

Metformin to Manage Side Effects of Psychiatric Medications

Findings from an Integrated Health Care Delivery System

Esti Iturralde, PhD¹
Boriska Toth, PhD¹
Lucas Van Dyke, MD²
Roy Eyal, MD²
Jacqueline Kiang, MD²

Linda Kim, MD²
Maggie Mullen, LCSW²
J. Jewel Shim, MD²
Stacy Sterling, DrPH, MPH, MSW¹

¹ Kaiser Permanente Northern California Division of Research

² The Permanente Medical Group

HEALTH CARE SYSTEMS RESEARCH NETWORK (HCSRN) CONFERENCE

APRIL 8-10, 2019 | PORTLAND, OREGON

ACKNOWLEDGMENT

Kaiser Permanente Northern California Community Benefit Program

Severe Mental Illness & Chronic Disease

- 11 million adults in the U.S. have a severe form of mental illness (SMI)¹
- People with SMI die prematurely of chronic disease

¹ SAMHSA, 2017

The Largest Health Disparity We Don't Talk About

Americans with serious mental illnesses die 15 to 30 years earlier than those without.

By Dhruv Khullar

May 30, 2018



Death and Mental Illness

Patients with schizophrenia are at a greater risk of dying at any given age than the population at large, and this disparity has been increasing.

Standardized mortality ratio of patients with schizophrenia vs. the general population.



Medication-related Weight Gain

- Type 2 diabetes risk specifically associated with atypical antipsychotic medications¹
- Antipsychotic prescribing on the rise^{2,3}
- Rapid, noticeable weight gain⁴
- Mechanisms include antagonism of serotonin, dopamine and histamine receptors, hormones regulating appetite⁵

¹ Chwastiak et al., 2015; ² Olfson et al., 2012; ³ Hálfðánarson et al., 2017; ⁴ Kinon et al., 2005;

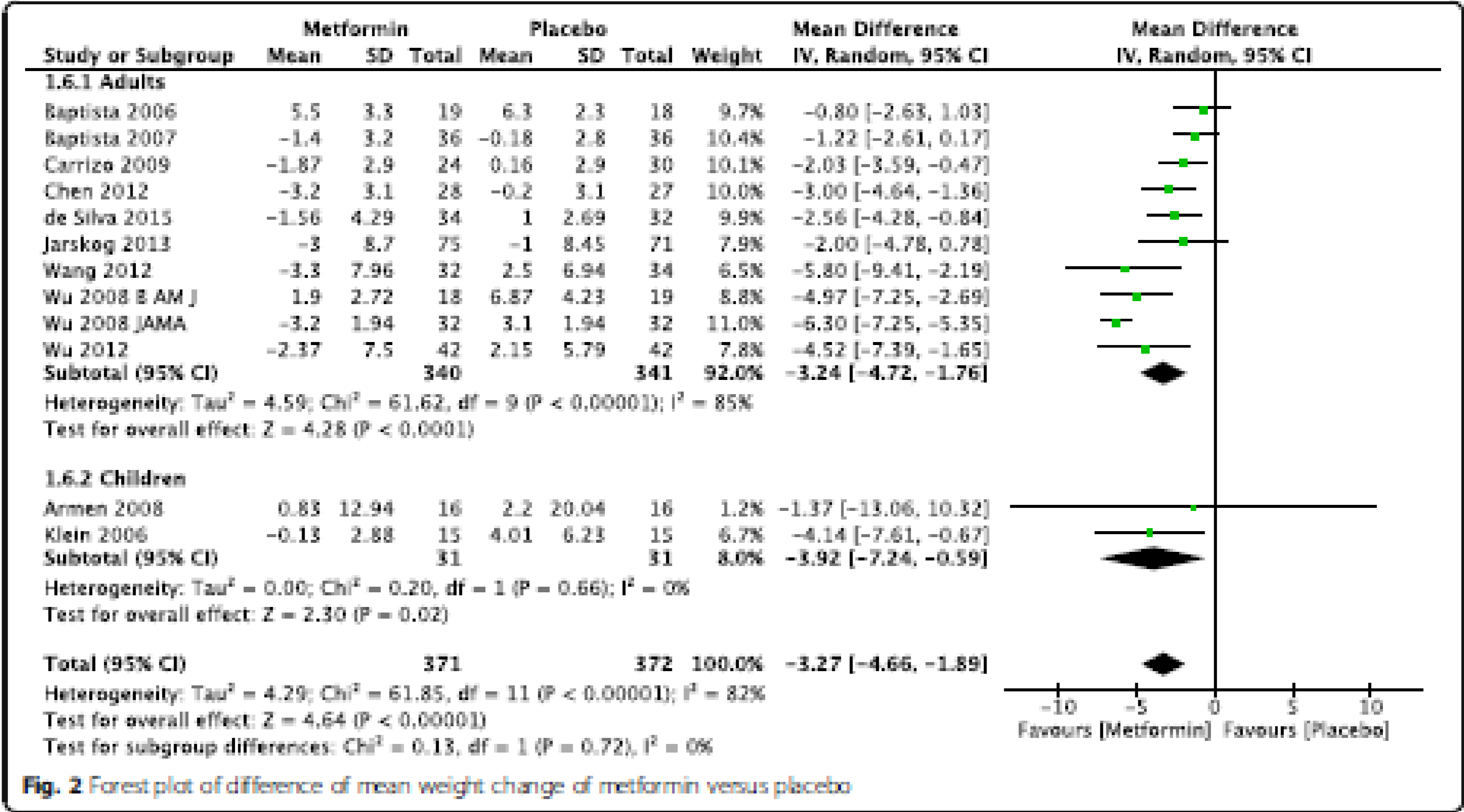
⁵ Prajapati, 2014

“Zyprexa is a great drug but it kills you”



Lauren Slater

Metformin for Medication-related Weight Gain



de Silva et al., *BMC Psychiatry*, 2016

Metformin for Medication-related Weight Gain

For both BMI and weight, the strength of the evidence was high and the effects of metformin were beneficial.²

McGinty et al., *Schizophrenia Bulletin*, 2016

This meta-analysis suggests that adjunctive metformin is an effective, safe, and reasonable choice for antipsychotic-induced weight gain.

