



Almost all antipsychotics result in weight gain. Meta-analysis

Maarten Bak

GLOBAL THREAT
WAITING AREA



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FLORIDA
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Severe Mental Illness

Health

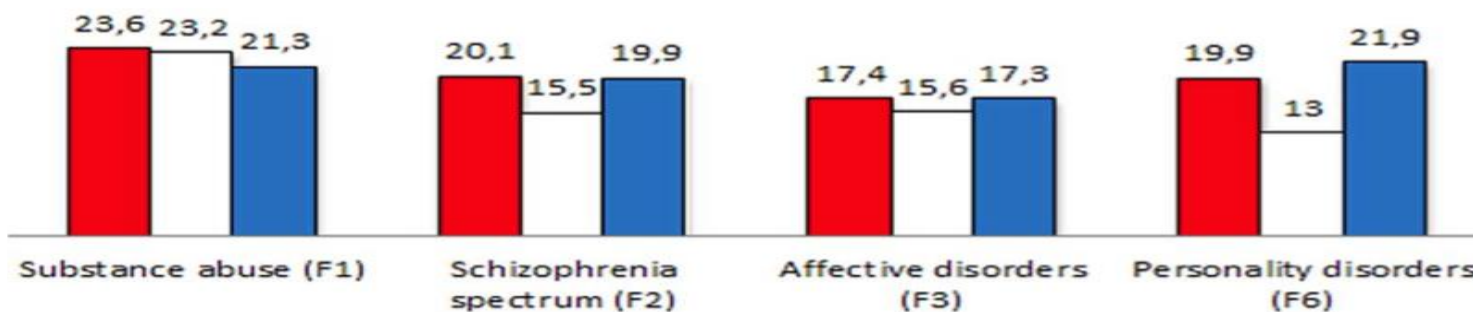


People with SMI decrease at a younger age

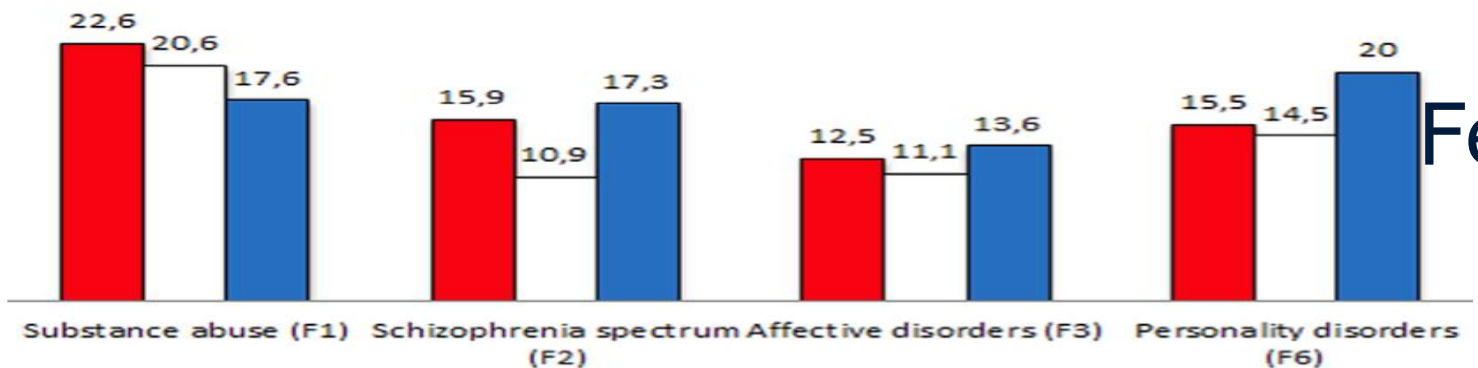
Population	Denmark		Finland		Sweden	
	Life expectancy	Difference	Life expectancy	Difference	Life expectancy	Difference
Men						
General population	75.7	–	75.7	–	78.2	–
Patients with schizophrenia	55.7	20.0	58.6	17.1	59.3	18.9
Women						
General population	80.3	–	82.5	–	82.6	–
Patients with schizophrenia	63.8	16.5	66.9	15.6	65.7	16.9

In SMI life expectancy is shortened

■ Denmark □ Finland ■ Sweden



Man



Female

Risks of severe physical problems in SMI

Risk factor	General Australian population		
	%	SMI versus GAP	
		RR (95% CI)	P-value
Smoking	19	3.5 (2.9–4.2)	<0.0001
Obesity	25	2.0 (1.6–2.6)	<0.0001
Hypertension	29	0.7 (0.4–1.2)	0.16
Diabetes	7	2.3 (1.3–4.0)	0.01
MetS	31	2.1 (1.8–2.6)	<0.0001

GAP =General Australian population

Physical problems & SMI: review

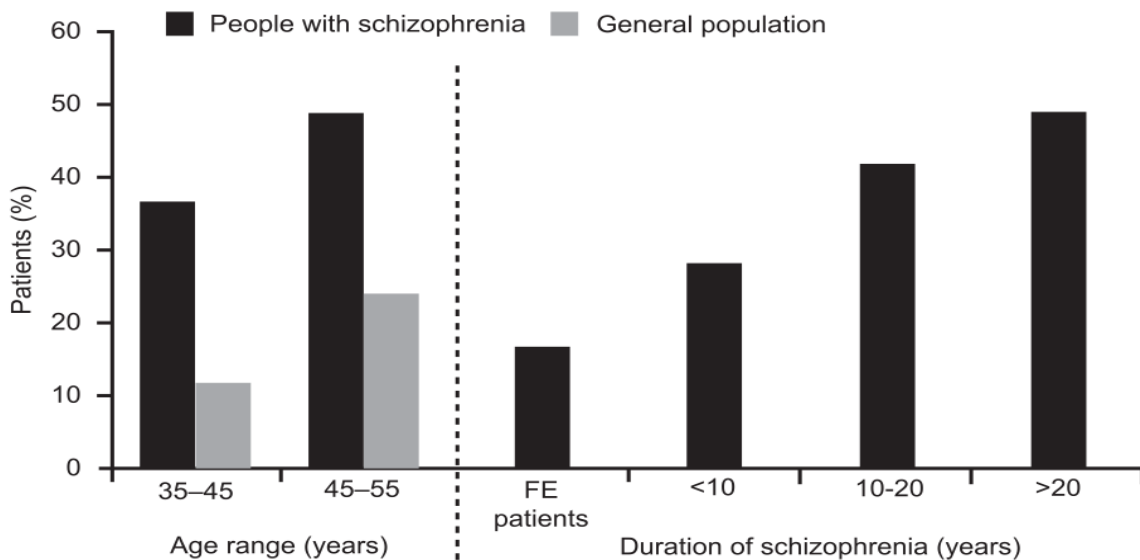
Disease category	Physical diseases with increased frequency
Bacterial infections and mycoses	Tuberculosis (+)
Viral diseases	HIV (++) , hepatitis B/C (+)
Neoplasms	Obesity-related cancer (+)
Musculoskeletal diseases	Osteoporosis/decreased bone mineral density (+)
Stomatognathic diseases	Poor dental status (+)
Respiratory tract diseases	Impaired lung function (+)
Urological and male genital diseases	Sexual dysfunction (+)
Female genital diseases and pregnancy complications	Obstetric complications (++)
Cardiovascular diseases	Stroke, myocardial infarction, hypertension, other cardiac and vascular diseases (++)
Nutritional and metabolic diseases	Obesity (++) , diabetes mellitus (+) , metabolic syndrome (++) , hyperlipidemia (++)

