WEIGHT CHANGE IN PATIENTS WITH BIPOLAR DISORDER DURING TREATMENT WITH OLANZAPINE

Description of Studies Included in the Analysis

Study code	Age	Indication	Dosing (mg)	Design
HGEH[3]	18-65	Acute mania or mixed	OLZ 5-20	3 wks OLZ vs PBO, 1 y OL extension
HGFU[4]	18-70	BPI, acute mania or mixed	OLZ 5-20 plus Li or DVPX	6 wksOLZ + Li or DVPX vs PBO+DVPX or Li 18 mos DB for responders, 18 mos OL OLZ for non responders
HGGY[5]	≥18	BPI depressed	OLZ 5-20, OLZ6+FLU, OLZ12+FLU	8 wks OLZ + FLU vs OLZ vs PBO 6 mos OL extension
HGHD[6]	≥18	Acute mania or mixed	OLZ 5-20 HAL 3-15	12 wks DB OLZ vs HAL 6 mos OL extension
HGHL[7]	≥18	BPI; index manic or mixed	OLZ 5-20	OLZ OL 6-12 wks, responders randomized to DB OLZ vs PBO 12 mos
HGHQ[8]	18-75	Acute mania or mixed	OLZ 5-20 DVPX 500-2500	3 wks DB OLZ vs DVPX 11 mos DB OLZ vs DVPX
HGHT[9]	≥18	BPI manic or mixed	OLZ 5-20 +/- Li	6-12 wks OL +Li and 1 y DB OLZ vs Li

PBO, placebo; OL, open label; BPI, bipolar I; DB, double-blind; HAL, haloperidol

Baseline Characteristics of Patients

|	HGEH N=122	HGFU N=290	HGGY N=714	HGHD N=230	HGHL N=321	HGHQ N=125	HGHT N=429
BMI (kg/h^2)	28.83	29.15	28.65	25.84	28.75	27.96	26.45
Weight (kg)	84.22	85.86	80.75	69.20	82.57	80.86	75.46
YMRS	25.81	20.21	5.03	31.07	25.28	27.42	25.96
CGI-S (overall)	4.23	3.90	4.45	4.84	4.27	4.52	4.43
MADRS	N/A	N/A	28.32	7.00	12.83	N/A	6.33
AGE	39.66	40.99	42.01	40.70	40.58	39.99	42.41
Gender (% male)	0.52	0.48	0.36	0.37	0.39	0.42	0.47
Caucasian race (%)	0.74	0.86	0.83	0.52	0.87	0.78	0.99
Rapid cycler (%)	0.34	0.45	0.37	0.02	0.51	0.61	0.03
Psychotic features	0.52	0.32	0.12	0.55	0.18	0.50	0.26
Mixed episode	0.19	0.52	N/A	0.06	0.33	0.45	0.06

N/A = not available

Number of Patients Available for Weight Change Analyses at Specified Intervals After Initiation of Olanzapine

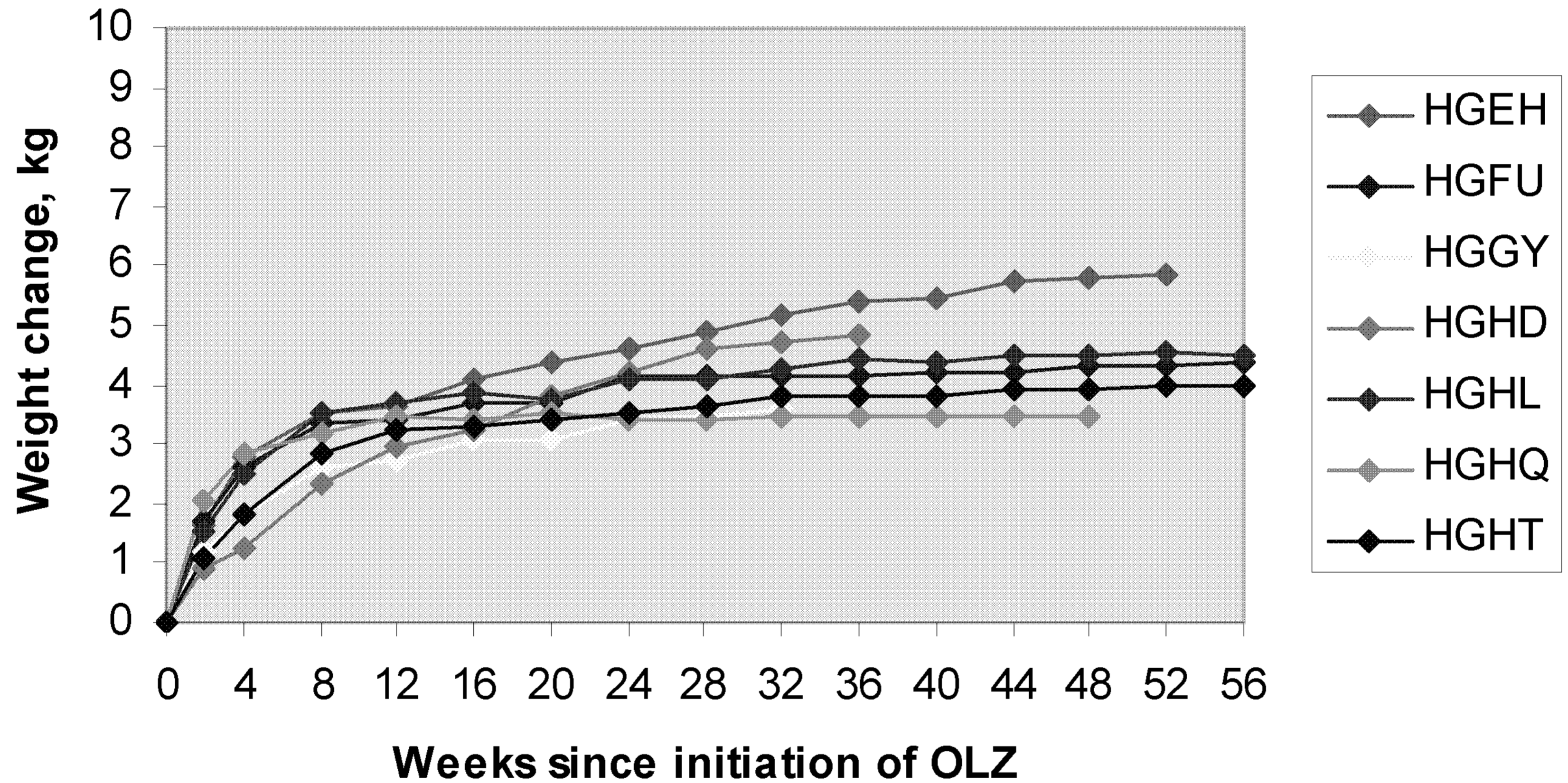| Weeks since initiation of OLZ (+/- 1 week)	**HGEH**	**HGFU**	HGGY	**HGHD**	HGHL	HGHQ	HGHT
baseline (initiation of OLZ)	120	290	711	344	321	125	429
2 weeks	120	280	682	341	320	114	429
4 weeks	105	248	600	205	320	90	429
8 weeks	95	206	537	271	320	67	428
12 weeks	77	94	276	246	265	57	263
16 weeks	70	122	388	217	224	46	196
20 weeks	65			206	203	39	173
24 weeks	61	102	322	194	176	32	156
28 weeks	53			105	158		144
32 weeks	49	86	160	99	144	25	141
36 weeks	48			94	120		131
40 weeks	45	73			93	24	
44 weeks	45				77		91
48 weeks	45	64			68	19	
52 weeks	23				64		83
56 weeks		59			60		
60 weeks					20		75