Zheng et al., *Journal of Clinical Psychopharmacology*, 2015

**IS METFORMIN BEING USED IN THE REAL WORLD TO
MANAGE WEIGHT GAIN-RELATED SIDE EFFECTS?**

Among our KPNC members with SMI who are treated with atypical antipsychotic medications...

1. How many are also prescribed metformin?

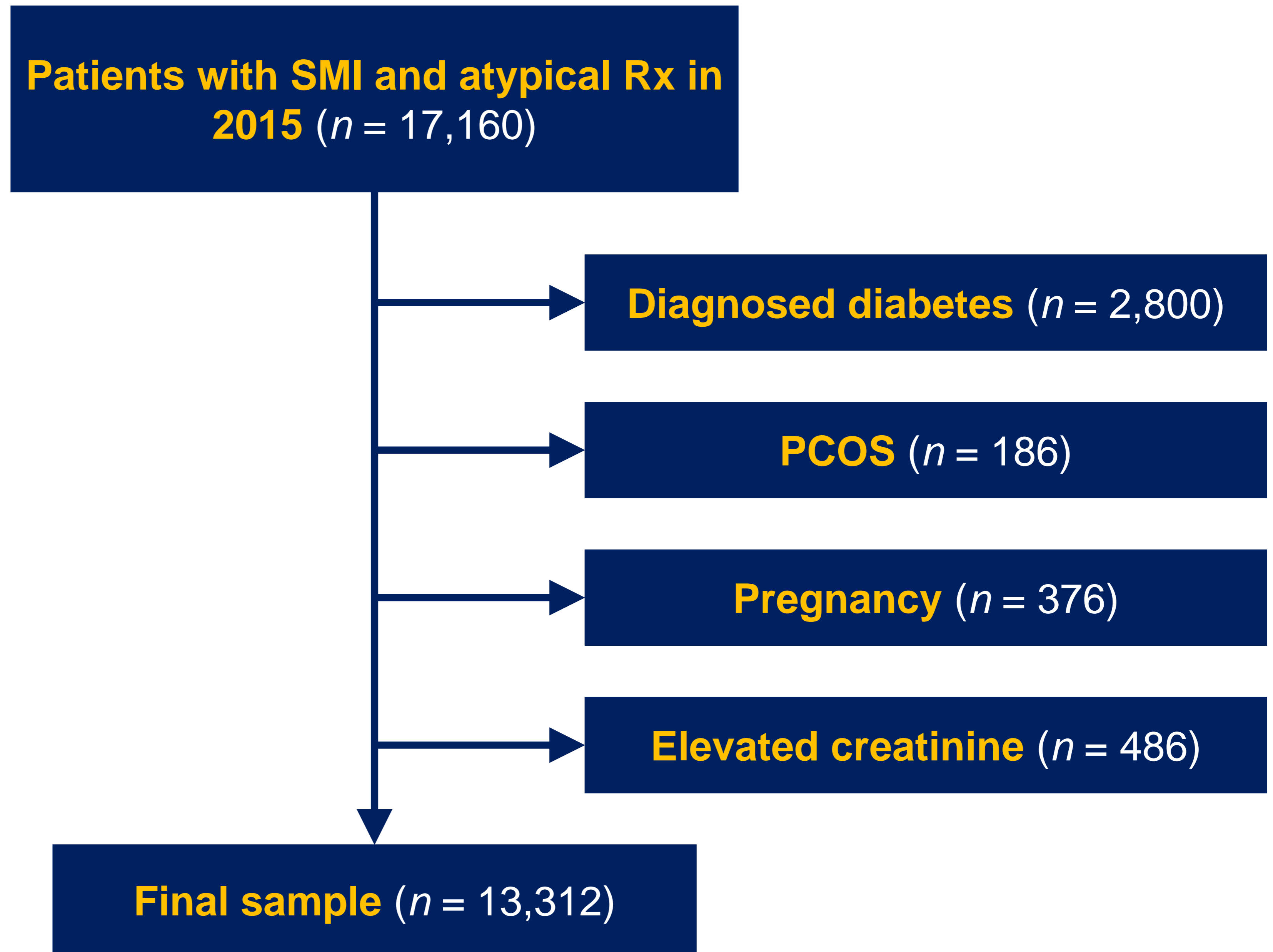
2. What predicts metformin prescriptions?