(++) very good evidence for increased risk, (+) good evidence for increased risk

DM-II

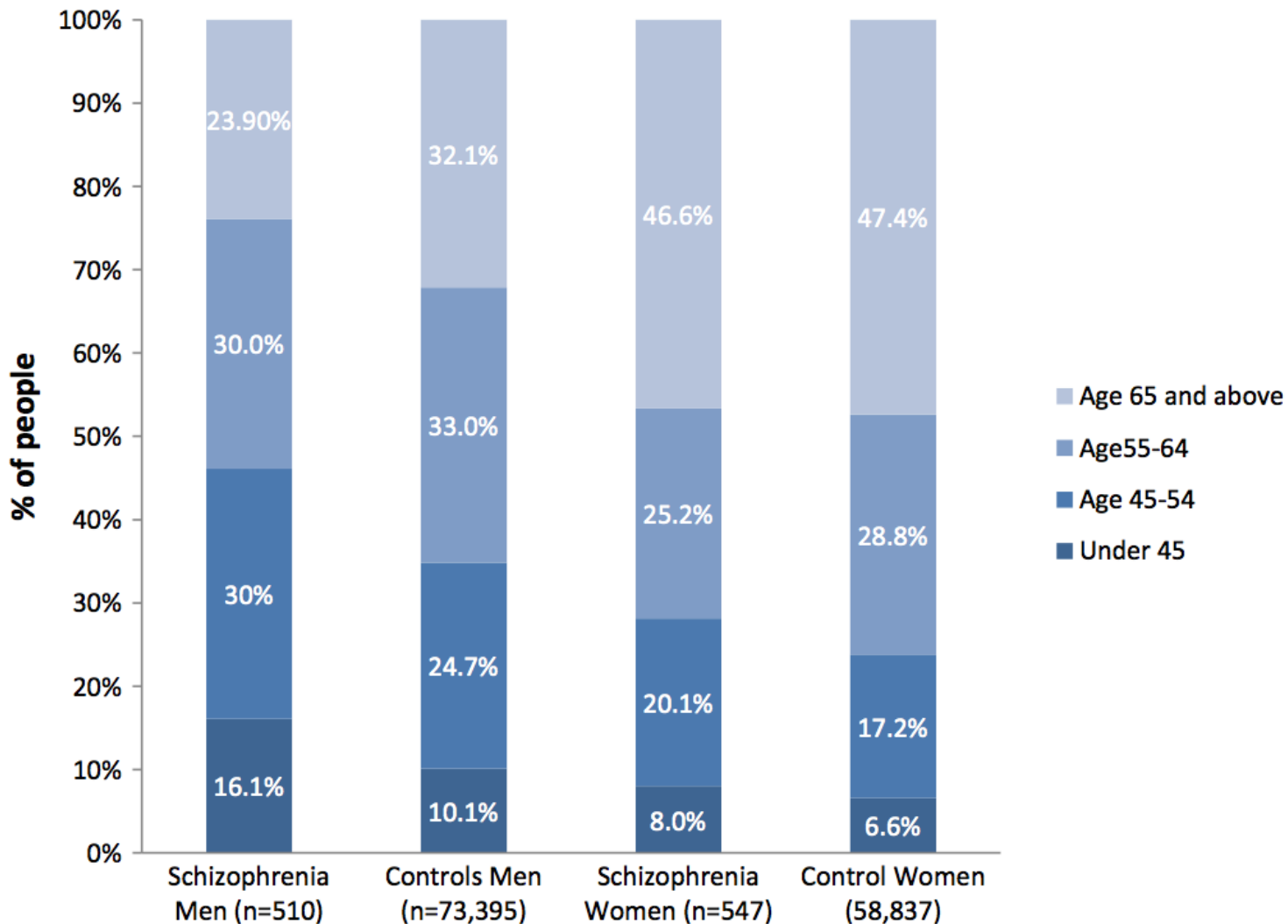


MetS



CVD risico

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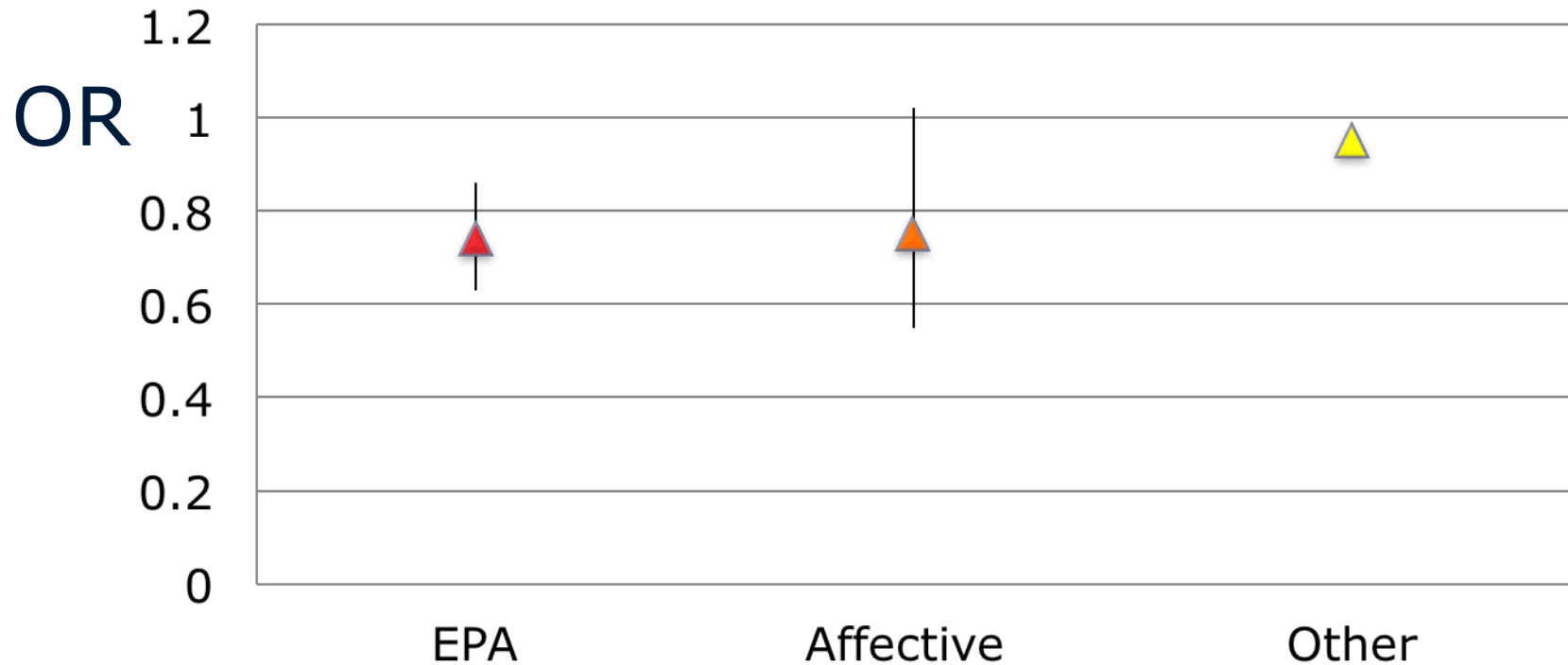


Note: figures represent the percentage of those with established CVD by age of first diagnosis

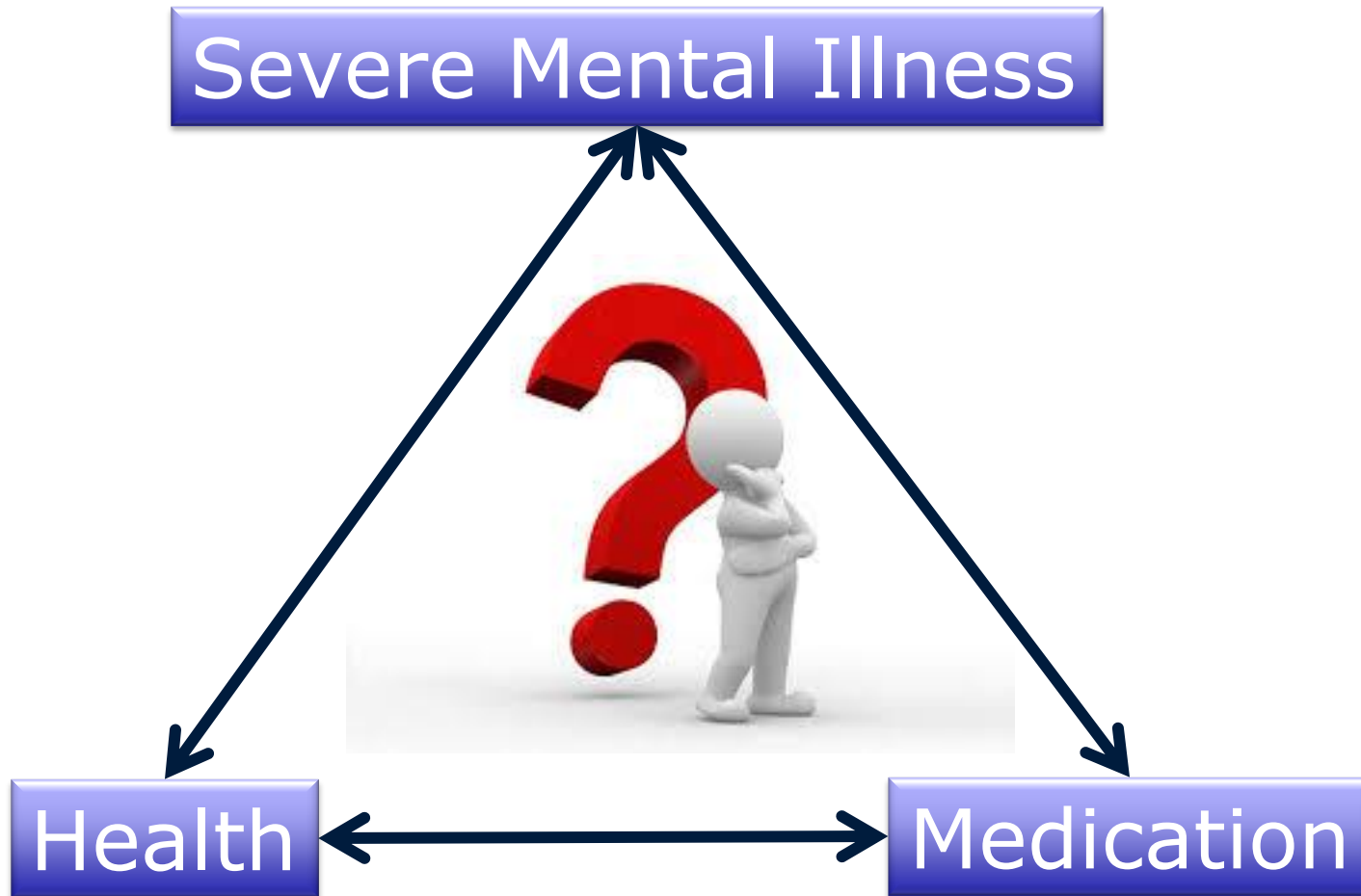
People with Schizophrenia decrease at a younger age

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Treatment of physical problems & SMI

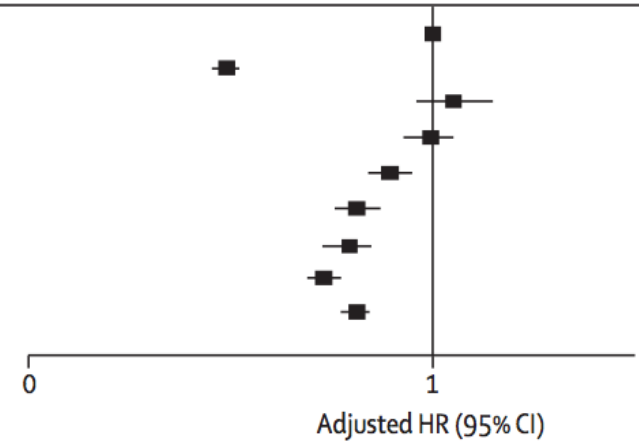


Meta-analysis of treatment with:
Antiviral compounds, ACE-blockers, β -blockers, anticoagulants
and Cholesterol decreasing medication



Mortality risk & AP

	Person-years	Number of deaths	Mortality*	Crude rate ratio (95% CI)	Adjusted HR (95% CI)
No antipsychotic drugs†	146 930	8277	56.33	1.00	1.00
0-0.5 years	59 920	1183	19.74	0.35 (0.33-0.37)	0.49 (0.46-0.52)
≥0.5-1.0 years	14 400	591	41.03	0.73 (0.67-0.79)	1.05 (0.96-1.15)
≥1.0-2.0 years	33 700	1272	37.74	0.67 (0.63-0.71)	0.99 (0.93-1.05)
≥2.0-3.0 years	34 030	1111	32.65	0.58 (0.54-0.62)	0.89 (0.84-0.95)
≥3.0-4.0 years	31 990	891	27.85	0.49 (0.46-0.53)	0.81 (0.76-0.87)
≥4.0-5.0 years	29 920	797	26.63	0.47 (0.44-0.51)	0.79 (0.73-0.85)
≥5.0-7.0 years	57 620	1359	23.59	0.42 (0.40-0.44)	0.73 (0.69-0.77)
≥7.0-11.0 years	165 360	4254	25.73	0.46 (0.44-0.47)	0.81 (0.77-0.84)



Largely explained by reduced risk of suicide

Mortality and medication

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TABLE 1. Schizophrenia Mortality (Hazard Ratios [HR])

Risk Factor	HR (Adjusted)	95% CI	P
Demographics			
Age per year	1.06	1.04–1.08	<0.0001
Female sex	1.03	0.65–1.63	0.91
No. changes in AP* therapy	1.00	0.97–1.04	0.98
Duration of hospitalization	0.99	0.92–1.07	0.83
Medication			
FGA	2.36	1.38–4.04	0.002
SGA	0.89	0.48–1.64	0.70
Concurrent AP* use	0.87	0.43–1.79	0.71
Mood stabilizers	8.42	3.06–24.07	<0.0001
Antidepressant	2.11	0.98–4.45	0.06
Anticholinergics	0.75	0.34–1.66	0.51
Benzodiazepines	1.38	0.79–2.38	0.26
Sensitivity Analyses			
FGA only	2.61	1.50–4.52	0.001
SGA only	1.03	0.59–1.83	0.91
AP* concomitantly or concurrently	1.05	0.61–1.80	0.86

