



# **Long-Term Medical Outcomes of Antipsychotic Treatment**

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## Disclosures

Received advisory  
board/speaker's  
fees/consultant fees/owns  
stock: BMS, Neopharm,  
Dexcel, Janssen, Lundbeck,  
Minerva, Pfizer, Acadia, Roche,  
Teva, Clearmind,  
MapiPharma

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John Davis
Jari Tiihonen
Heidi Taipale

# Some exposures take years before adverse outcomes become apparent



## Tobacco Use

Long-term smoking leads to a 12-fold increase in lung cancer risk for heavy smokers (> 21.3 pack-years) and a 30-year latency period for the onset of COPD.



## Chronic Obesity

Over 20 years of abdominal obesity is linked to a higher risk of coronary calcification (aHR 2.48; 95% CI, 1.53-4.01).



## Hypertension

Each year of untreated hypertension increases cardiovascular risk by ~4%, reaching over twofold risk after ~20 years..

# Drug Development & Approval Process

- ✓ **FDA Approval:** Typically requires at least two successful Phase 3 clinical trials (or 1 successful phase 3 with confirmatory evidence in specific cases)
- 🕒 **Observation Period:** Open-label extensions often monitor safety for ~12 months.

No mandatory monitoring after 12 months



# Short-term clinical trials failed to detect risks that only appeared after long-term use: Vioxx

**May 1999**

FDA Approval of Rofecoxib  
(Vioxx) as an anti-inflammatory  
based on efficacy

**Feb 2004**

Prospective randomized trial  
confirm increased CV risk at  
18 months

**Nov 2000**

First indication of  
cardiovascular (CV)  
complications

**Sep 2004**

Global withdrawal after  
mean use of 2.4 years

**How can we follow up  
patients for the appearance  
of adverse outcomes  
overtime: Use of clinical and  
administrative databases**

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# Clalit Health Services Database



## Largest HMO in Israel

Covering ~55% of the population (~4.8M).

Representative of the entire population.



## Longitudinal Data

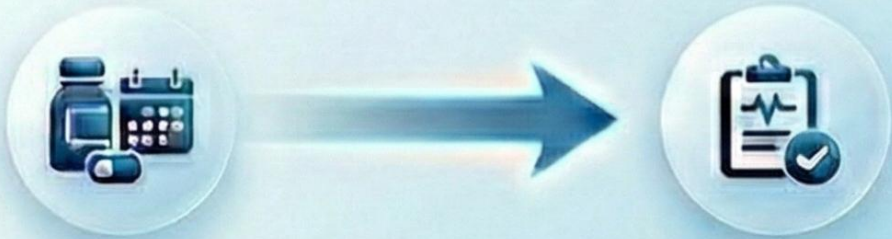
Centralized EMR since 2000.

- Diagnoses
- Hospitalization
- Filled prescriptions

Data are validated\*

# Potential Research Design

## Prospective Cohort Design \*

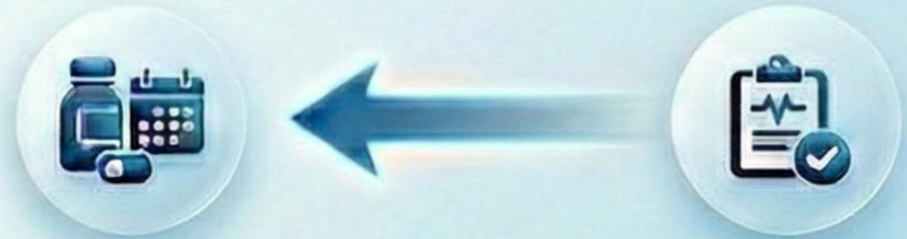


**Exposure**

**Outcome**

Studies look forward in time, starting from defined exposures and assessing outcomes at a specific point.

## Retrospective Case Control Design



**Look back for exposure**

**Start with outcome**

Studies look back in time, starting from established outcomes and assessing past exposures.

\*Risk of exclusion due to defined exposure windows

# Antipsychotics increase risk for osteoporosis and EPS; Do they increase risk for hip fracture?

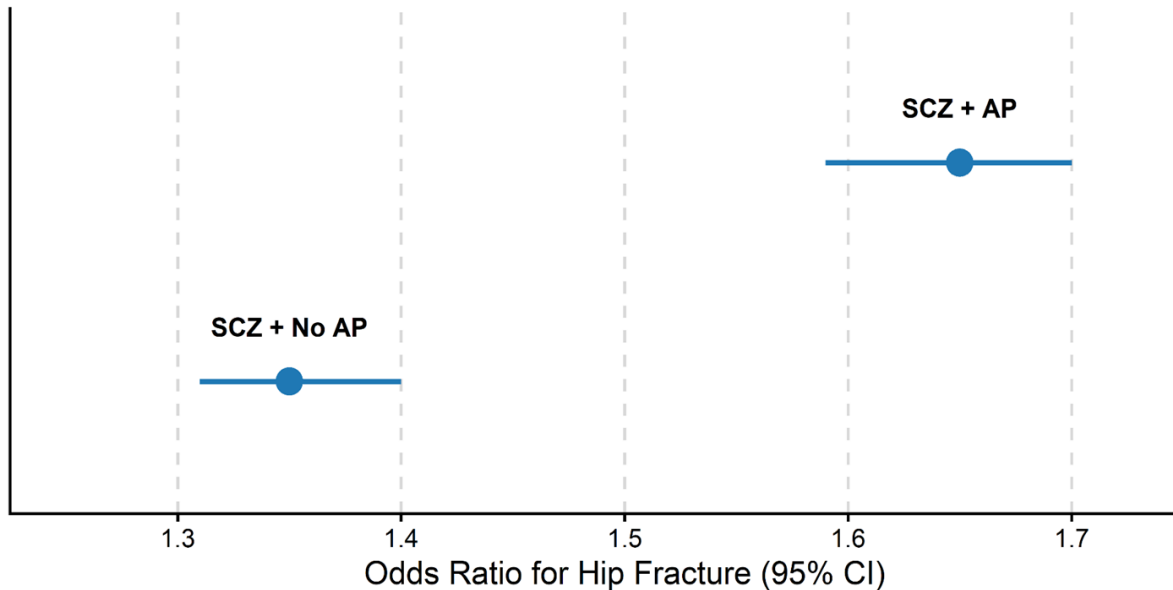
Retrospective nested case-control design.

