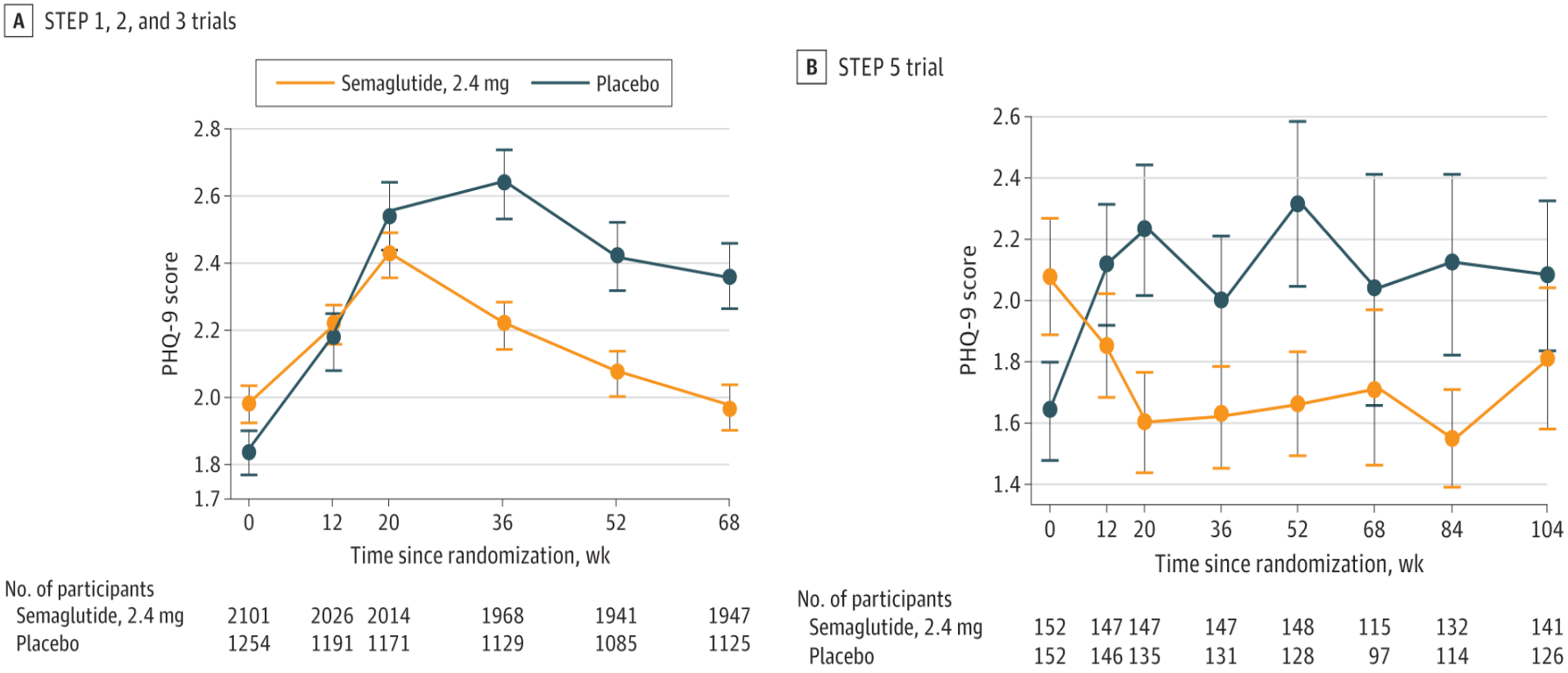
SUICIDAL IDEATION IN SEMAGLUTIDE TRIALS

Table 3. Proportion of Participants With Suicidal Ideation During the Studies as Assessed by the Columbia Suicide-Severity Rating Scale (C-SSRS)[a]

C-SSRS assessment (in trial)	No. (%)			
	STEP 1, 2, and 3		STEP 5	
	Semaglutide, 2.4 mg (n = 2116)	Placebo (n = 1261)	Semaglutide, 2.4 mg (n = 152)	Placebo (n = 152)
Postbaseline, No.	**2066**	**1228**	**152**	**146**
Participants with suicidal ideation	8 (0.4)	7 (0.6)	1 (0.7)	2 (1.4)
Low risk				
1. Wish to be dead	8 (100)	7 (100)	1 (100)	2 (100)
2. Nonspecific active suicidal thought	3 (37.5)	2 (28.6)	0	2 (100)
Moderate risk				
3. Active suicidal ideation with any method (no plan) without intent to act	1 (12.5)	1 (14.3)	0	0
High risk				
4. Active suicidal ideation with some intent to act without specific plan	1 (12.5)	0	0	0
5. Active suicidal ideation with specific plan and intent	0	0	0	0