Mean Weight Change Profiles
(Observed Case Analysis)
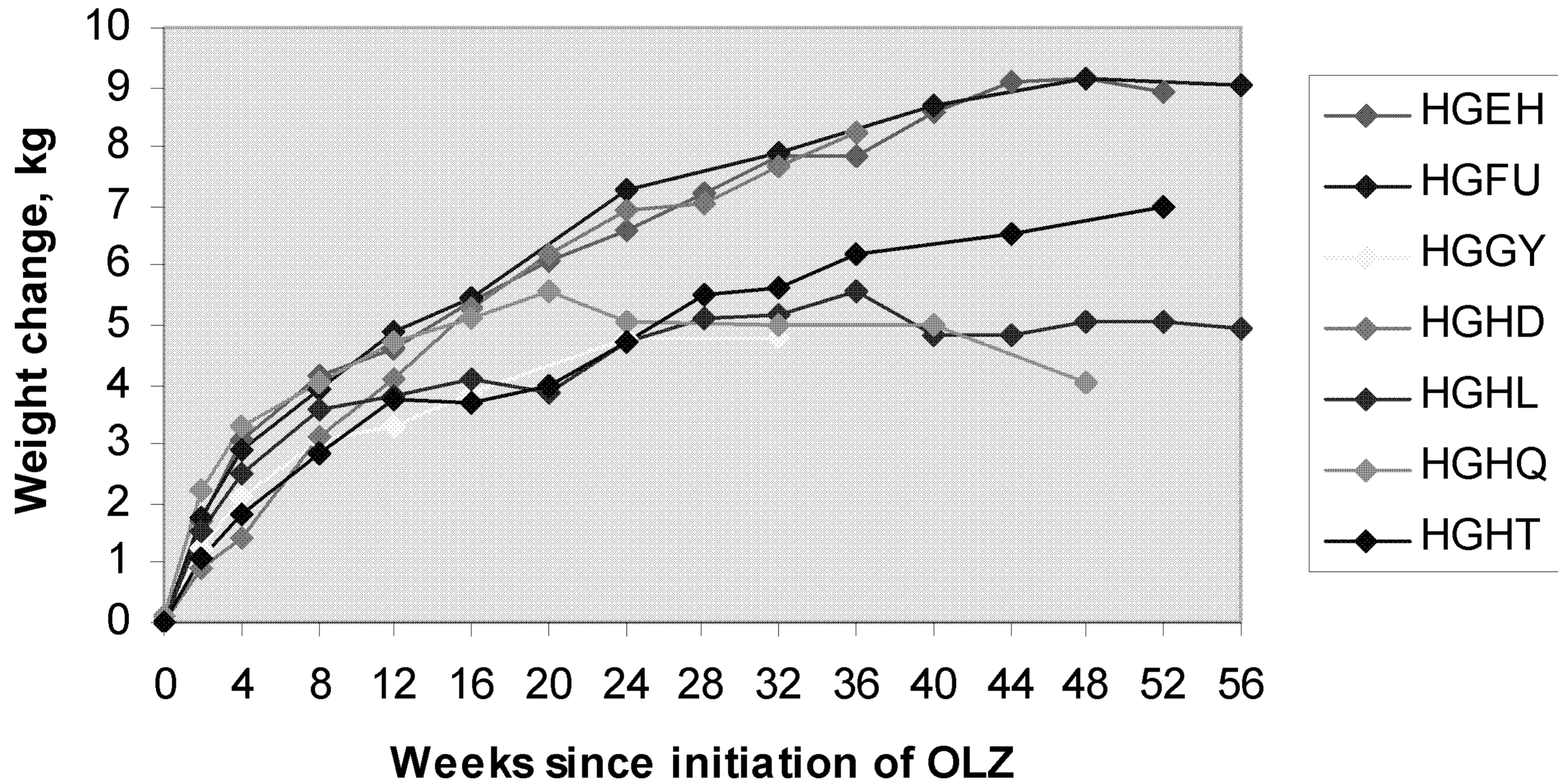
Mean Weight Change Profiles
(Last Observation Carried Forward Analysis)