Monitor side effects

Metabolic



- Body weight changes
- BMI
- Waist circumference
- Glucose
- Lipids

Other



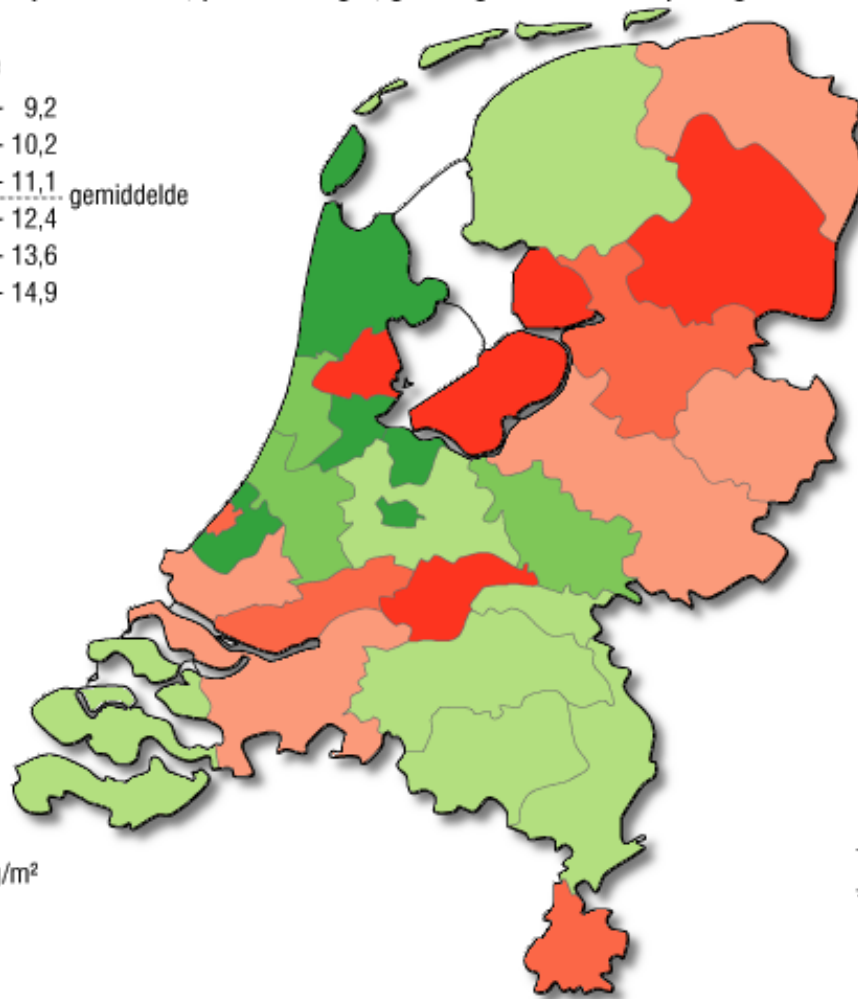
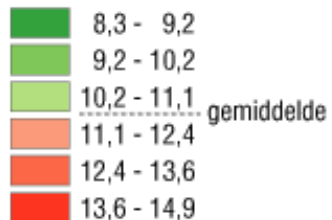
- Movement disorders
- Cardiovascular disorders
- Sexual problems

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Ernstig overgewicht 2005-2008

bevolking 20 jaar en ouder, per GGD-regio, gecorrigeerd voor leeftijd en geslacht

Percentage



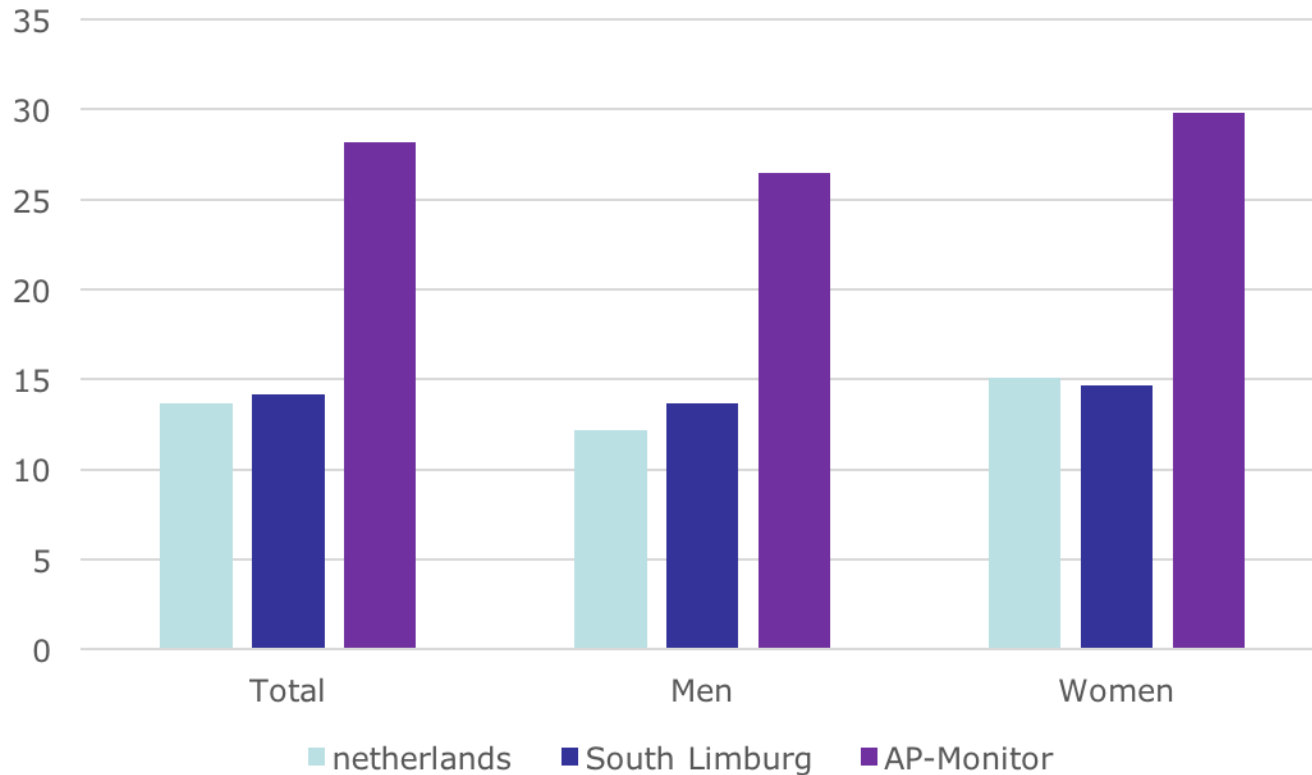
BMI \geq 30 kg/m²

Bron: CBS

www.zorgatlas.nl

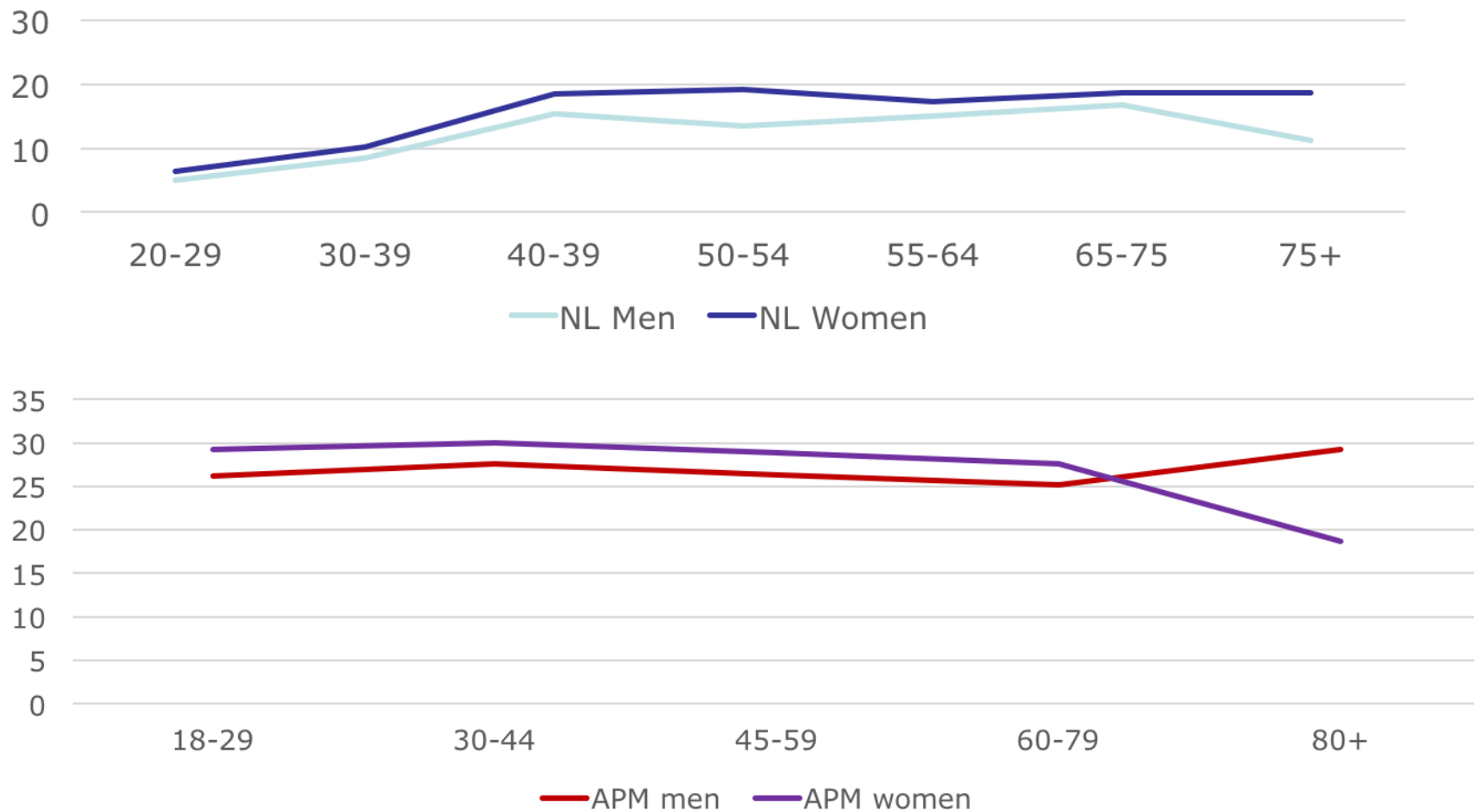
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Obesity differences