Population:

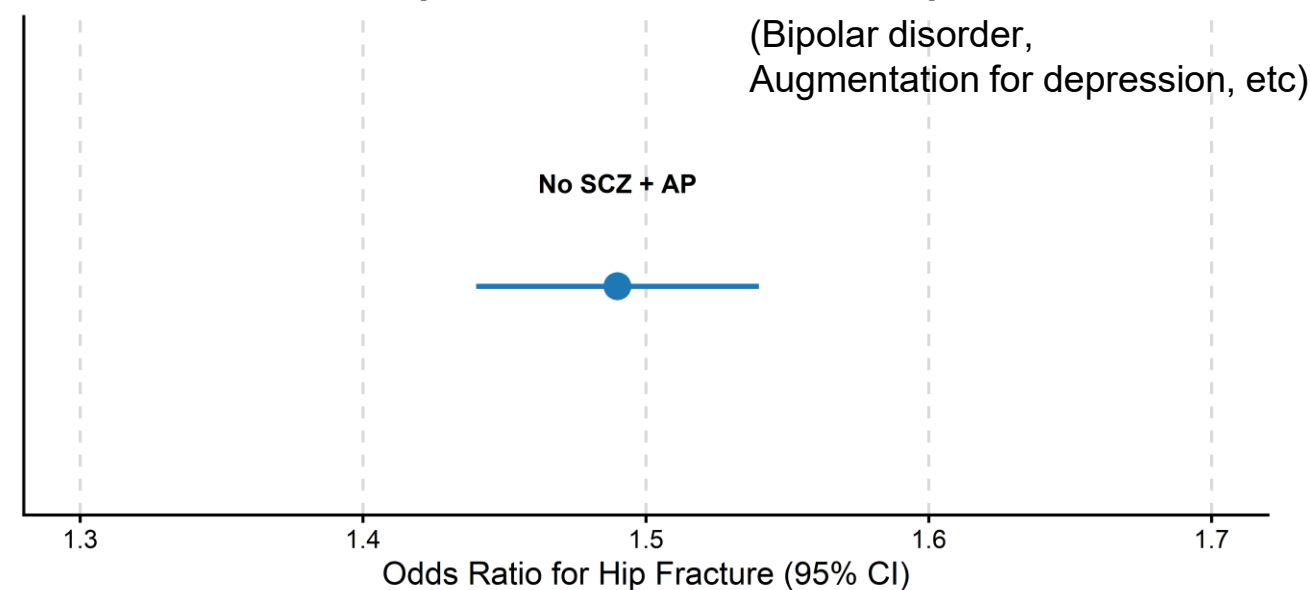
- 17,935 patients with hip fracture diagnosed with schizophrenia
- 17,935 controls matched for age, sex and SES\*.

Covariates: Sex, age, SES, obesity, COPD\* and CCI\*.

**Risk for Hip Fracture Risk – Schizophrenia**



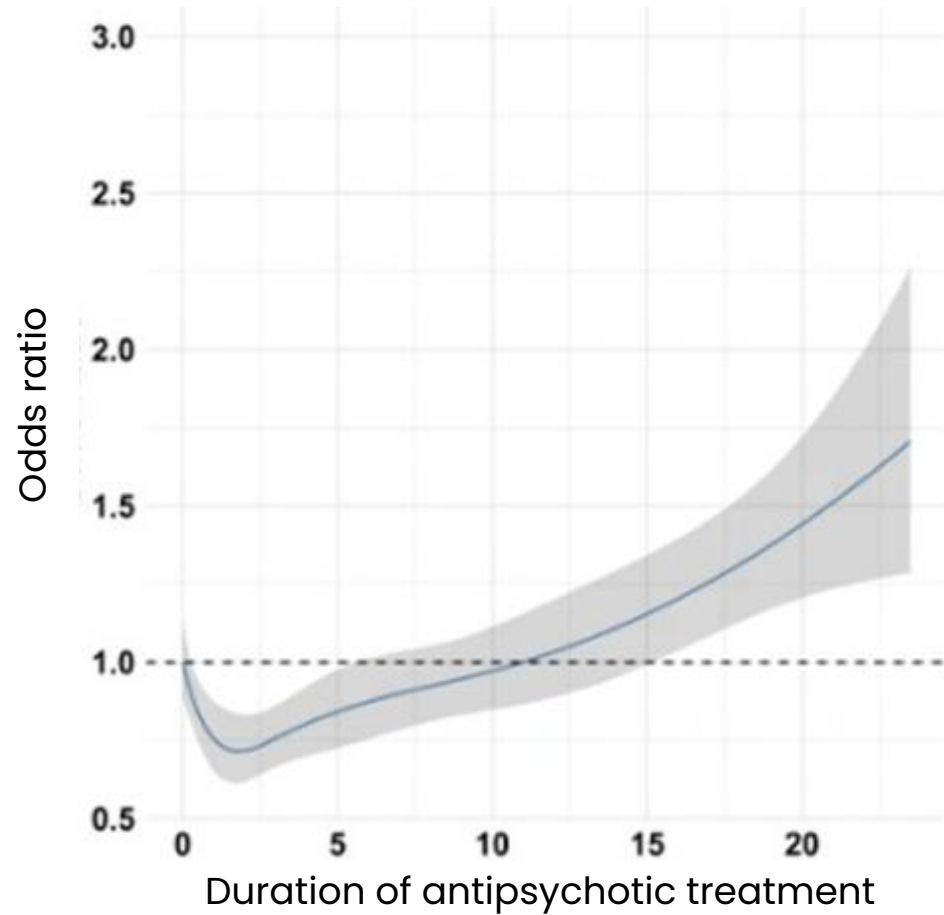
**Risk for Hip Fracture – Without Schizophrenia**