Wadden et al. *JAMA Intern Med*. doi:10.1001/jamainternmed.2024.4346

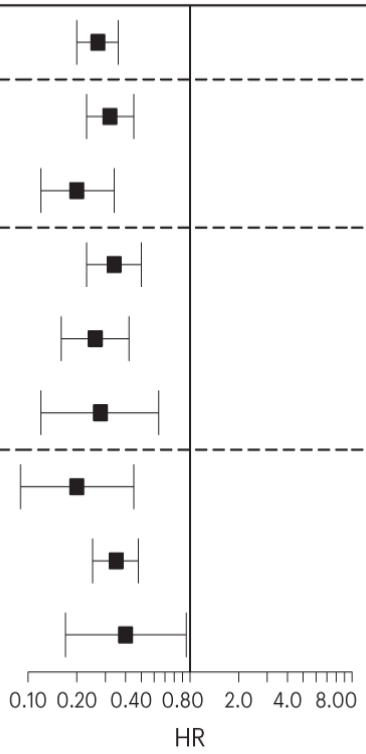
Depressed mood (PHQ-9) over time: Semaglutide vs. placebo



Wadden TA et al. *JAMA Intern Med*. doi:10.1001/jamainternmed.2024.4346

“REAL-WORLD” EMR STUDY: LOWER RISK OF S.I. WITH SEMAGLUTIDE??

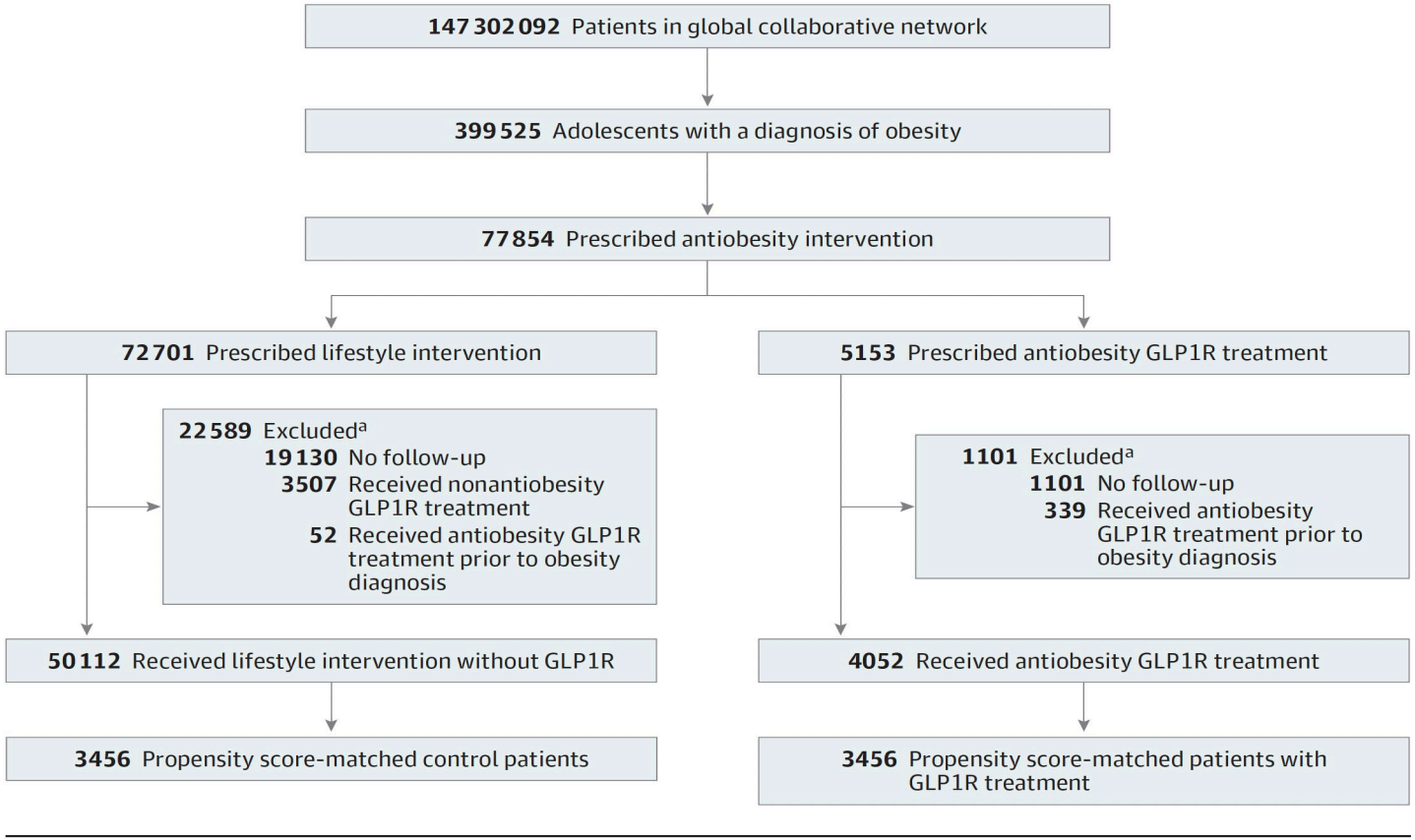
Obese sample	Semaglutide group	Non-GLP1R agonist anti-obesity medication group	HR (95% CI)
Overall (*n* = 52,783 per group)	0.11% (60)	0.43% (226)	0.27 (0.20–0.36)
Females (*n* = 39,004 per group)	0.11% (43)	0.35% (136)	0.32 (0.23–0.45)
Males (*n* = 13,191 per group)	0.13% (17)	0.64% (85)	0.20 (0.12–0.34)
Age ≤45 years (*n* = 19,650 per group)	0.17% (33)	0.51% (100)	0.34 (0.23–0.50)
Age 46–64 years (*n* = 24,508 per group)	0.09% (22)	0.34% (84)	0.26 (0.16–0.42)
Age ≥65 years (*n* = 8,106 per group)	0.12% (10)	0.31% (25)	0.28 (0.12–0.64)
Black (*n* = 8,288 per group)	0.12% (10)	0.42% (35)	0.20 (0.09–0.45)
White (*n* = 37,133 per group)	0.14% (50)	0.39% (145)	0.35 (0.25–0.48)
Hispanic ethnicity (*n* = 3,666 per group)	0.27% (10)	0.49% (18)	0.40 (0.17–0.95)