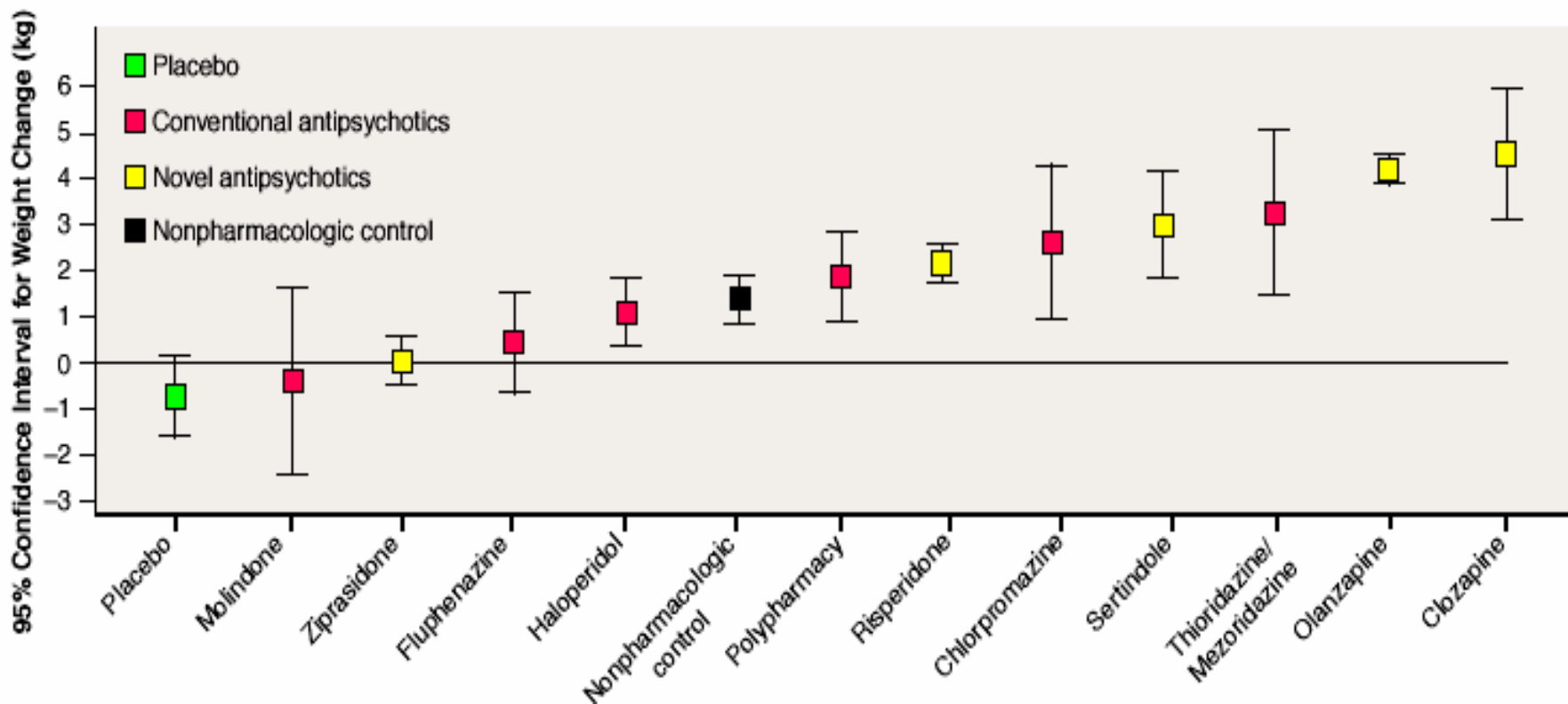
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Obesity per age group



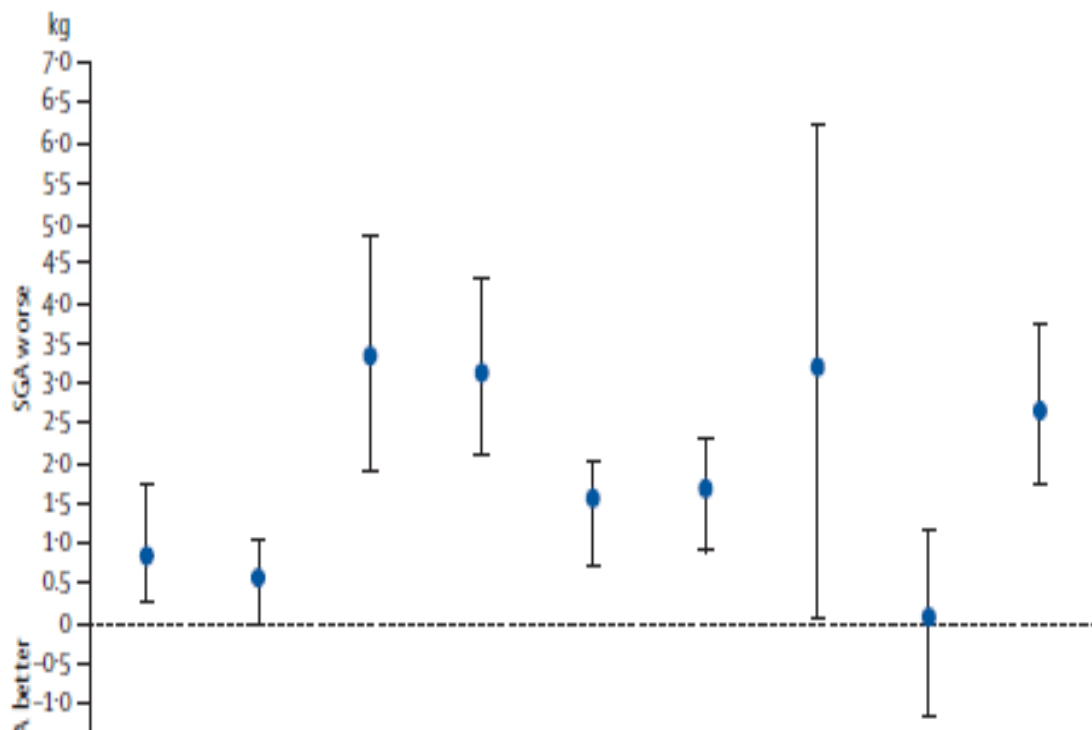
First review: AP associated with weight gain

FIGURE 1. 95% Confidence Intervals for Weight Change After 10 Weeks on Standard Drug Doses, Estimated From a Random Effects Model



Weight change: meta-analysis

	Number of studies	Number of participants	Mean weight-gain difference (kg; 95% CI)	p value
SGA versus haloperidol				
Amisulpride	2	373	0.9 (0.2 to 1.6)	0.012
Aripiprazole	2	1598	0.6 (-0.1 to 1.2)	0.071
Clozapine	3	170	3.4 (2.0 to 4.9)	<0.0001
Olanzapine	9	2952	3.3 (2.2 to 4.4)	<0.0001
Quetiapine	3	945	1.4 (0.7 to 2.1)	<0.0001
Risperidone	9	1366	1.7 (0.9 to 2.4)	<0.0001
Sertindole	2	779	3.3 (0.2 to 6.4)	0.040
Ziprasidone	1	301	0.1 (-1.2 to 1.3)	0.887
Zotepine	3	321	2.7 (1.7 to 3.7)	<0.0001



Study duration: 4-12 wks
Compared with haloperidol

BMI changes in first episode schizophrenia

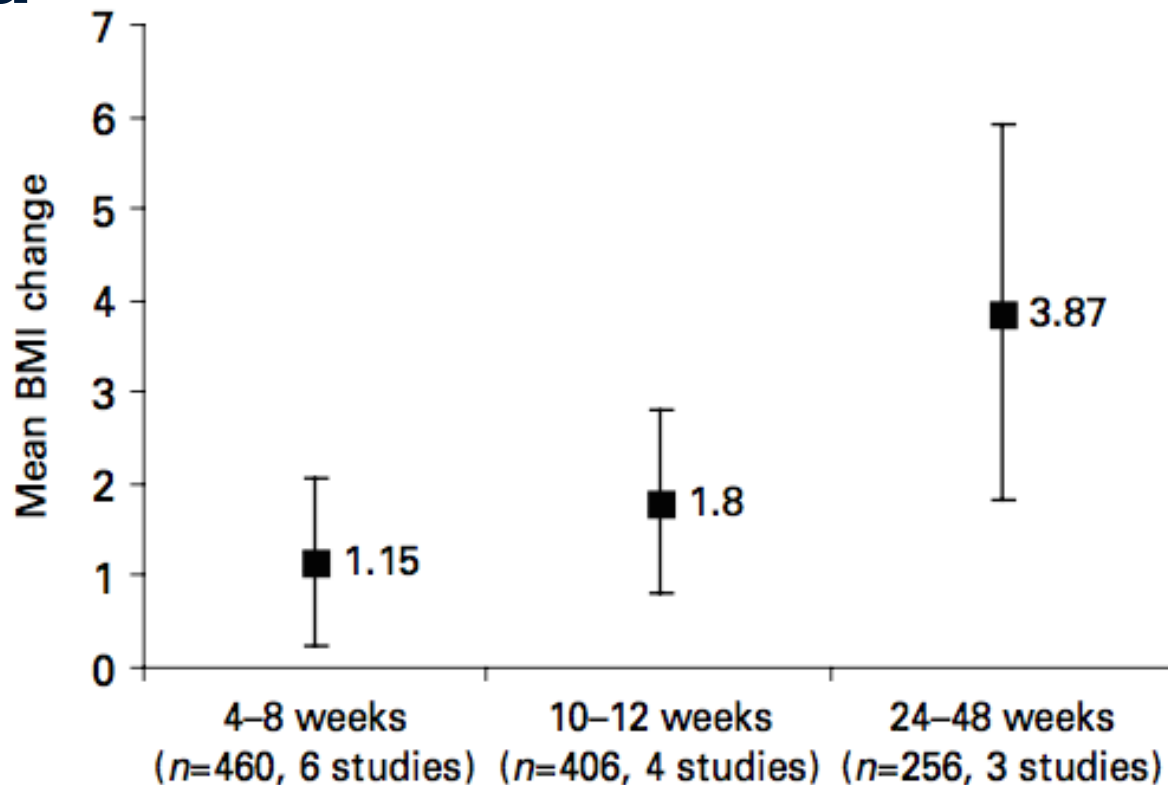


Fig. 3. Body mass index (BMI) mean change at three different follow-up times.

Almost All Antipsychotics Result in Weight Gain: A Meta-Analysis

Maarten Bak^{1*}, Annemarie Fransen², Jouke Janssen¹, Jim van Os^{1,3}, Marjan Drukker¹