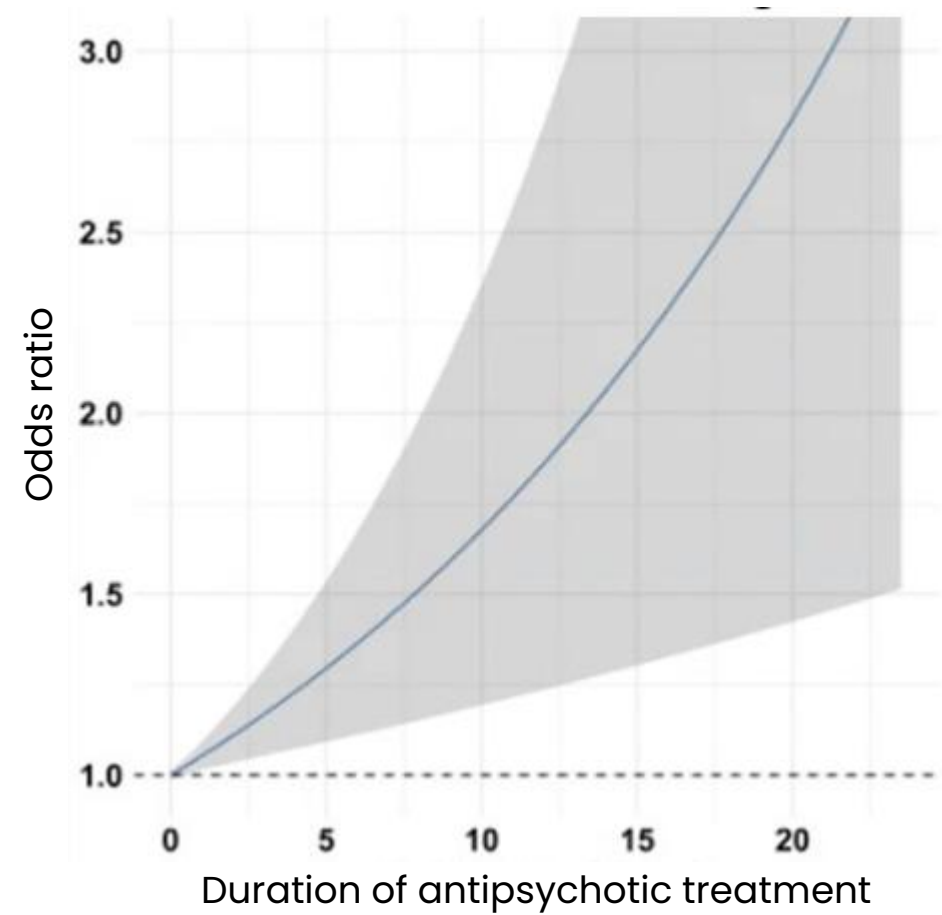
\*SES = socioeconomic status; COPD = chronic obstructive pulmonary disease; CCI = Charlson Comorbidity Index