3. Who might benefit from further intervention?

Inclusion Criteria

- Continuously enrolled KPNC members age 18-65
- Atypical antipsychotic medication dispensed in 2015
- SMI
 - Psychotic disorder
 - Bipolar spectrum disorder
 - Other major affective disorder

Exclusions



Participant Characteristics

CHARACTERISTIC	MEAN ± SD OR %
Age	43.8 ± 13.4
18-34	28.4
35-49	32.4
50-65	39.3
Women	59.9
Race/ethnicity	
Non-Hispanic White	61.3
Latino/Hispanic	13.5
Black/African-American	8.8
Asian/Pacific Islander	8.2
Multiple	5.7
Other	2.6
High neighborhood poverty	11.9
Medicaid	16.0

RISK FACTORS FOR WEIGHT GAIN AND TYPE 2 DIABETES

Metabolic Risk Factors

37% with obesity



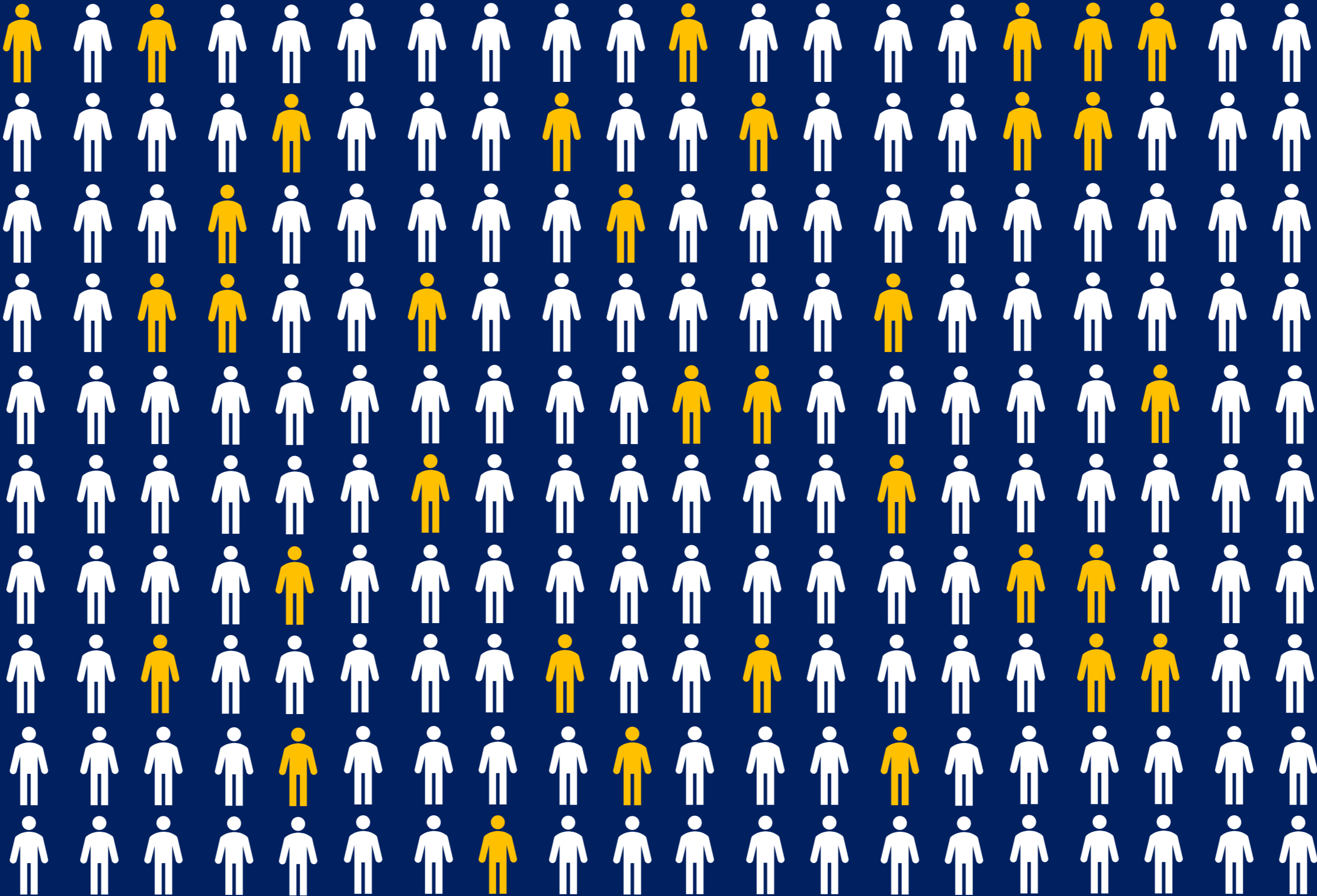
Metabolic Risk Factors

76% prescribed moderate- or high-risk atypical



Metabolic Risk Factors

17% prescribed olanzapine



Metabolic Risk Factors

25% newly prescribed atypical



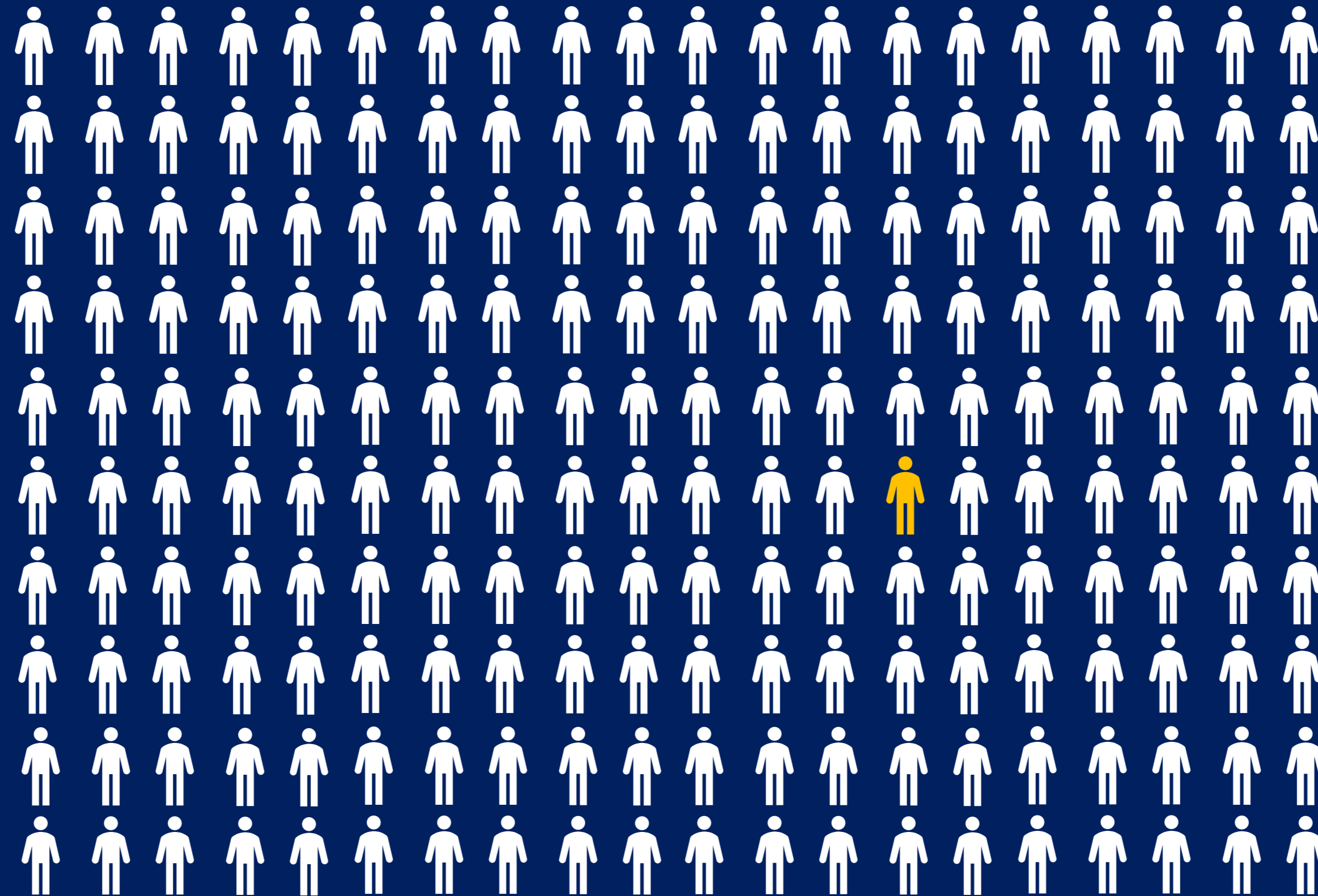
Metabolic Risk Factors

46% have a high glucose/A1C lab value

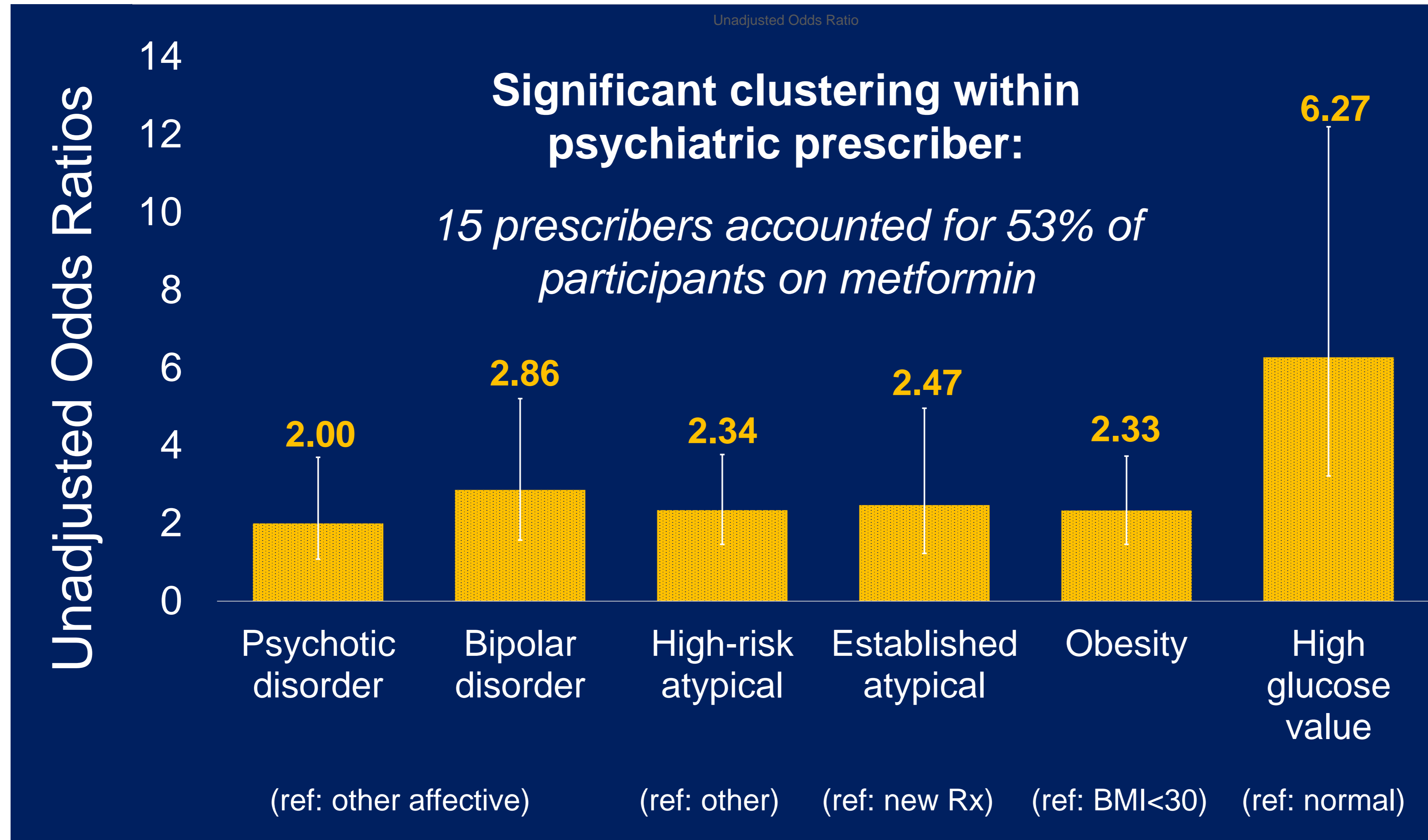


How many KPNC members with metformin prescriptions?