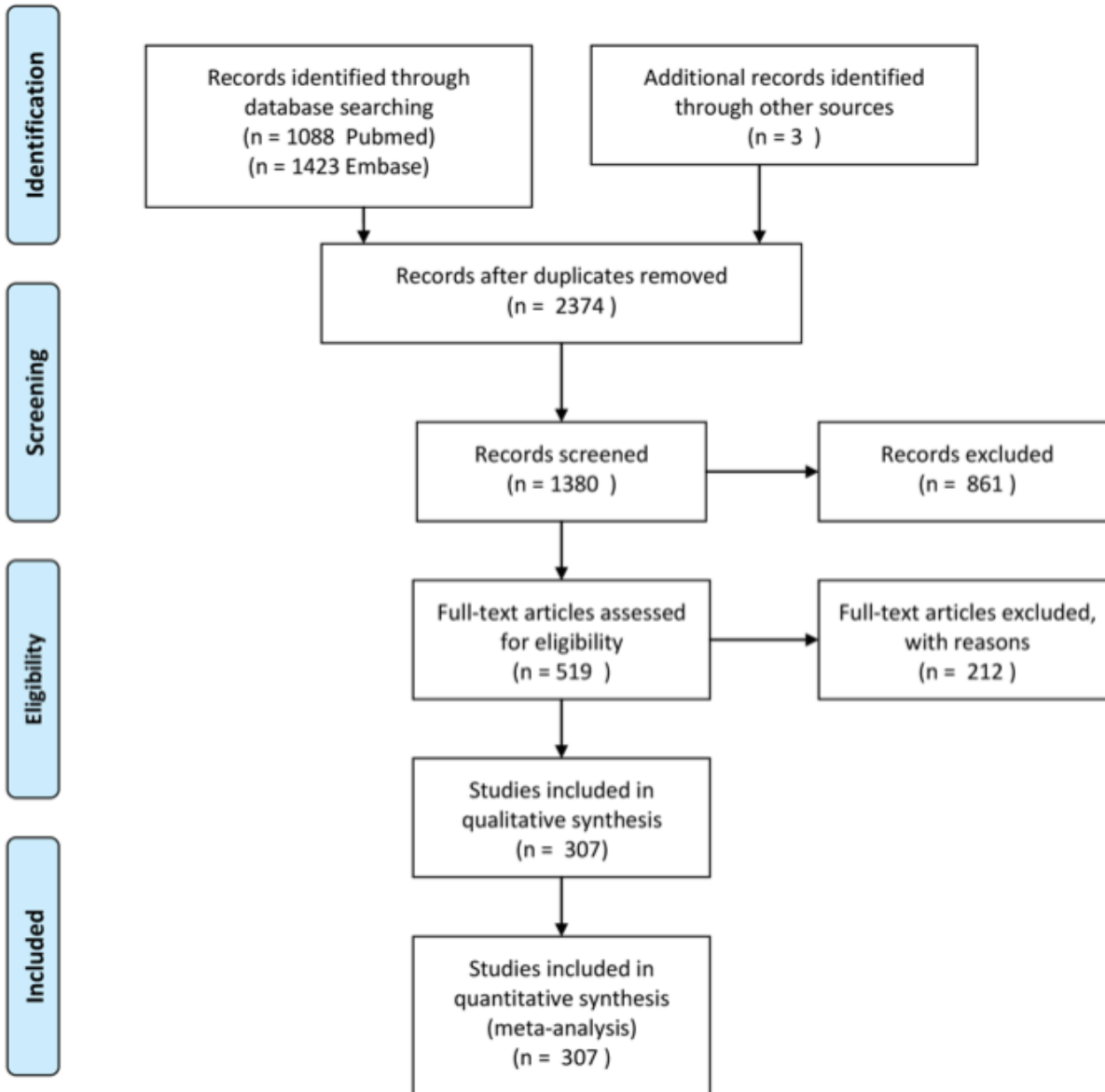
April 2014 | Volume 9 | Issue 4 | e94112

Are all AP associated with weight gain?

Are AP-naive patients more at risk?

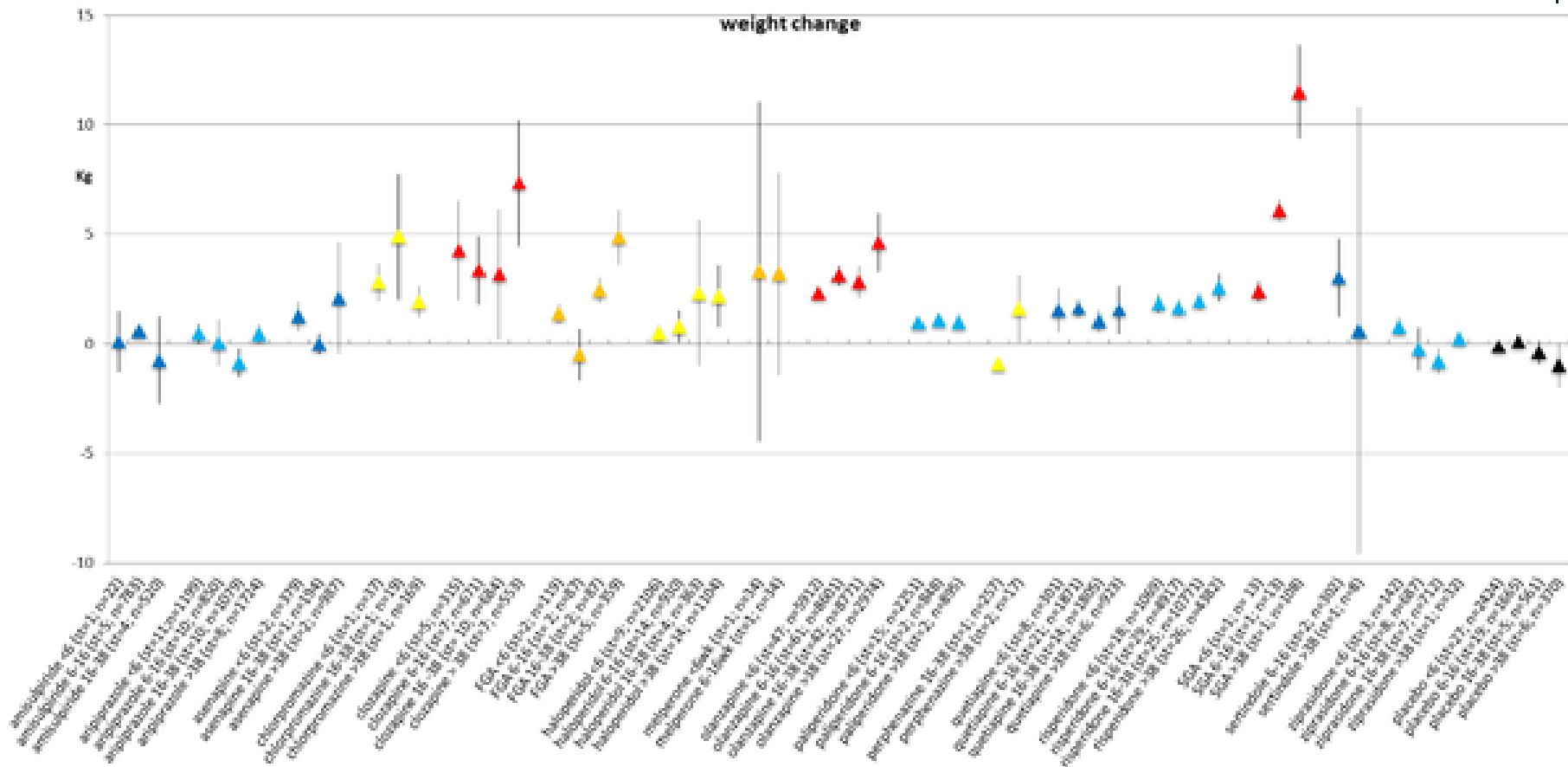
Is duration of AP-use related with more weight gain?

Flow chart



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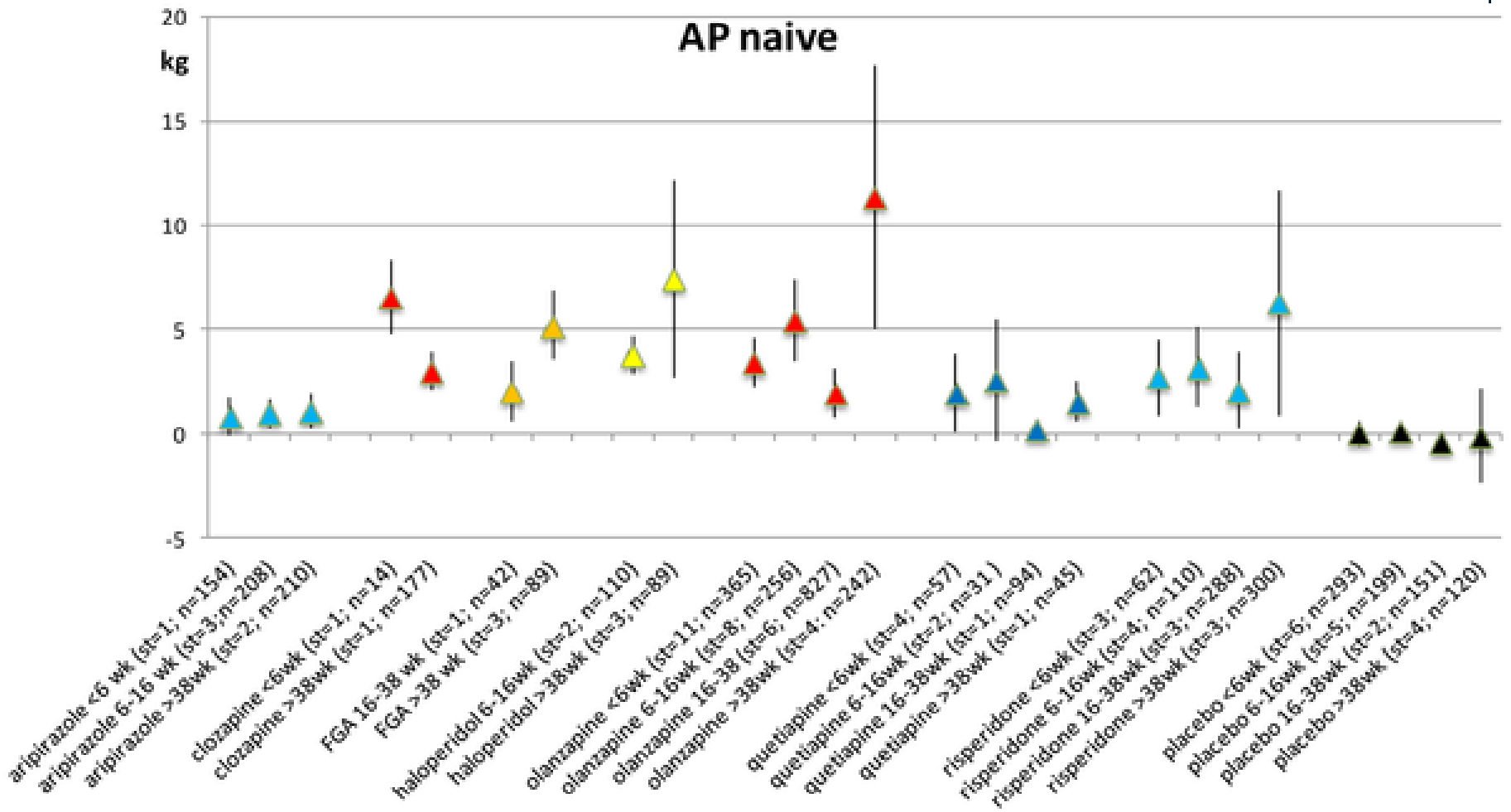
Figure 2. Weight change (in kg) per period per antipsychotic medication.



Bak M, Fransen A, Janssen J, van Os J, Drukker M (2014) Almost All Antipsychotics Result in Weight Gain: A Meta-Analysis. PLoS ONE 9(4): e94112. doi:10.1371/journal.pone.0094112
<http://journals.plos.org/plosone/article?id=info:doi/10.1371/journal.pone.0094112>

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Figure 3. Weight change (kg) per period only including AP-naïve samples.