Legend:
- HGEH
- HGFU
- HGGY
- HGHD
- HGHL
- HGHQ
- HGHT

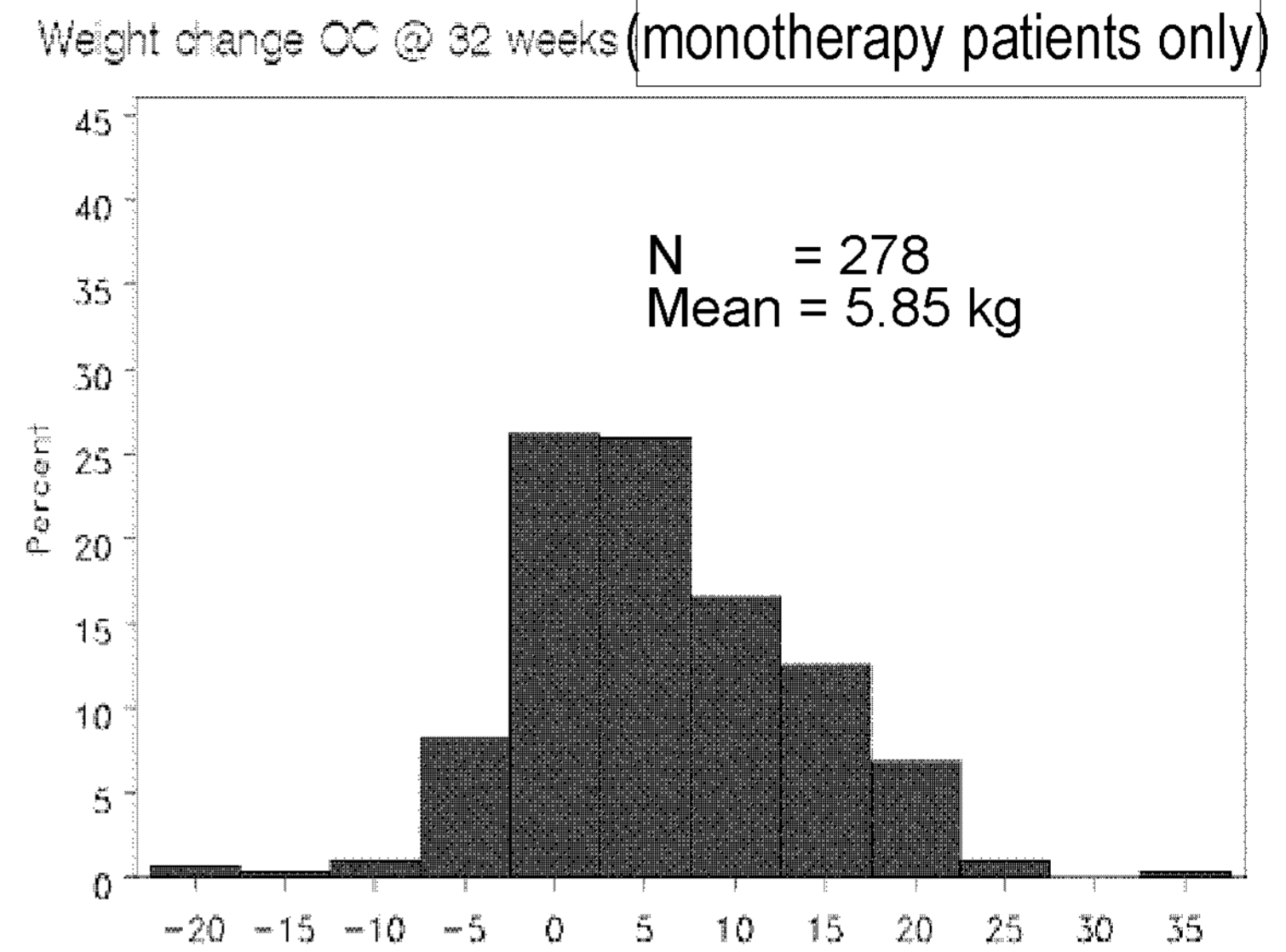Y-axis: Weight change, kg

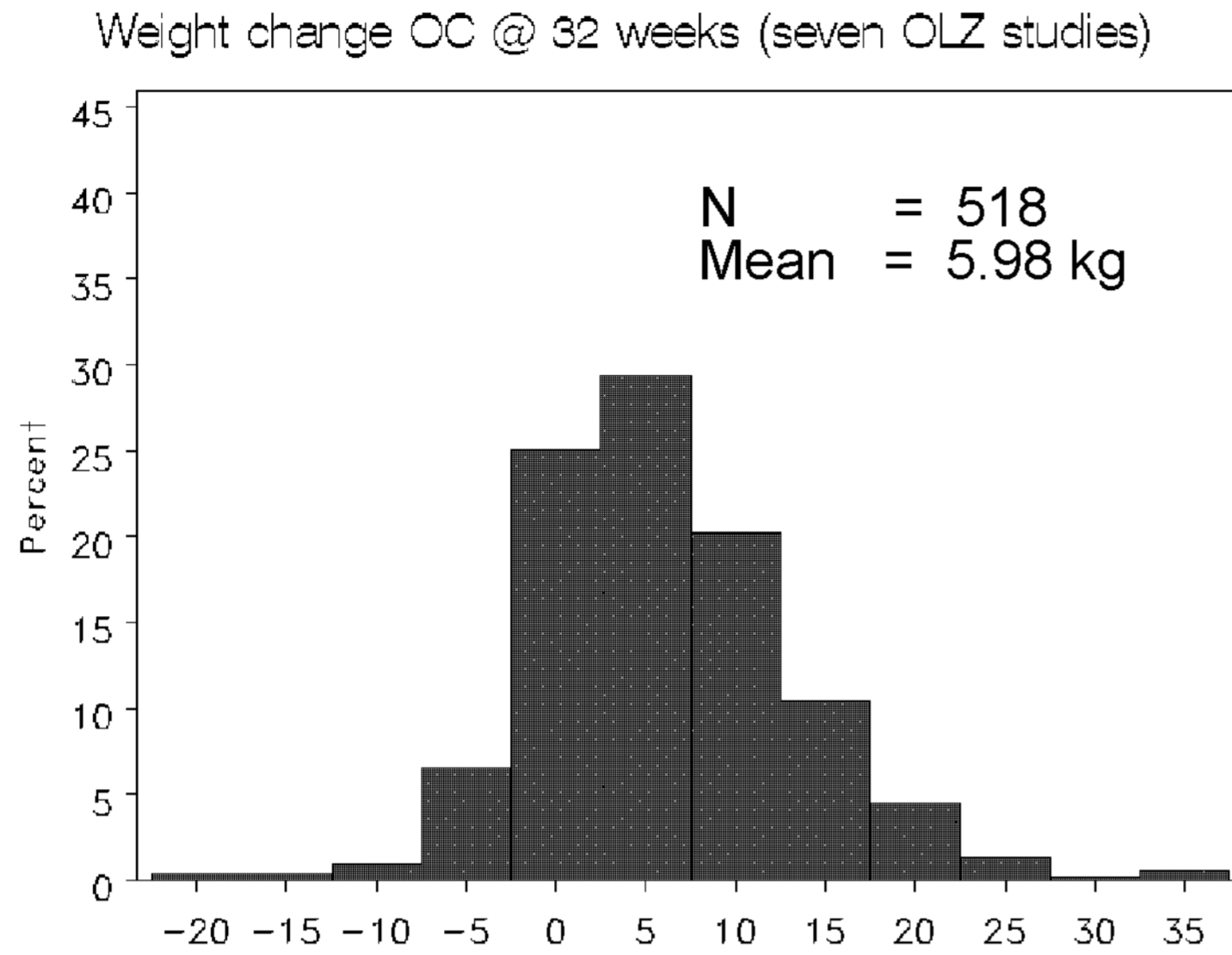X-axis: Weeks since initiation of OLZ