Wang, W, et al. *Nat Med* **30**, 168–176 (2024)

Adolescents on GLP-1 agonists and psychiatric AEs

Figure 1. Flowchart of Patient Selection for Study and Control Cohorts



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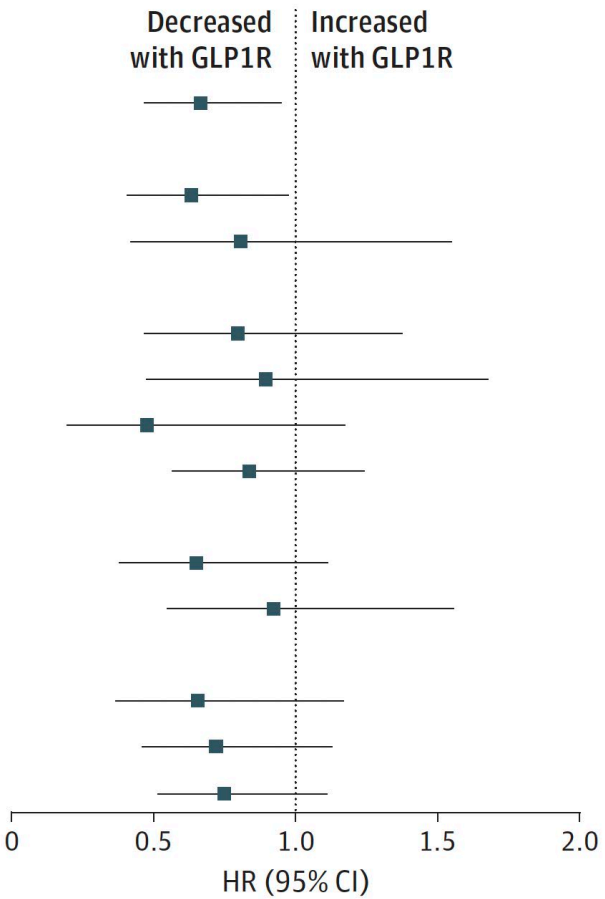
Adolescents on GLP-1 agonists and suicidal AEs

A Risk for suicidal ideation or attempts by subgroup

Subgroup (No./cohort)	No. (%) GLP1R	No. (%) Control	HR (95% CI)
Overall (3456)	50 (1.5)	78 (2.3)	0.67 (0.47-0.95)
Sex			
Female (2064)	33 (1.6)	54 (2.6)	0.63 (0.41-0.98)
Male (1323)	16 (1.2)	21 (1.6)	0.81 (0.42-1.16)
Race and ethnicity			
White (1621)	23 (1.4)	30 (1.9)	0.80 (0.46-1.38)
Black (770)	18 (2.3)	21 (2.7)	0.89 (0.48-1.68)
Hispanic (764)	10 (1.3)	15 (2.0)	0.48 (0.20-1.18)
Non-Hispanic (2190)	45 (2.1)	56 (2.6)	0.84 (0.57-1.24)
GLP1R			
Liraglutide (1602)	22 (1.4)	34 (2.1)	0.65 (0.38-1.11)
Semaglutide (1553)	26 (1.7)	31 (2.0)	0.92 (0.55-1.56)
Diabetes status			
Diabetes (1191)	19 (1.6)	29 (2.4)	0.66 (0.37-1.17)
No diabetes (2215)	32 (1.4)	48 (2.2)	0.72 (0.46-1.13)
No bariatric surgery (3235)	49 (1.5)	68 (2.1)	0.75 (0.52-1.08)



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