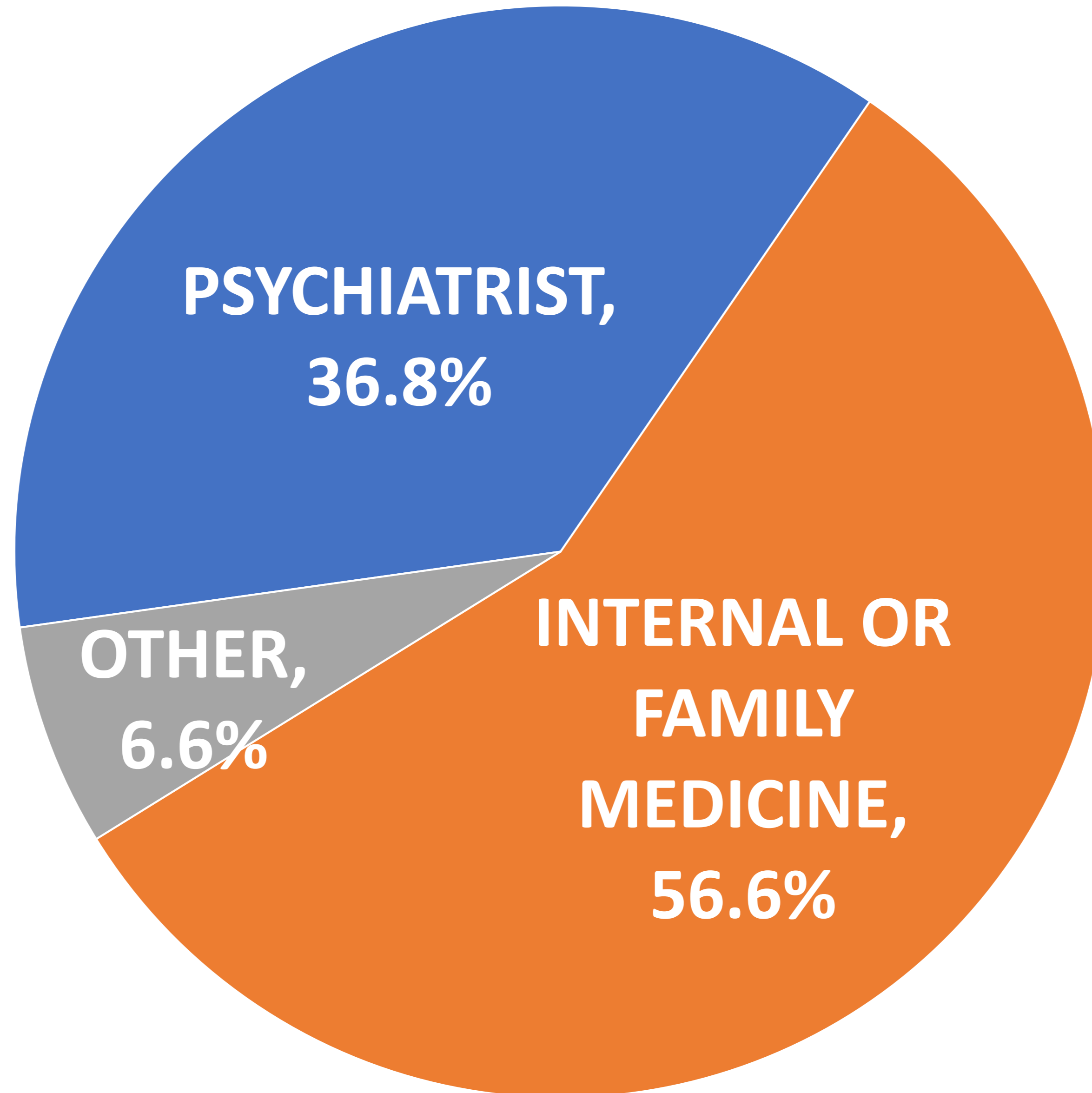
77 out of 13,312



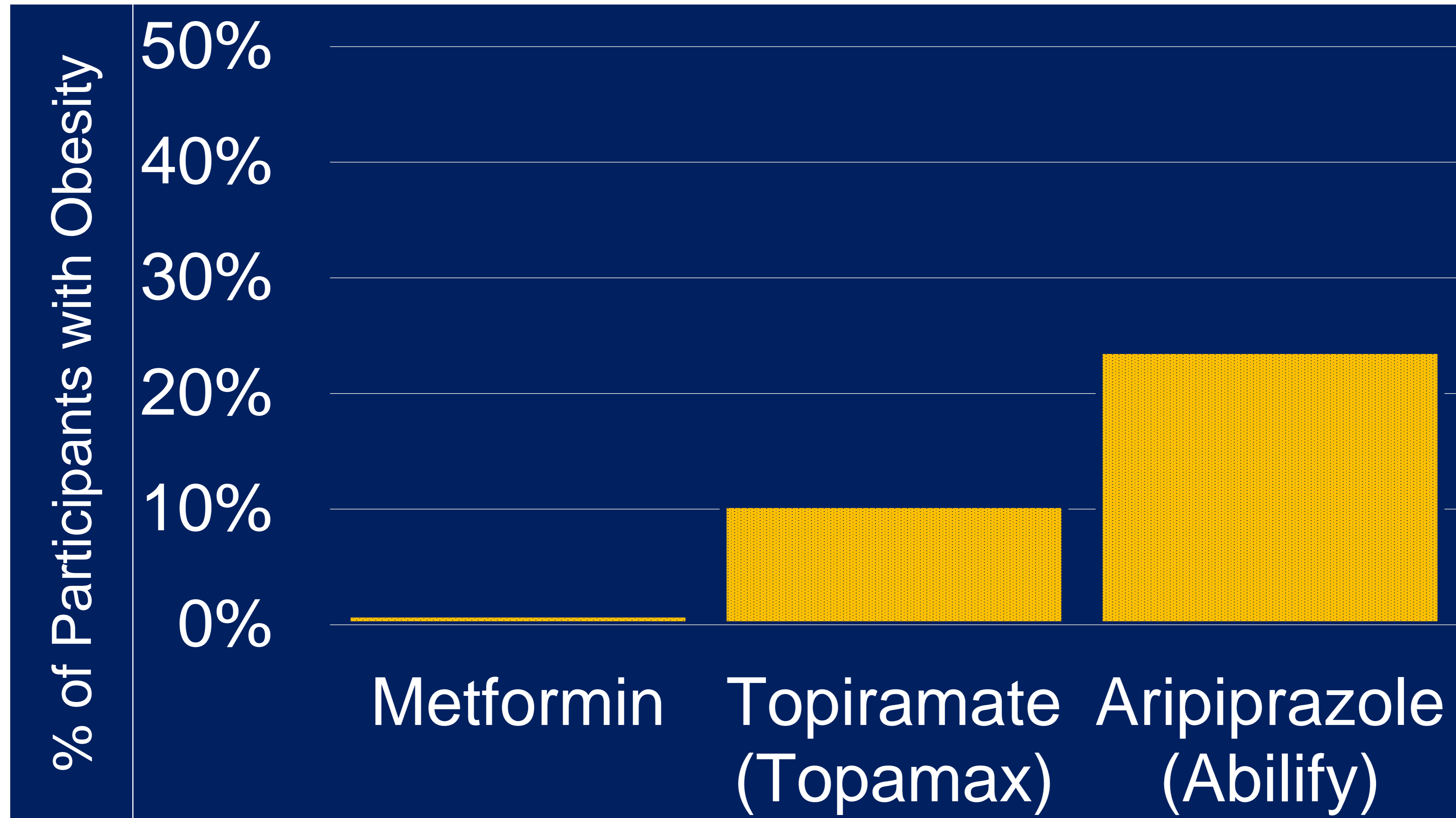
What predicts metformin co-prescription?



Who Prescribes Metformin?



Alternative approaches favored by psychiatrists?