Mean Weight Change Profiles by Study
(Least squares means from mixed effects repeated measures analysis)
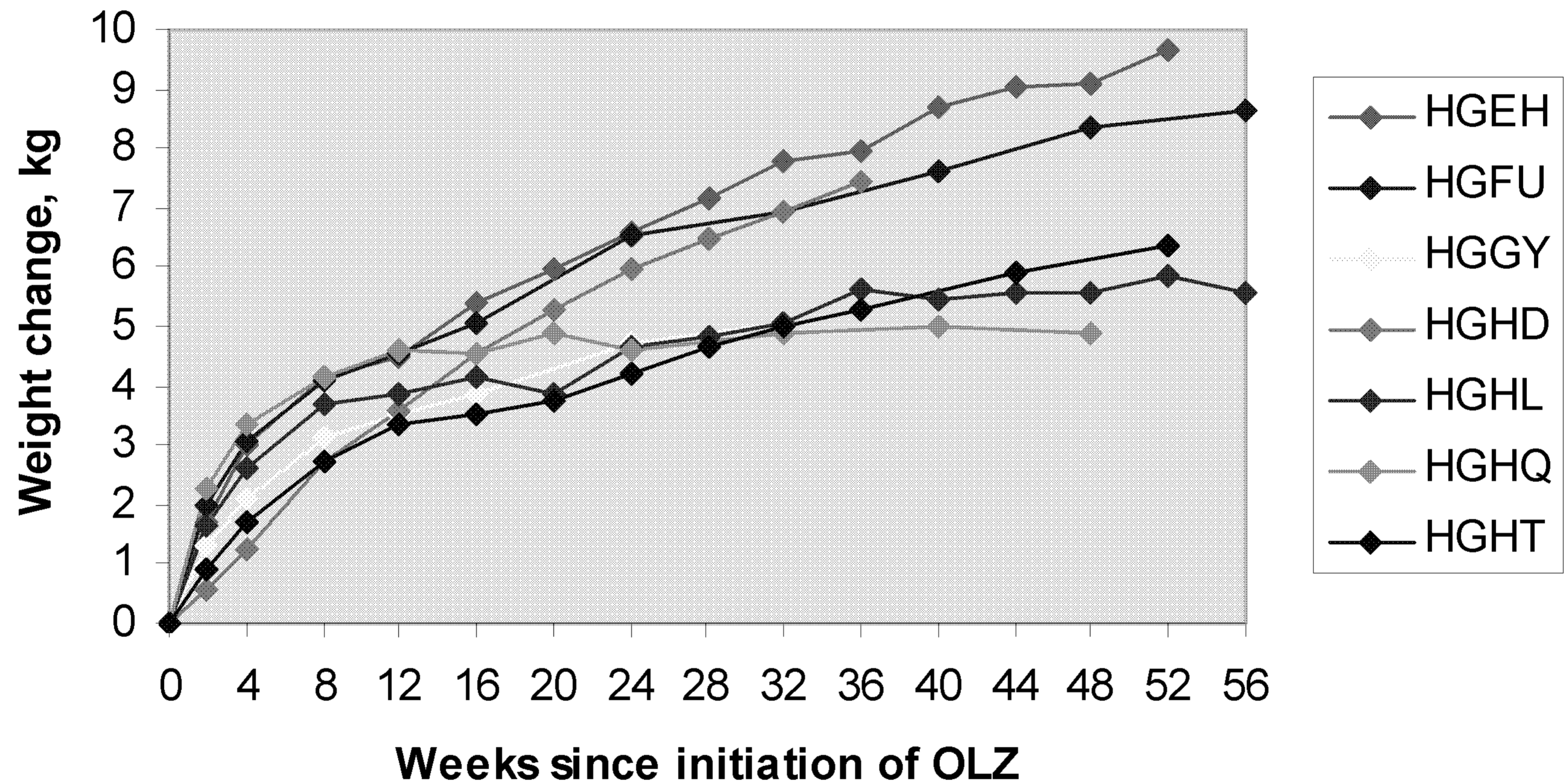