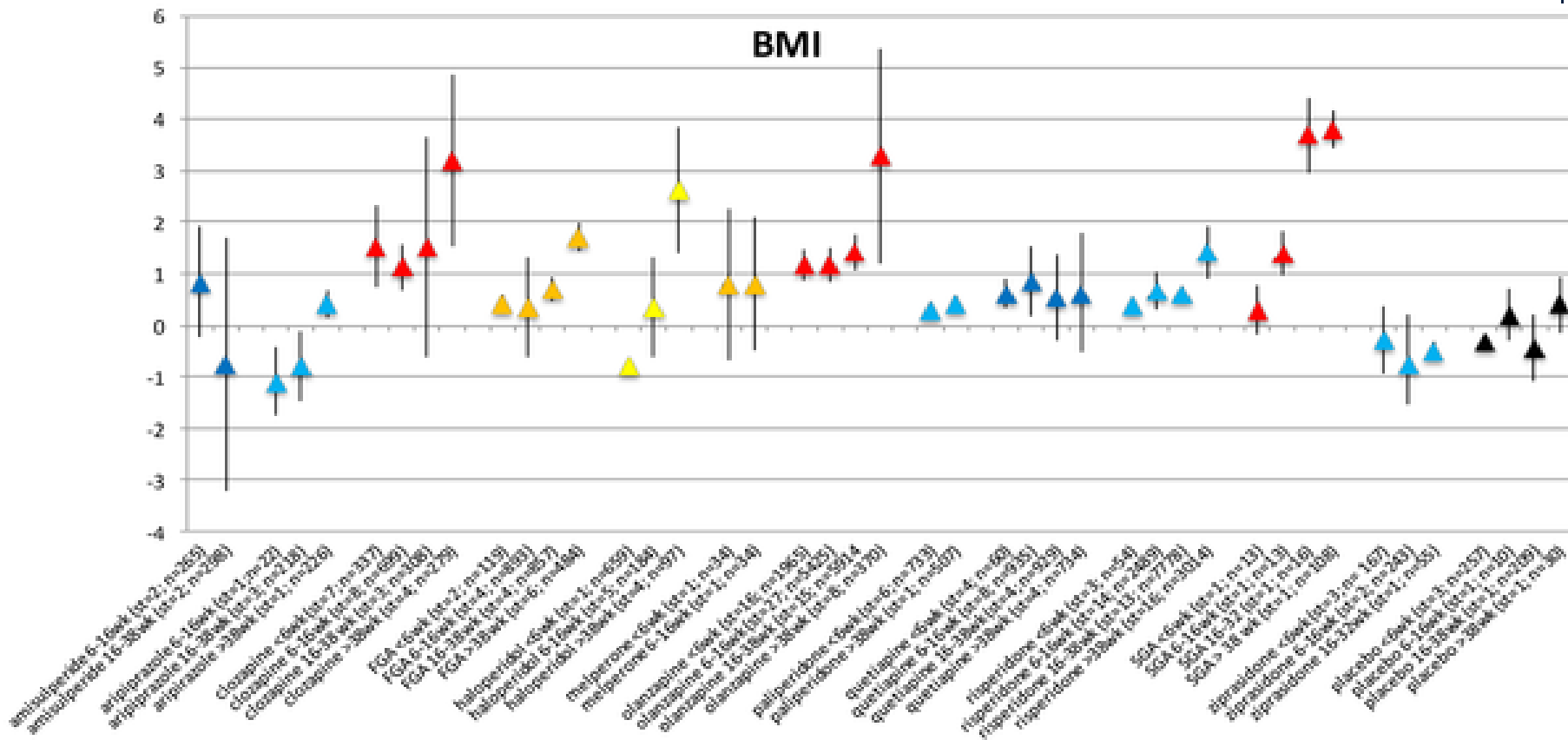


Bak M, Fransen A, Janssen J, van Os J, Drukker M (2014) Almost All Antipsychotics Result in Weight Gain: A Meta-Analysis. PLoS ONE 9(4): e94112. doi:10.1371/journal.pone.0094112

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Figure 4. BMI change per period.

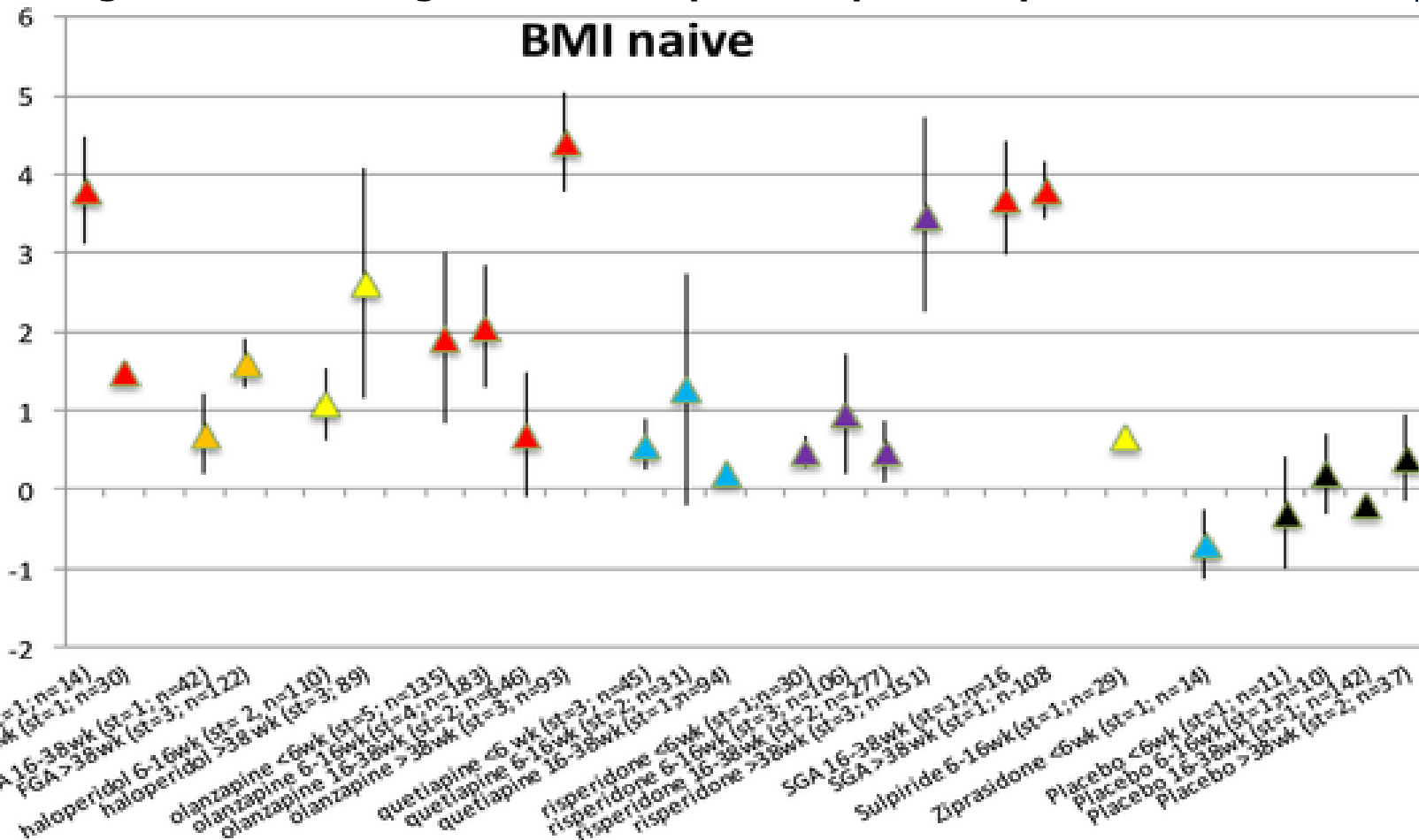


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<http://journals.plos.org/plosone/article?id=info:doi/10.1371/journal.pone.0094112>

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Figure 5. BMI change in AP naive patients per time period.