# Antipsychotics and the Risk for Hip Fracture

## Patients with Schizophrenia



## Patients without Schizophrenia

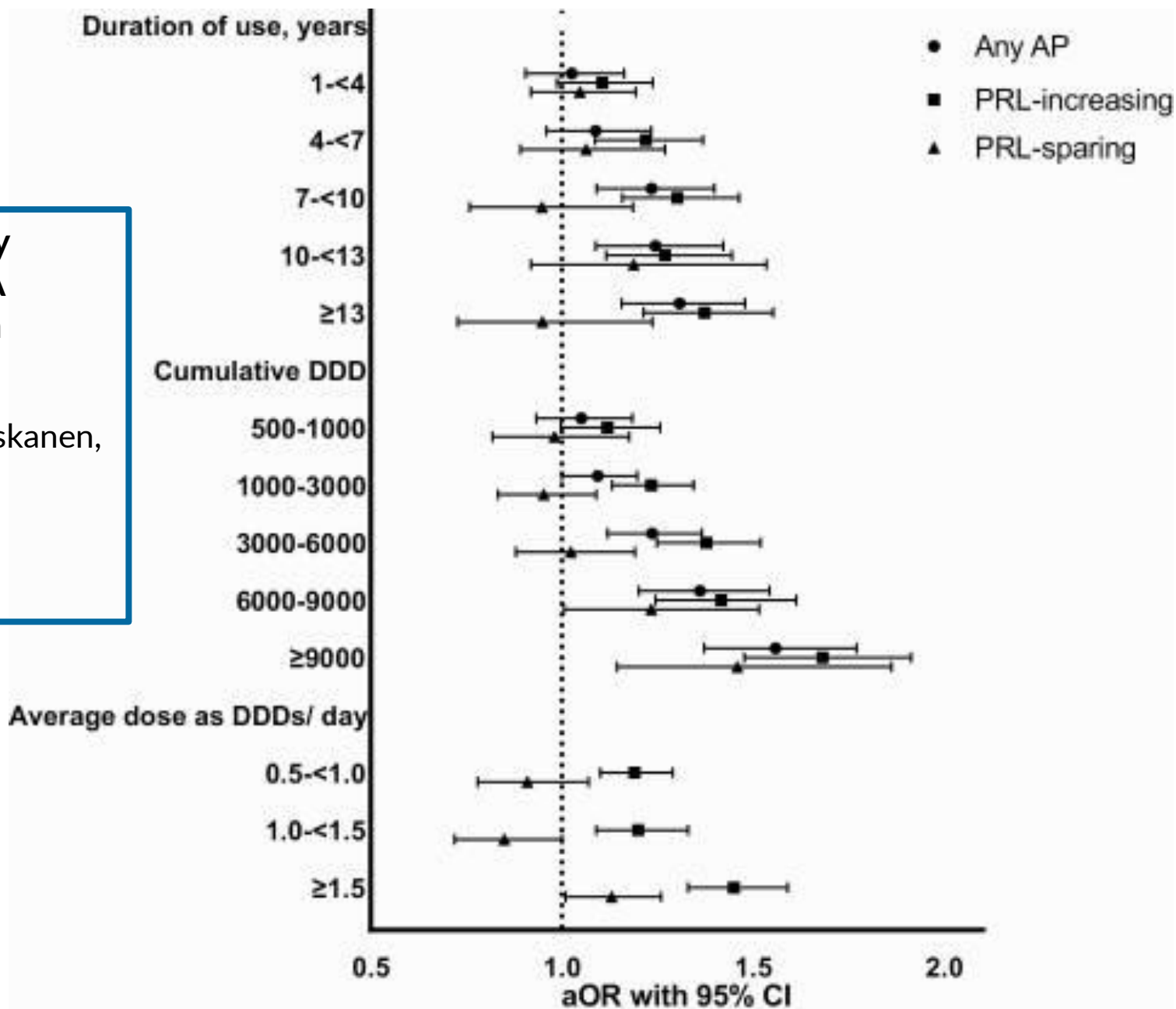


# Replication

## Antipsychotic Use and Risk of Low-Energy Fractures in People With Schizophrenia: A Nationwide Nested Case-Control Study in Finland.

Solmi, M., Lähteenvuo, M., Correll, C. U., Tanskanen, A., Tiihonen, J., & Taipale, H.(2023).

*Schizophrenia Bulletin*, 49(1), 78–89.



# Do antipsychotics increase risk for breast cancer?

Antipsychotics increase prolactin levels, which have been implicated in breast tumorigenesis\* and may contribute to an increased risk for breast cancer.