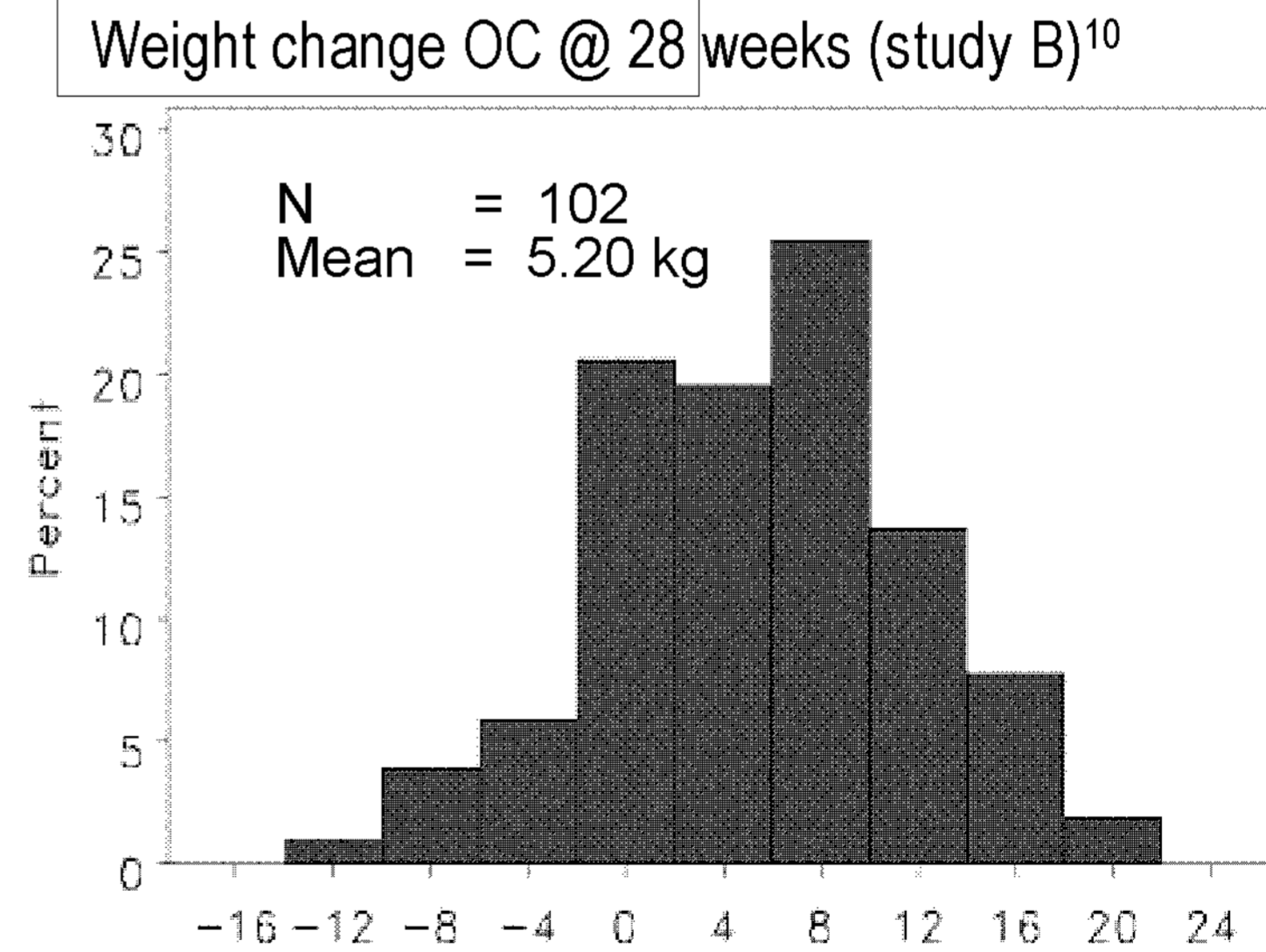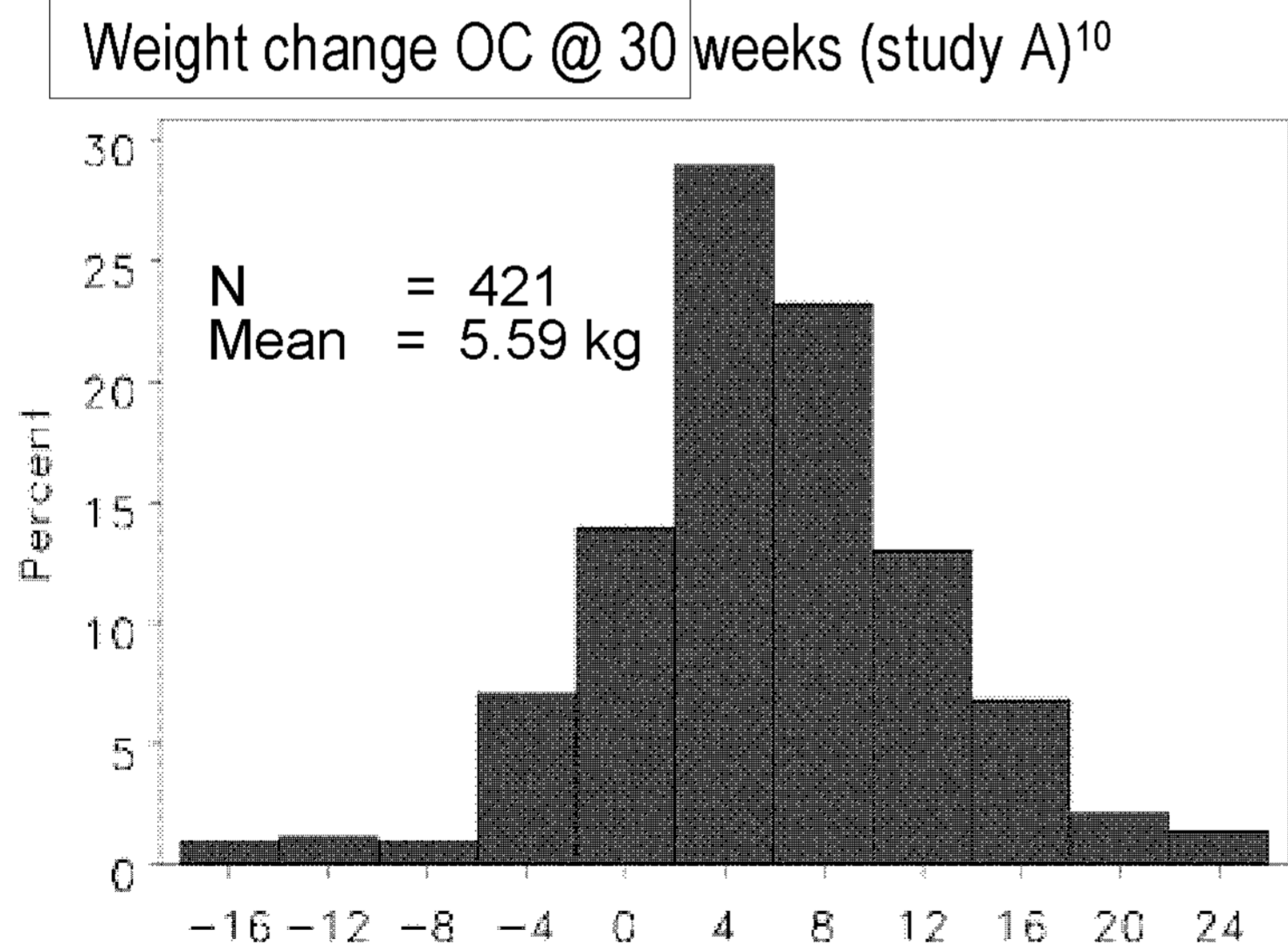# Weight Change from Baseline by Observed Case (OC) Analysis
(28-32 weeks precedes "plateau" in weight change for some studies)