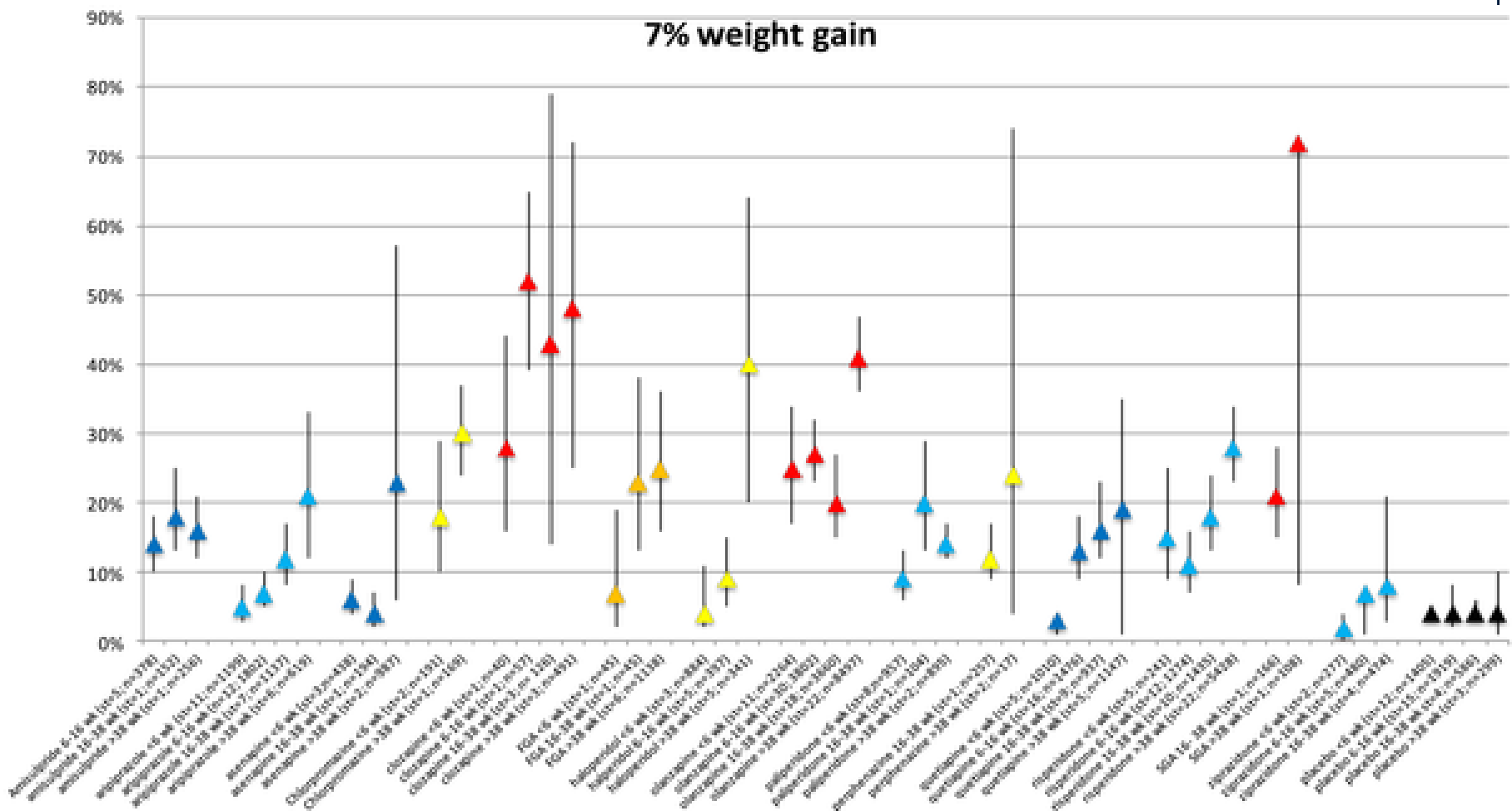


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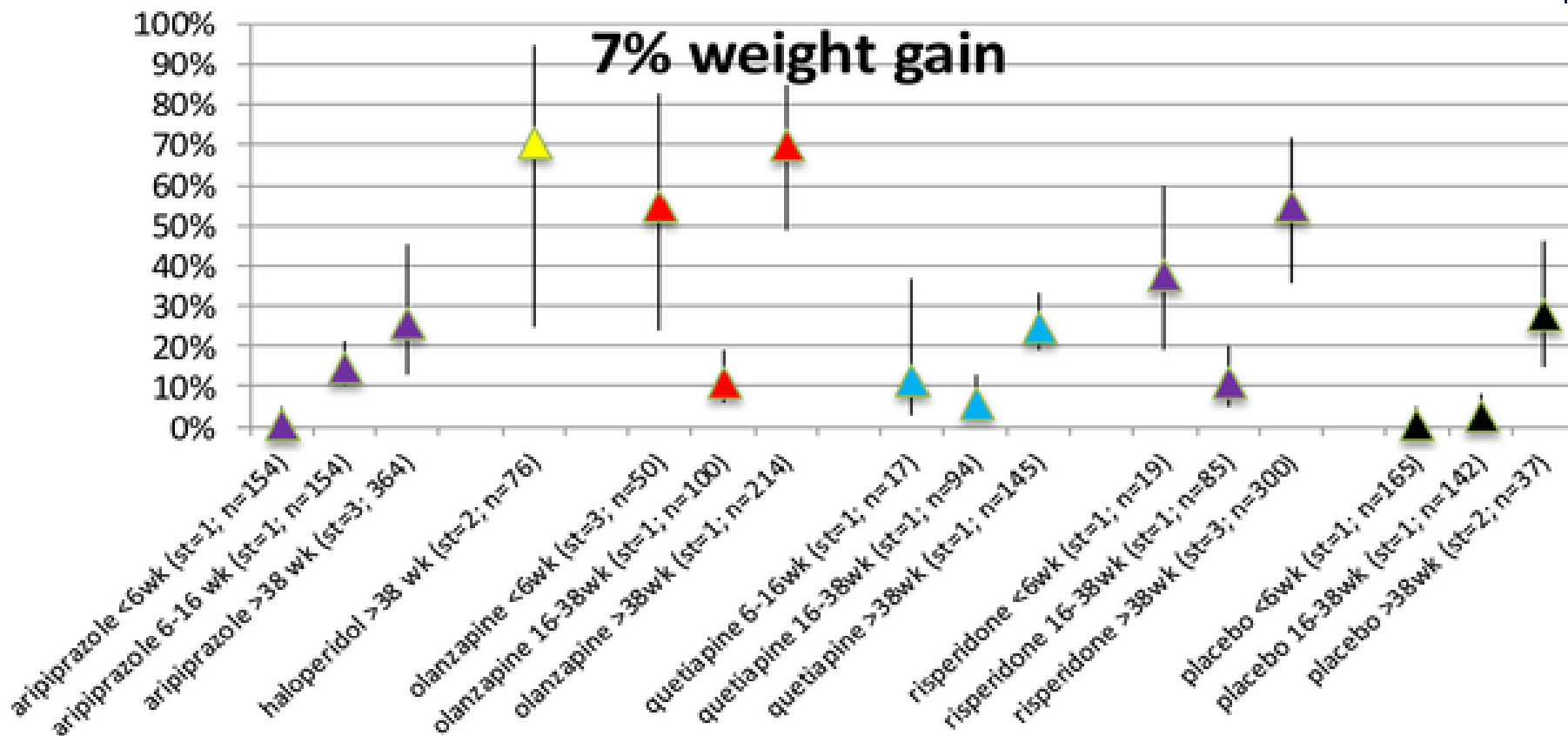
Figure 6. Proportion of weight increase per antipsychotic per time period.



Bak M, Fransen A, Janssen J, van Os J, Drukker M (2014) Almost All Antipsychotics Result in Weight Gain: A Meta-Analysis. PLoS ONE 9(4): e94112. doi:10.1371/journal.pone.0094112
<http://journals.plos.org/plosone/article?id=info:doi/10.1371/journal.pone.0094112>

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Figure 7. Proportion of weight increase in AP naïve.

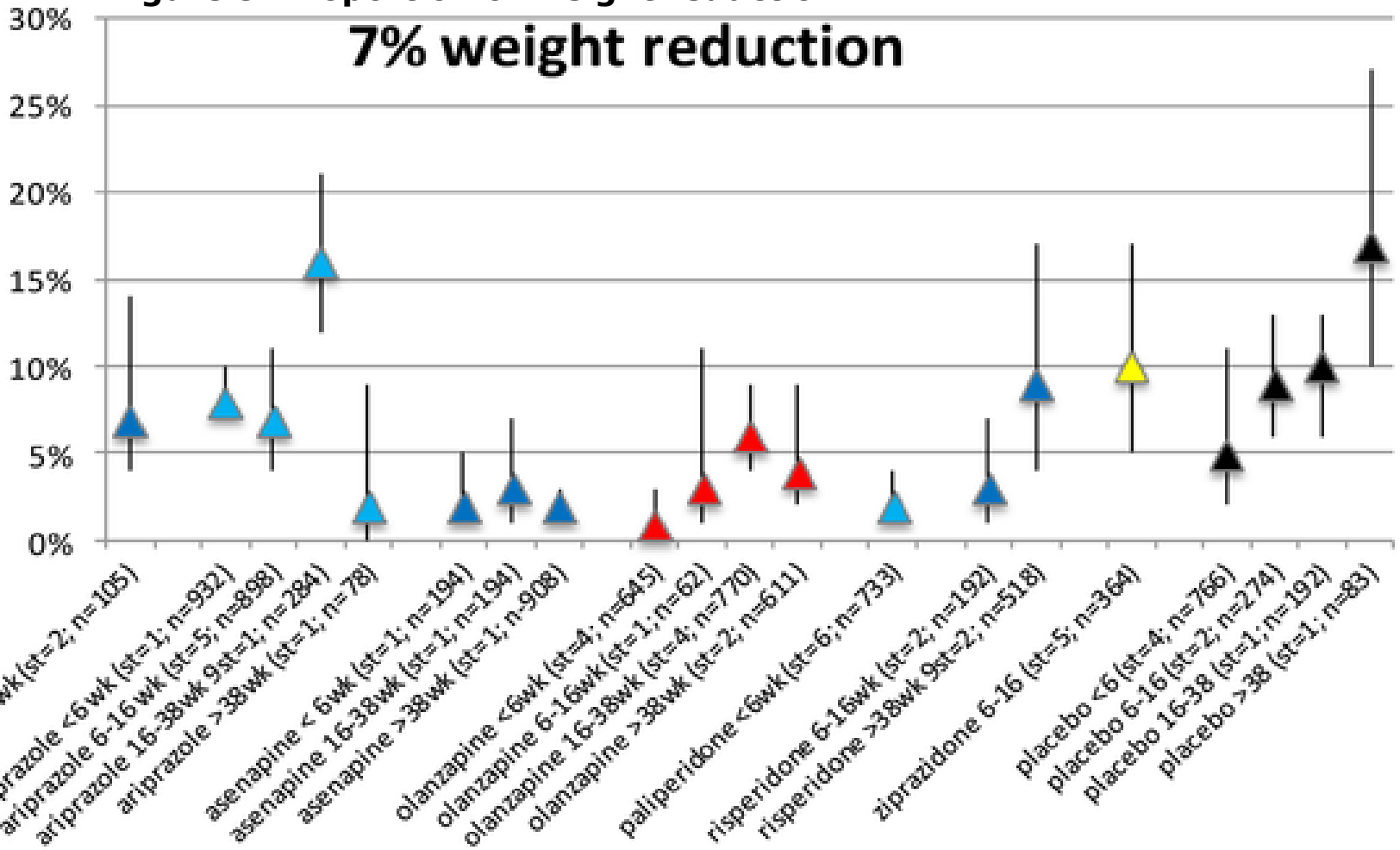


Bak M, Fransen A, Janssen J, van Os J, Drukker M (2014) Almost All Antipsychotics Result in Weight Gain: A Meta-Analysis. PLoS ONE 9(4): e94112. doi:10.1371/journal.pone.0094112

<http://journals.plos.org/plosone/article?id=info:doi/10.1371/journal.pone.0094112>

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Figure 8. Proportion of weight reduction.



Bak M, Fransen A, Janssen J, van Os J, Drukker M (2014) Almost All Antipsychotics Result in Weight Gain: A Meta-Analysis. PLoS ONE 9(4): e94112. doi:10.1371/journal.pone.0094112

<http://journals.plos.org/plosone/article?id=info:doi/10.1371/journal.pone.0094112>

Table 1. Metaregression of weight changes per period.

Period	aripiprazole	asenapine	clozapine	FGA	haloperidol	olanzapine	quetiapine	risperidone	ziprasidone	placebo
≤6 wk*	0	0	0	0	0	0	0	0	0	0
6–16 wk	<i>-0.46 -1.78-0.85</i>		<i>-2.37 -6.93-2.19</i>	<i>-2.19 -6.63-2.25</i>	<i>-0.25 -2.50-1.99</i>	<i>0.472 -0.16-1.60</i>	<i>0.05 -1.26-1.36</i>	<i>-0.58 -1.57-0.72</i>	<i>-0.97 -3.08-1.13</i>	<i>0.25 -0.14-0.64</i>
16–38 wk	-1.43 <i>-2.75-0.12</i>	<i>-1.25 -5.98-3.48</i>	<i>-3.81 -8.18-0.55</i>		<i>2.75 -0.58-6.08</i>	<i>0.26 -0.68-1.20</i>	<i>-0.54 -1.94-0.86</i>	<i>-0.03 -1.03-0.96</i>	<i>-1.68 -3.78-0.41</i>	<i>-0.26 -0.81-0.28</i>
>38 wk	<i>-0.20 -1.64-1.24</i>	<i>0.74 -3.24-4.72</i>	<i>1.09 -3.47-5.66</i>	<i>2.79 -1.12-6.70</i>	<i>1.81 -0.53-4.15</i>	1.74 <i>0.50-2.99</i>	<i>-0.85 -2.56-0.87</i>	<i>0.37 -0.63-1.38</i>	<i>-0.50 -3.07-2.68</i>	-1.08 <i>-1.88-0.29</i>

The coefficient indicates the changes of weight compared with the constant (period 1).
 * period 1 (≤6 wk) is the reference category.
 Data in italics indicate 95% confidence interval.
 The data in **bold** indicate significant difference in weight change of reference category.
 doi:10.1371/journal.pone.0094112.t001

Bak M, Fransen A, Janssen J, van Os J, Drukker M (2014) Almost All Antipsychotics Result in Weight Gain: A Meta-Analysis. PLoS ONE 9(4): e94112. doi:10.1371/journal.pone.0094112
<http://journals.plos.org/plosone/article?id=info:doi/10.1371/journal.pone.0094112>

Table 2. Metaregression of weight changes per period in drug-naïve patients.