## Prospective cohort design

### Population:

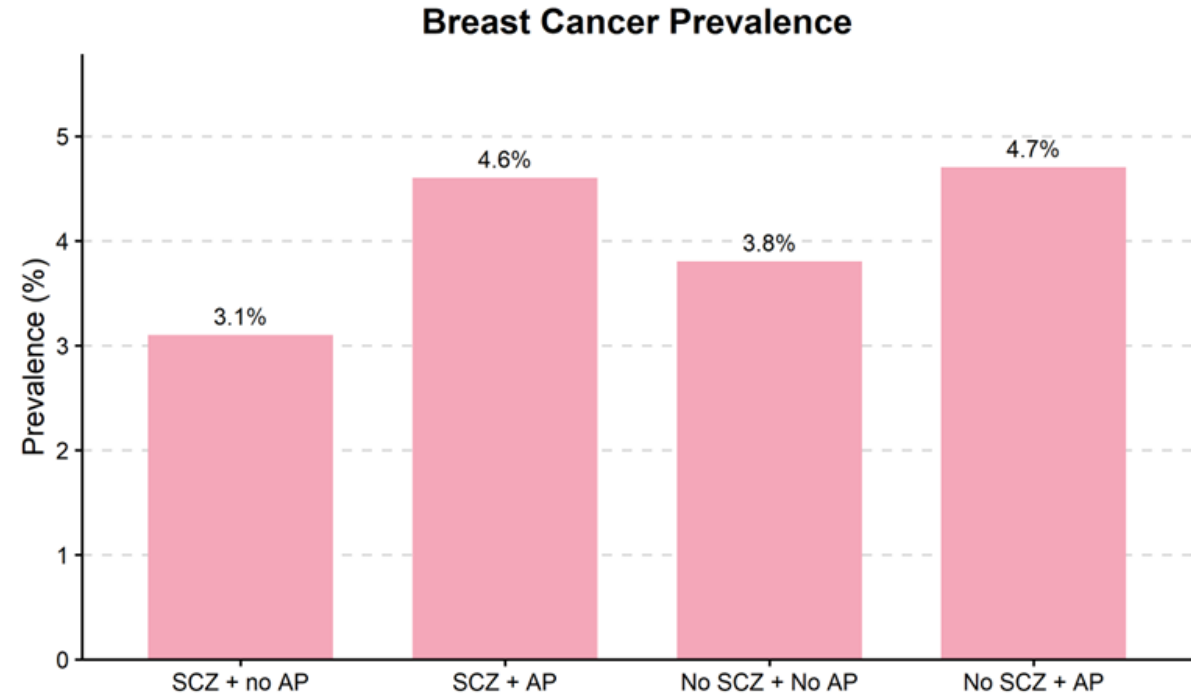
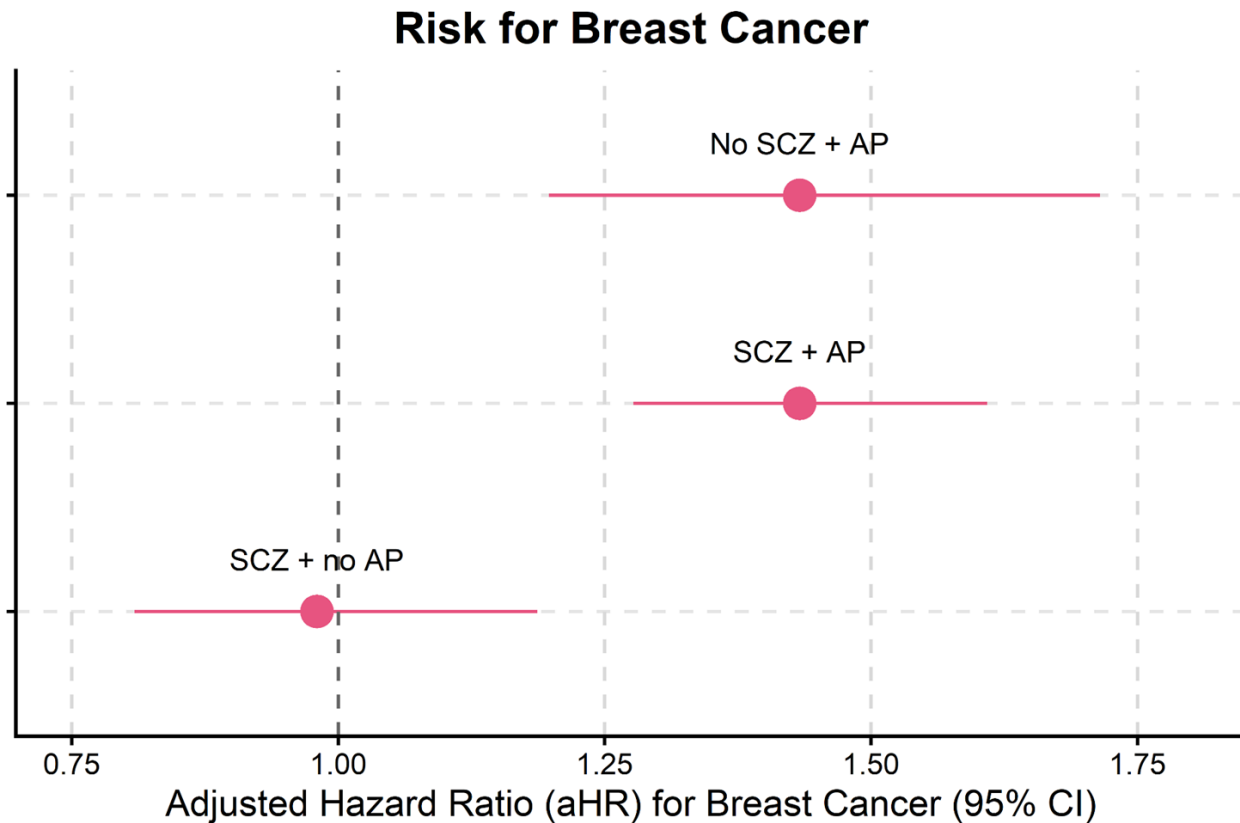
- 6,293 women with SCZ using antipsychotics
- 3,384 women with SCZ not using antipsychotics
- 2,561 women without SCZ (depression, OCD, PTSD) using antipsychotics
- 569,049 women without SCZ not using antipsychotics

AP exposure 2005-2009

Breast cancer diagnosis 2010-2021

\*Nordentoft M, et al. Curr Opin Psychiatry. 2021;34(3):260-265.