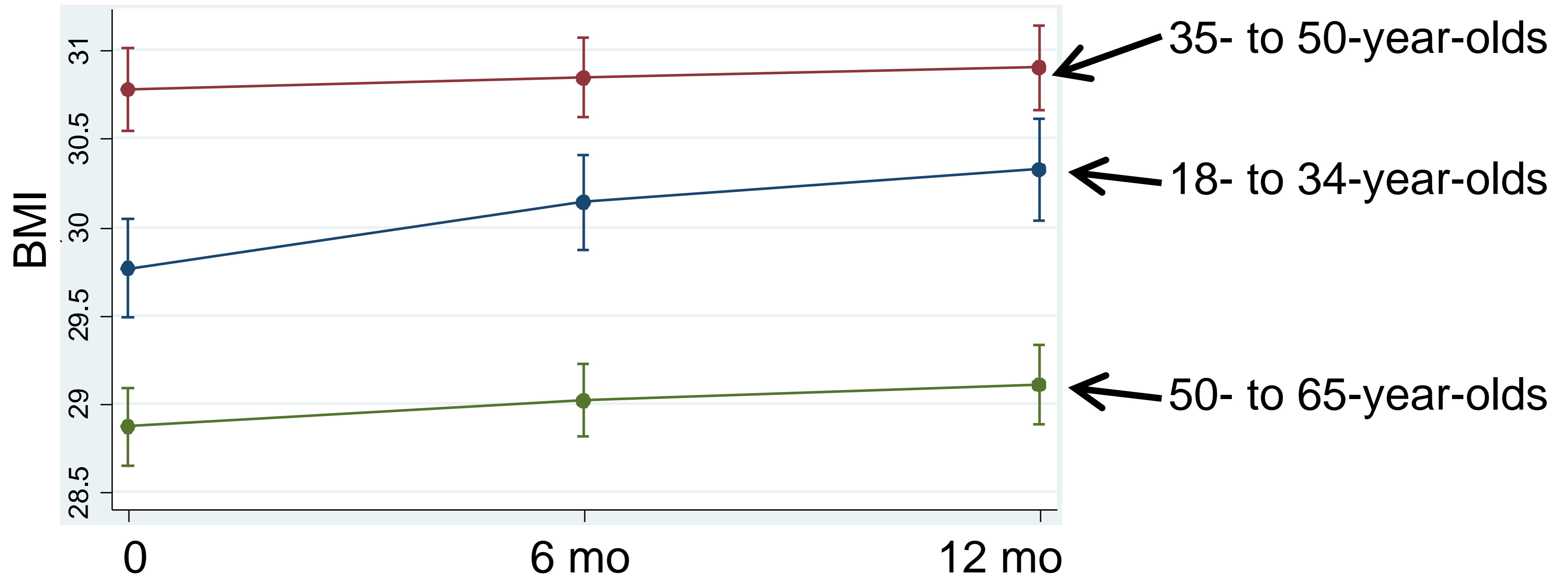


WHO MIGHT BENEFIT FROM FURTHER INTERVENTION?

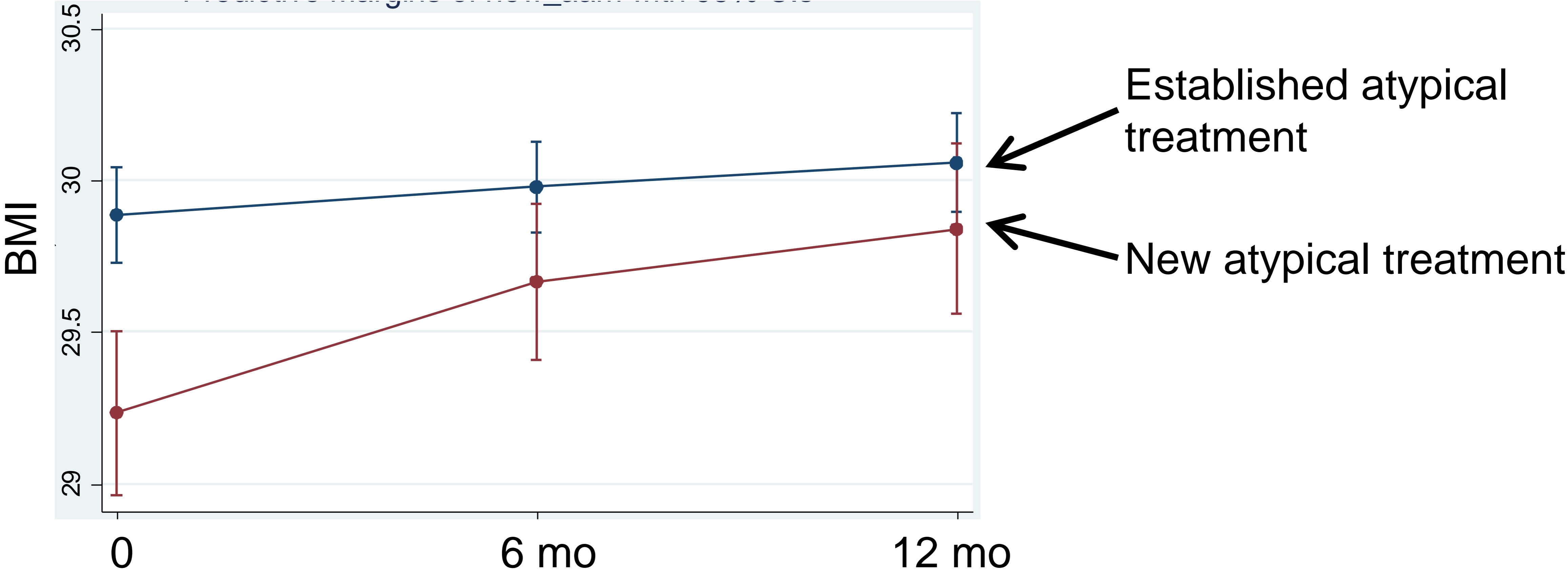
Predictors of BMI Over 1 Year

- BMI available for $N = 11,747$ (88%)
- Linear mixed effects model to assess predictors of BMI trajectory over time
 - What predicts BMI growth?
 - What predicts higher BMI level?