Period	aripiprazole	olanzapine	Quetiapine	risperidone	placebo
≤6 wk*	0	0	0	0	0
6–16 wk	0.15 (–1.55–1.27)	1.30 (–2.34–4.93)	0.09 (–6.47–6.65)	–1.26 (–6.83–4.32)	0.24 (–0.69–1.17)
16–38 wk		–1.19 (–5.00–2.63)	–2.34 (–9.95–5.27)	–1.30 (–6.83–4.23)	–0.38 (–1.48–0.71)
>38 wk		5.41 (0.17–6.13)	–0.98 (–8.70–6.74)	2.31 (–3.38–7.91)	–0.36 (–2.0–1.29)

The coefficient indicates the changes of weight compared with the constant (period 1).

*constant is period 1 that serves as reference in change.

Data in italics indicate 95% confidence interval.

The outcome in **bold** indicate significant difference in weight change of reference category.

doi:10.1371/journal.pone.0094112.t002

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<http://journals.plos.org/plosone/article?id=info:doi/10.1371/journal.pone.0094112>

Is diagnosis a factor?

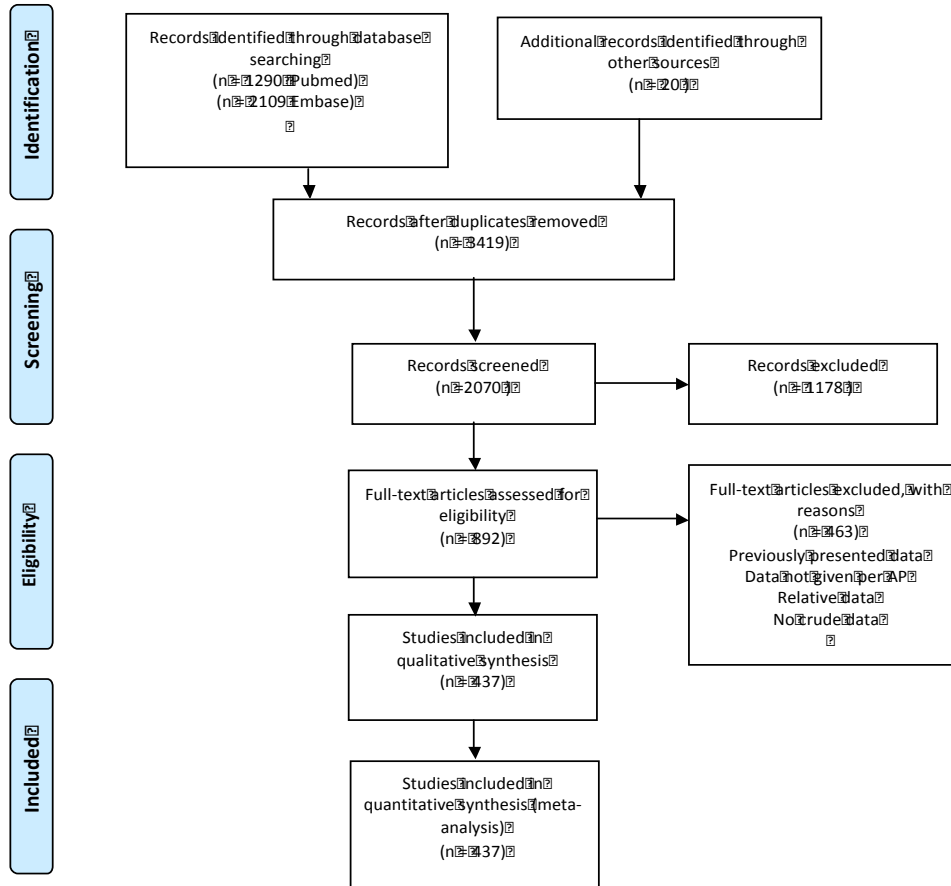


PRISMA 2009 Flow Diagram

1960-2014

Data period:
1960 – 2015

437 papers





	No med				Light med				Moderate med				Severe med			
	< 6	6-16	16-38	>38	< 6	6-16	16-38	>38	< 6	6-16	16-38	>38	< 6	6-16	16-38	>38
Sz	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Psy NAO																
Aff	0.29	1.64	0.27	-0.81	-1.03	-0.98	9.54	-5.13	-0.2	-0.23	-0.1	-1.09	-0.53	-0.17	-1.77	1.14
Cog	0.37		0.46		-0.1						-1.27		-2.0		-1.92	-4.75
Add													2.97			
No	0.34				-0.8								-0.9			
Rest	-0.98		0.52												-1.51	

Atypical Binding Profiles (K_i nM)

	D ₂	H ₁	5HT _{2C}	5HT _{2A}
Haloperidol	1.4	440	120	700
Clozapine	130	1.8	17	8.9
Olanzapine	20	2.8	10	3.3
Quetiapine	180	8.7	1400	220
Risperidone	2.2	19	10	0.29
Ziprasidone	3.1	47	0.72	0.39
Aripiprazole	0.34*	61	15	3.1

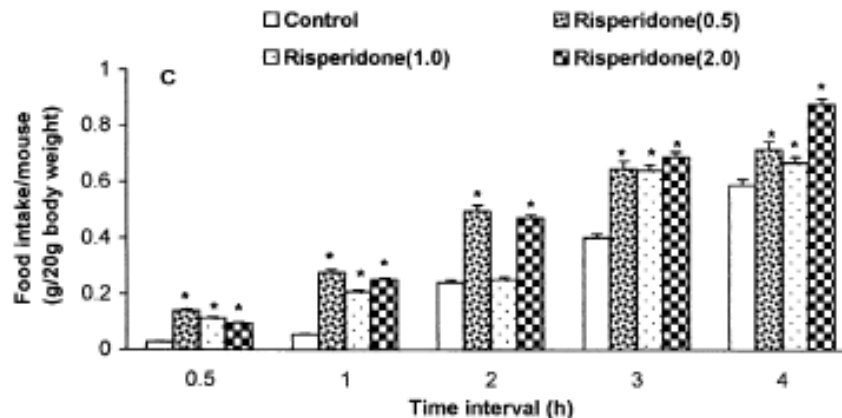
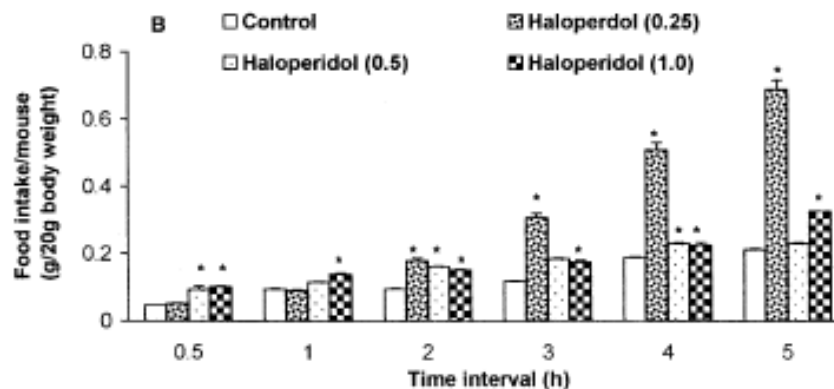
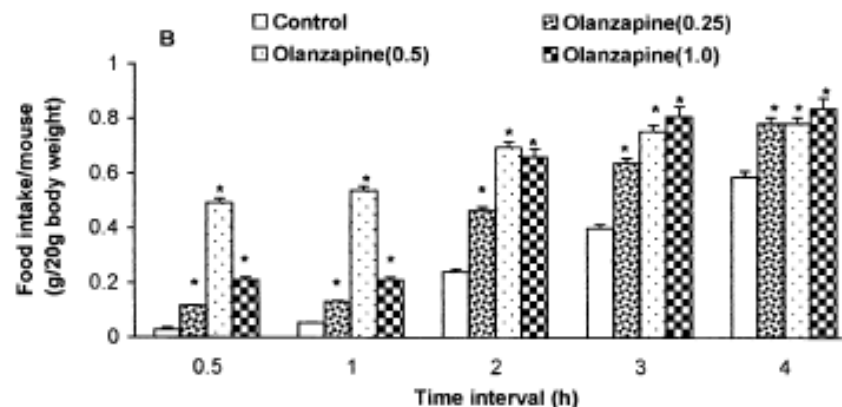
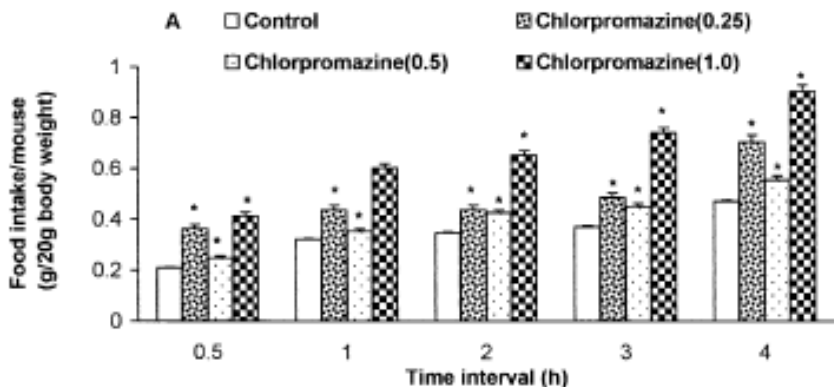
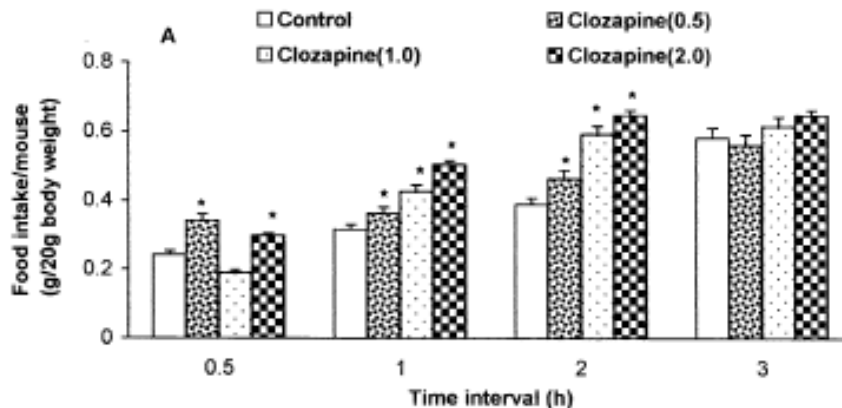
Remt "reward" systeem

D2 → blokkade negatieve feedback → Leptine stijgt → Appetite stijgt

Vergroot honger gevoel en eetlust

→ Meer voedsel intake

Intake changes in rats after AP use



Conclusion

- All antipsychotics result in weight gain
- Three risk groups
 - Limited: aripiprazol, amisulpride, ziprasidone
 - Moderate: haloperidol, risperidon, paliperidon, quetiapine
 - Severe: olanzapine & clozapine
- Weight gain is not associated with diagnosis