Weight change OC @ 32 weeks (seven OLZ studies)

N = 518
Mean = 5.98 kg

Weight change OC @ 32 weeks (monotherapy patients only)

N = 278
Mean = 5.85 kg

Weight change OC @ 30 weeks (study A)[10]

N = 421
Mean = 5.59 kg

Weight change OC @ 28 weeks (study B)[10]
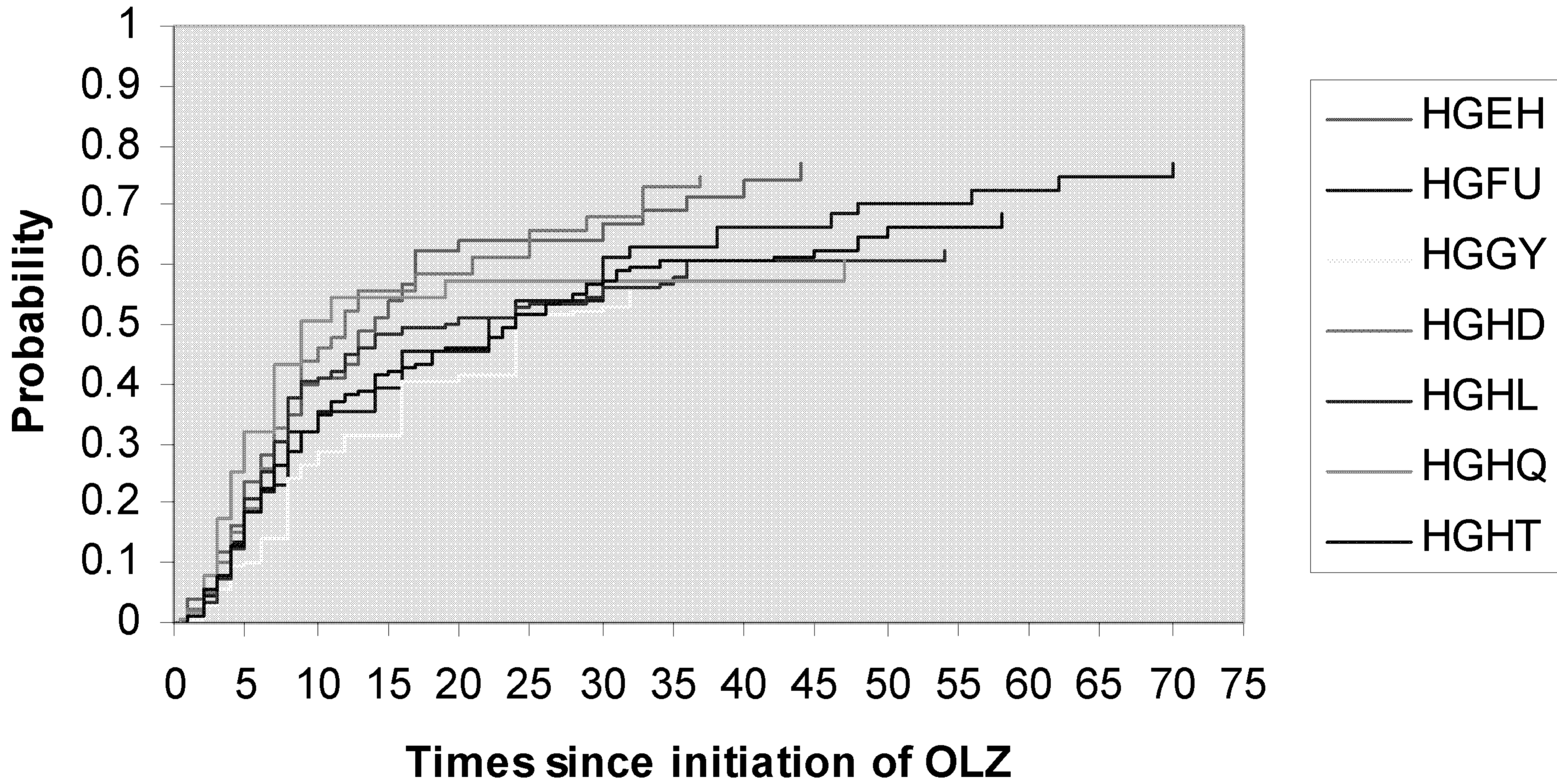
N = 102
Mean = 5.20 kg

Bipolar studies

Schizophrenia studies
(for comparison)[10]

Cumulative Probability of Gaining at Least 7% of Initial Body Weight in 7 poly-therapy Studies at Anytime Since Initiation of Olanzapine