# Do antipsychotics increase risk for breast cancer?

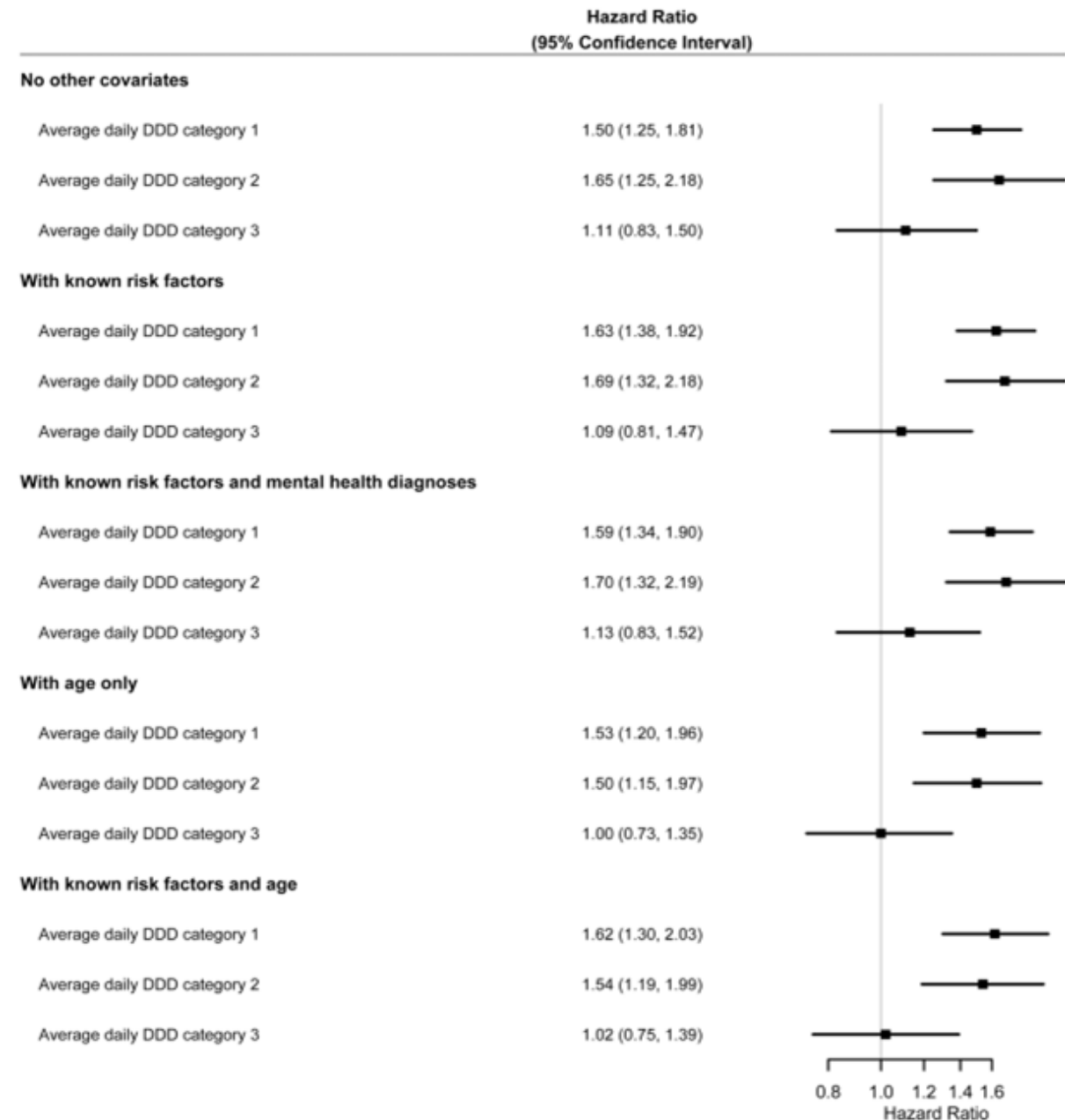


# Replication

## Risk of Breast Cancer With Prolactin-Elevating Antipsychotic Drugs: An Observational Study of US Women (Ages 18–64 Years).

Rahman, T., Sahrman, J. M., Olsen, M. A., Nickel, K. B., Miller, J. P., Ma, C., & Grucza, R. A. (2022)

*Journal of Clinical Psychopharmacology*, 42(1), 7–16.



**Figure 1. Bivariate and Multivariable Analyses of Risk of Invasive Breast Cancer in Women Treated with Pooled Antipsychotic Agents, Compared to Women Treated Only with Anticonvulsants or Lithium.**

# Clozapine and Antipsychotics: Risk for Hematological Cancer

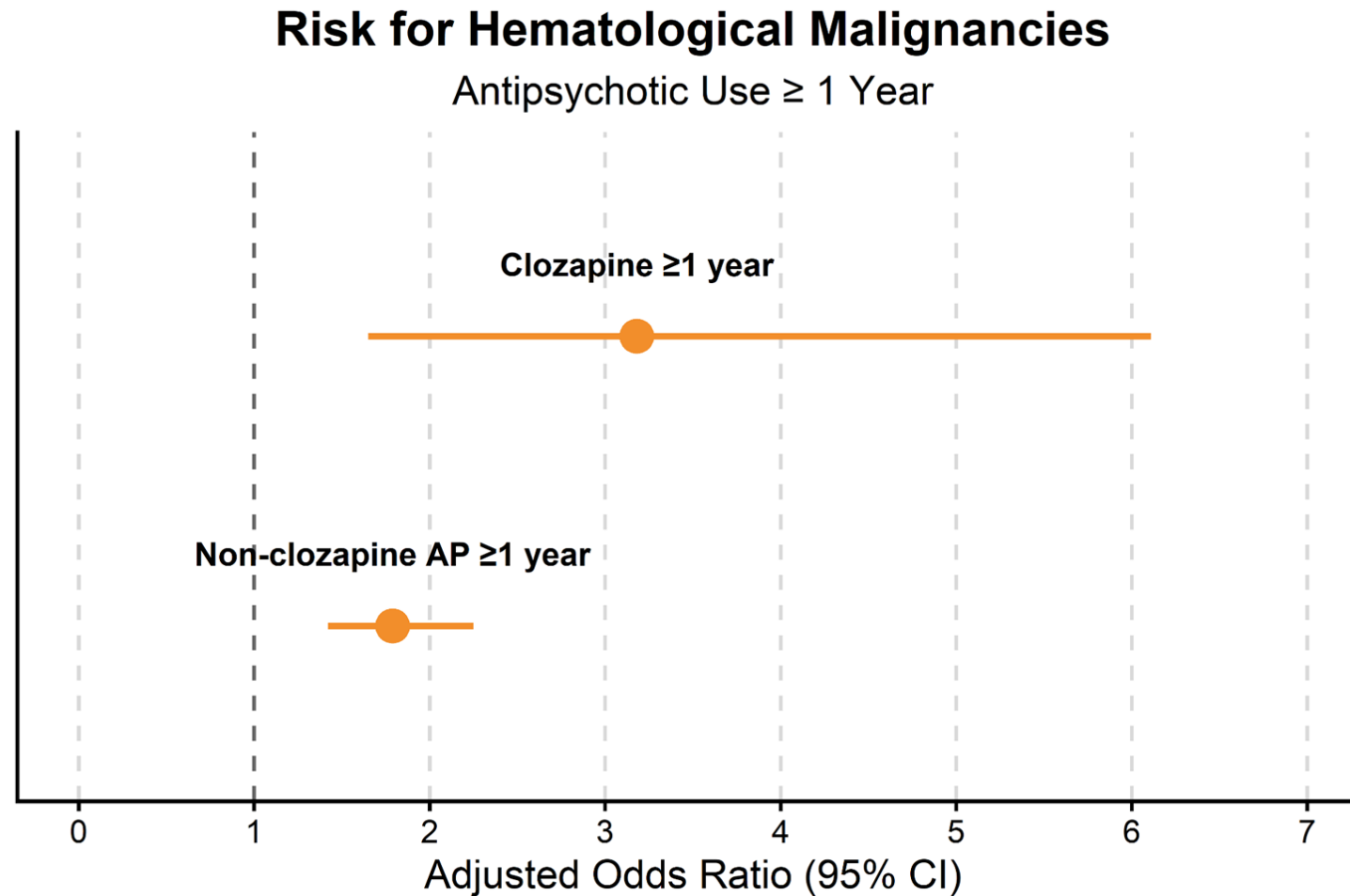
**Rationale:** Clozapine increases risk for agranuloctyosis, does it increase risk for hematologic malignancies?