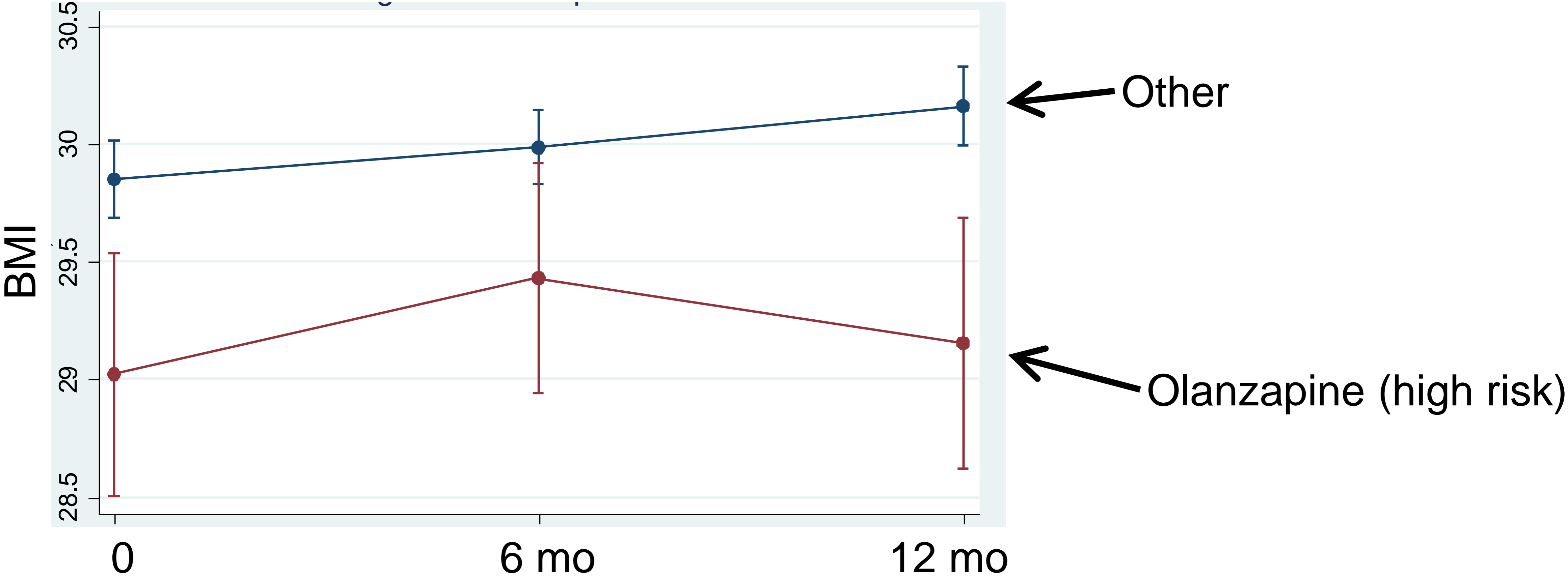
Younger and middle-aged adults



Established & new atypical treatment



Patients on high-risk atypicals



Discussion

- Metformin was infrequently prescribed to patients on atypical antipsychotic medications despite prevalent risk factors for medication-related weight gain and type 2 diabetes
- When prescribed, metformin may have been initiated to treat prediabetes, not medication-related weight gain
- Provider-level effects further suggest non-systematic implementation

Discussion (cont'd)

- BMI increased over 12 months for younger participants, those new to atypicals, and those prescribed higher-risk atypicals, holding other factors constant
- Study limitations included the correlational design and lack of data on non-pharmacological management
- Psychiatrists may benefit from more information about metformin and more collaboration with primary care on how to manage weight gain side effects

Questions?

estibaliz.m.iturralde@kp.org

References

- Ahrnsbrak, R., Bose, J., Hedden, S., Lipari, R., & Park-Lee, E. (2017). Key substance use and mental health indicators in the United States: Results from the 2016 National Survey on Drug Use and Health. Center for Behavioral Health Statistics and Quality, Substance Abuse and Mental Health Services Administration: Rockville, MD, USA.
- Chwastiak, L. A., Freudenreich, O., Tek, C., McKibbin, C., Han, J., McCarron, R., & Wisse, B. (2015). Clinical management of comorbid diabetes and psychotic disorders. *Lancet Psychiatry*, 2(5), 465-476.
- de Silva, V. A., Suraweera, C., Ratnatunga, S. S., Dayabandara, M., Wanniarachchi, N., & Hanwella, R. (2016). Metformin in prevention and treatment of antipsychotic induced weight gain: a systematic review and meta-analysis. *BMC Psychiatry*, 16(1), 341-350.
- Hálfðánarson, Ó., Zoëga, H., Aagaard, L., Bernardo, M., Brandt, L., Fusté, A. C., . . . Huybrechts, K. F. (2017). International trends in antipsychotic use: a study in 16 countries, 2005–2014. *European Neuropsychopharmacology*, 27(10), 1064-1076.
- Kinon, B. J., Kaiser, C. J., Ahmed, S., Rotelli, M. D., & Kollack-Walker, S. (2005). Association between early and rapid weight gain and change in weight over one year of olanzapine therapy in patients with schizophrenia and related disorders. *Journal of Clinical Psychopharmacology*, 25(3), 255-258.
- McGinty, E. E., Baller, J., Azrin, S. T., Juliano-Bult, D., & Daumit, G. L. (2015). Interventions to address medical conditions and health-risk behaviors among persons with serious mental illness: a comprehensive review. *Schizophrenia Bulletin*, 42(1), 96-124.
- Olfson, M., Blanco, C., Liu, S., Wang, S., & Correll, C. U. (2012). National trends in the office-based treatment of children, adolescents, and adults with antipsychotics. *Archives of General Psychiatry*, 69(12), 1247-1256. doi:10.1001/archgenpsychiatry.2012.647
- Prajapati, A. R. (2014). Role of metformin in the management of antipsychotic-induced weight gain. *Progress in Neurology and Psychiatry*, 18(6), 33-38.
- Wu, R.-R., Zhao, J.-P., Jin, H., Shao, P., Fang, M.-S., Guo, X.-F., . . . Li, L.-H. (2008). Lifestyle intervention and metformin for treatment of antipsychotic-induced weight gain: a randomized controlled trial. *JAMA*, 299(2), 185-193.
- Zheng, W., Zhang, Q.-E., Cai, D.-B., Yang, X.-H., Ungvari, G. S., Ng, C. H., . . . Xiang, Y.-T. (2019). Combination of metformin and lifestyle intervention for antipsychotic-related weight gain: a meta-analysis of randomized controlled trials. *Pharmacopsychiatry*, 52(01), 24-31.