Baseline Patient, Disease, and Episode Characteristics Used in Statistical Model

| Patient Characteristics	Disease History	Episode Features
Age Gender Caucasian race Baseline BMI	Family history of bipolar I or II or Major Depressive Disorders Family history of major Depressive disorder Family history of substance abuse Previous Lithium Use Age on onset of illness Rapid cycling Previous lithium response Number of Previous Manic, Depressive, and Mixed Episodes (during lifetime and last 12 months) Number of hospital admissions for Bipolar disorder in past year	Baseline YMRS (mania rating), MADRS, HAMD-21 (depression rating) and CGI-S Current Episode Length Mixed vs. Pure Mania Diagnosis of Substance Abuse – Current Presence of Psychotic Features Melancholic features (HGGY)

Unadjusted Correlation Coefficients of Weight Change and Baseline Patients Characteristics (OC @ 32 weeks)

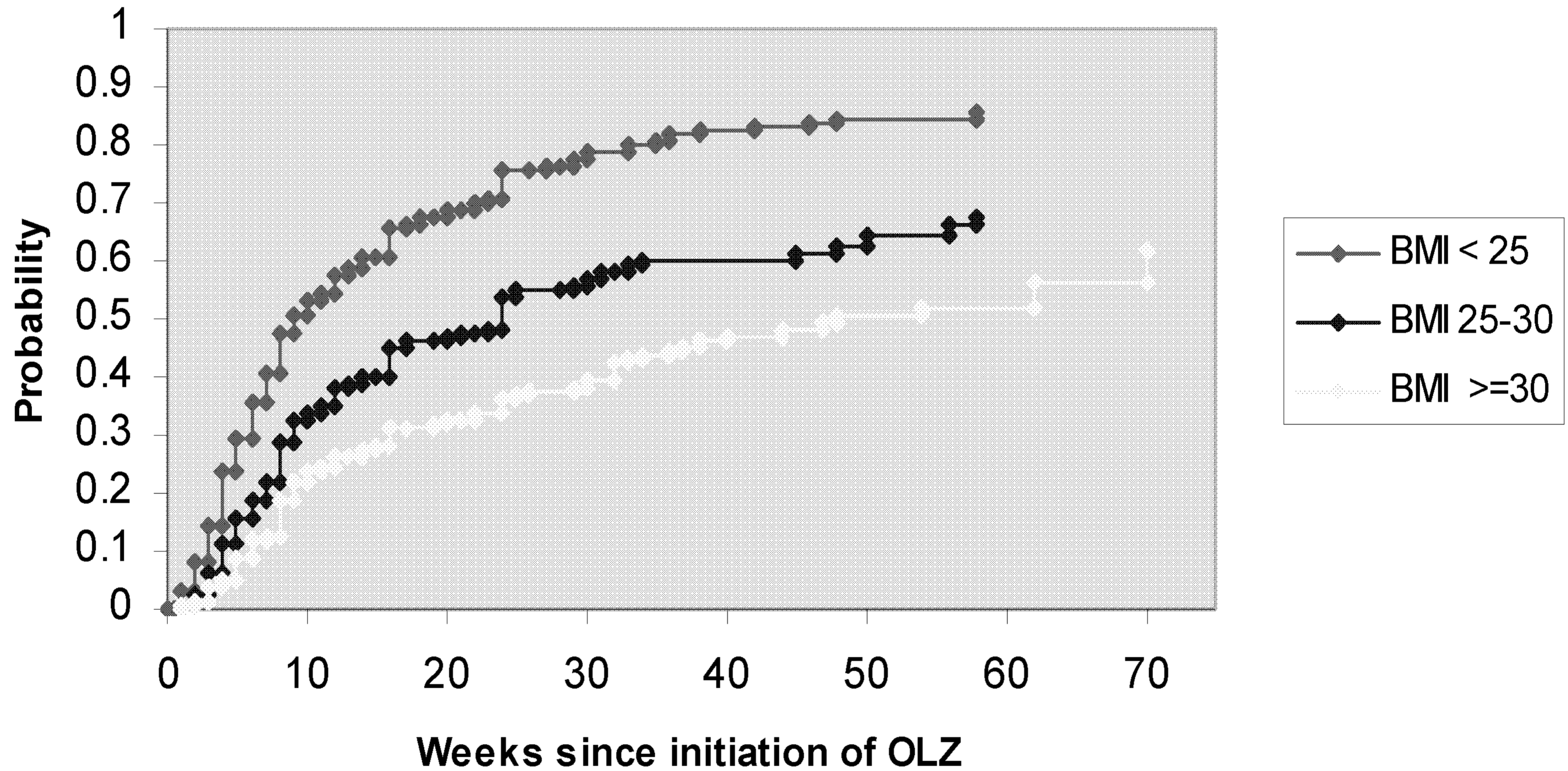| Patients characteristics	Weight change	Weight change≥7%	N
Age	-0.274**	-0.180**	518
Caucasian race	-0.121**	-0.107*	518
Baseline BMI	-0.187**	-0.261**	514
Psychotic features of current episode	0.125**	0.118**	518
Baseline MADRS	-0.101*	-0.069	423