## Retrospective nested case-control design

### Population:

- 333 schizophrenia patients diagnosed with a hematological malignancy (lymphoma, leukemia, multiple myeloma)
- 3,330 controls matched for age, sex, and time since diagnosis of schizophrenia.

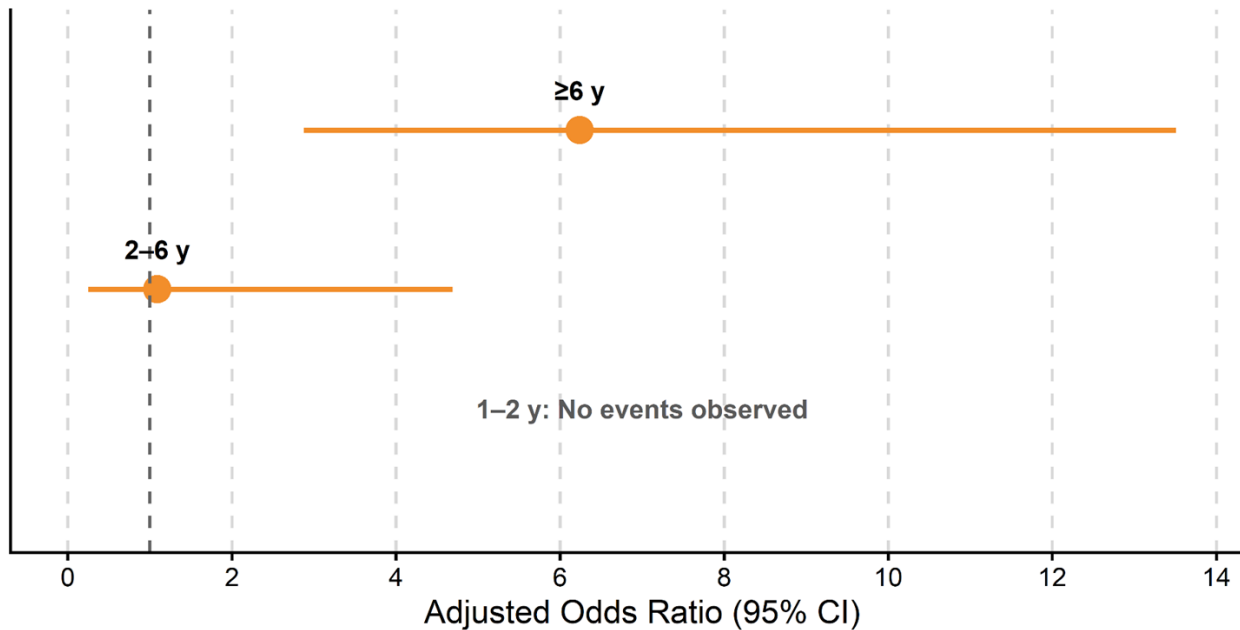
# Clozapine and Antipsychotics: Risk for Hematological Cancer