* p<.05
**p<.01

Visitwise Mean Weight Change Profiles by Baseline BMI Category (LS Means from MMRM)
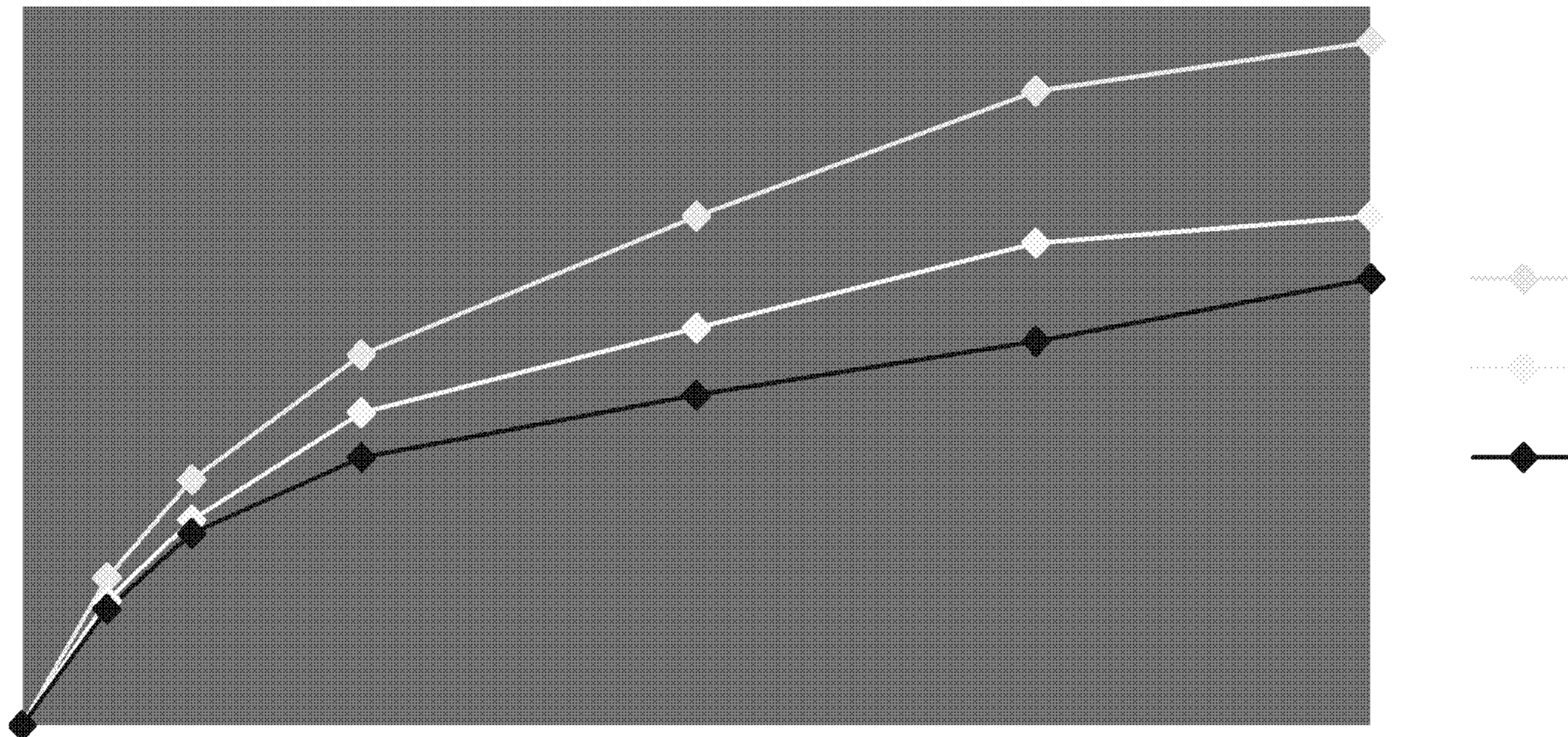
Cumulative Probability of Gaining at Least 7% of Initial Body Weight Anytime After Initiation of OLZ (by baseline BMI category)
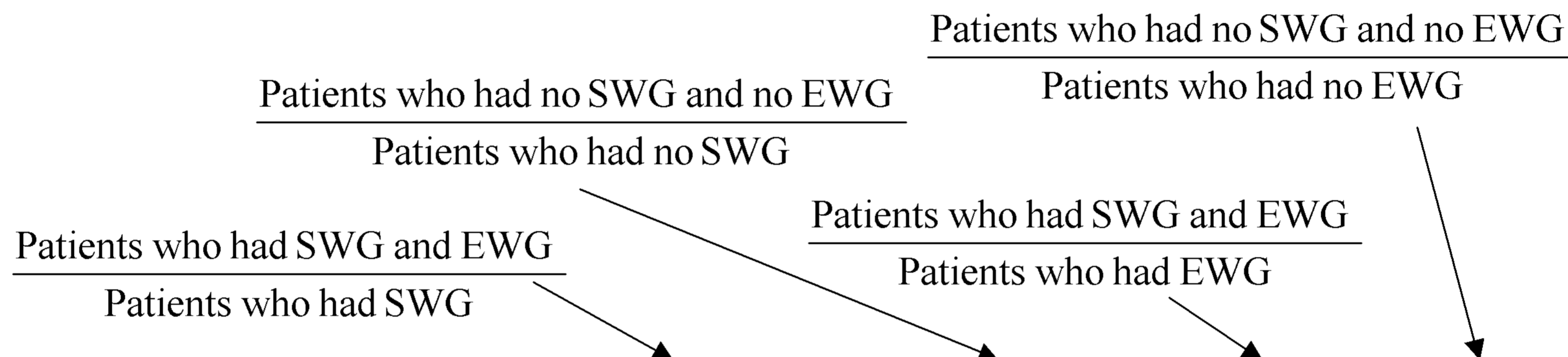
Adjusted Correlation Coefficients of Weight Change and Baseline Patients Characteristics
(OC @ 32 weeks, adjusted by baseline BMI and by study)

Patients characteristics	Weight change	Weight change$\geq$7 %	N
Age	-0.247**	-0.152**	508

**p<.01

Operational Characteristics for Different Outcomes for EWG at Week 3 on OLZ

$$\frac{\text{Patients who had no SWG and no EWG}}{\text{Patients who had no EWG}}$$

$$\frac{\text{Patients who had no SWG and no EWG}}{\text{Patients who had no SWG}}$$

$$\frac{\text{Patients who had SWG and EWG}}{\text{Patients who had EWG}}$$

$$\frac{\text{Patients who had SWG and EWG}}{\text{Patients who had SWG}}$$

Weight gain (kg) @ Week 32	Cut-off for EWG (kg)	Sensitivity	Specificity	PPV	NPV
At least 5	1.69	64.14	68.53	68.80	63.86
At least 7	1.90	62.56	68.75	57.55	73.06
At least 10	2.19	60.77	68.84	41.80	82.65

Issues and Questions?

1. Wt gain leads to metabolic issues (v. direct effect)
2. Is weight gain predictable?
3. How widespread is the the problem of olanzapine wt gain related discontinuations in clinical practice?
4. Are there some patients who should be discontinued due to weight gain during olanzapine treatment?
5. Is weight gain manageable?
6. Is weight gain dose-dependent (in clinically efficacious range)?
7. Are atypical antipsychotic agents comparable in their association with weight gain?