# Clozapine and Antipsychotics: Risk for Hematological Cancer

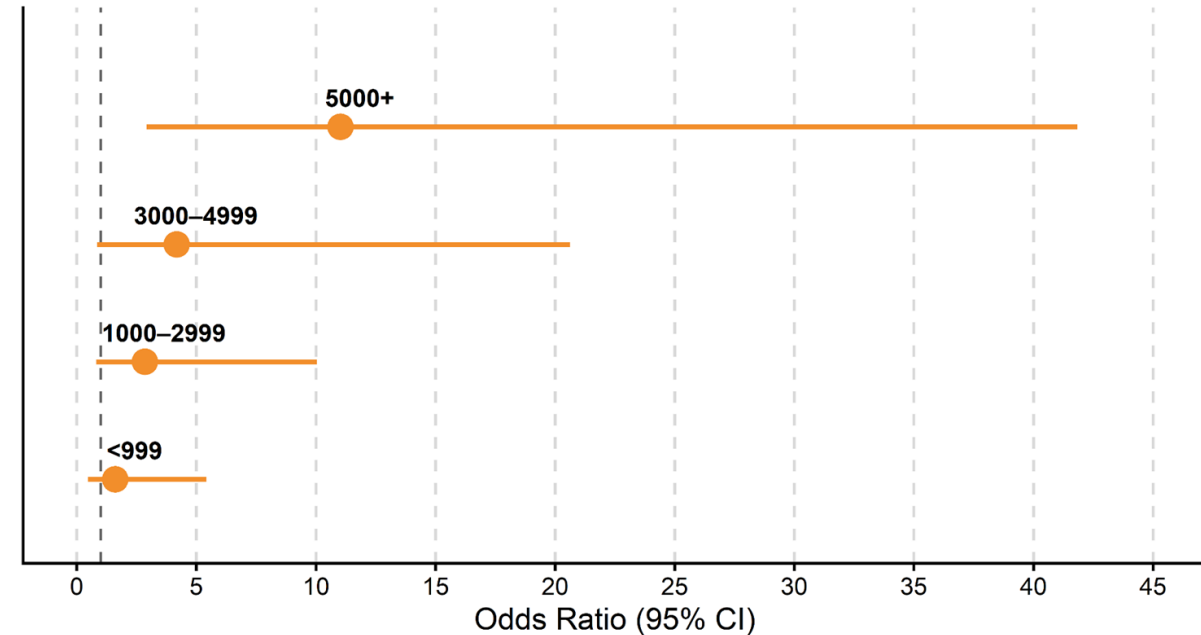
## Risk for Hematological Malignancies

Duration of Clozapine Use



## Risk for Hematological Malignancies

Cumulative Clozapine Dose (DDD)



# Replication

**Long-Term Treatment With Clozapine and Other Antipsychotic Drugs and the Risk of Haematological Malignancies in People With Schizophrenia: A Nationwide Case-Control and Cohort Study in Finland.**

Tiihonen, J., Tanskanen, A., Bell, J. S., Dawson, J. L., Kataja, V., & Taipale, H. (2022)

*The Lancet Psychiatry*, 9(5), 353–362.

# Antipsychotic and Risk for Prostate Cancer Data from Sweden and Israel

**Rationale:** Antipsychotics → ↑ Prolactin → ↓ Testosterone → ↓ Prostate cancer risk

**Retrospective, nested case-control design with data from two continents**

## **Swedish Cohort:**

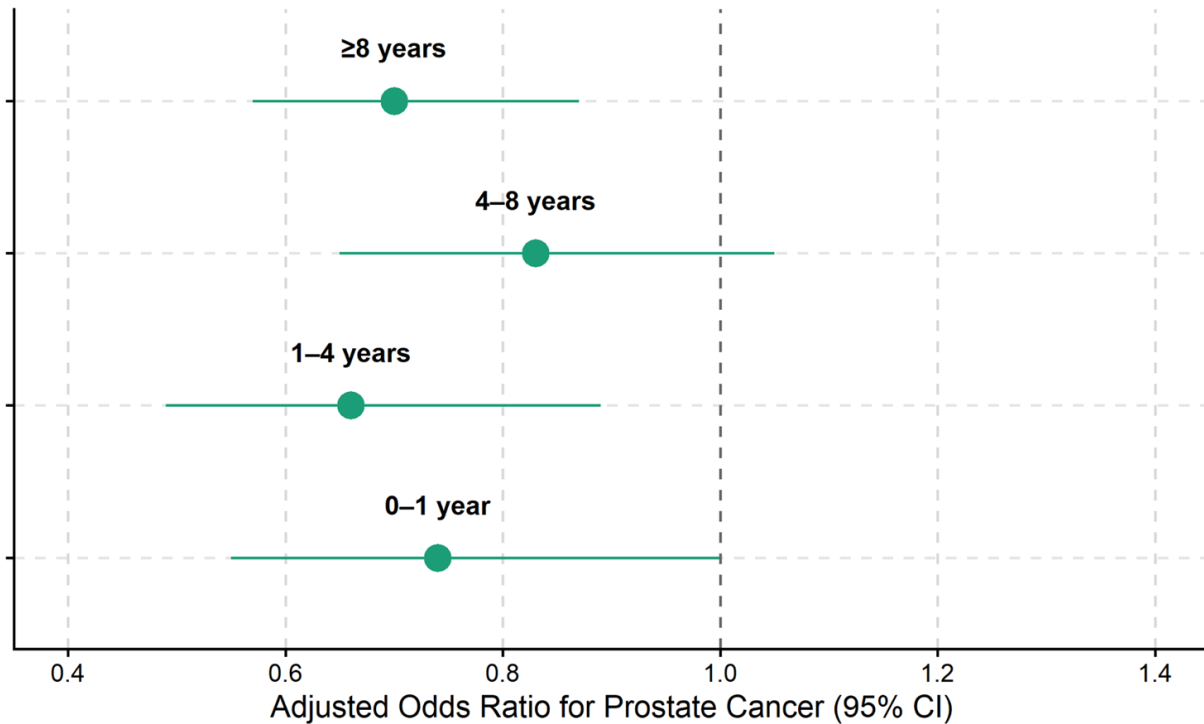
- 884 schizophrenia patients diagnosed with prostate cancer
- 4,405 controls matched for age, years from SCZ diagnosis and SES.

## **Israeli Cohort:**

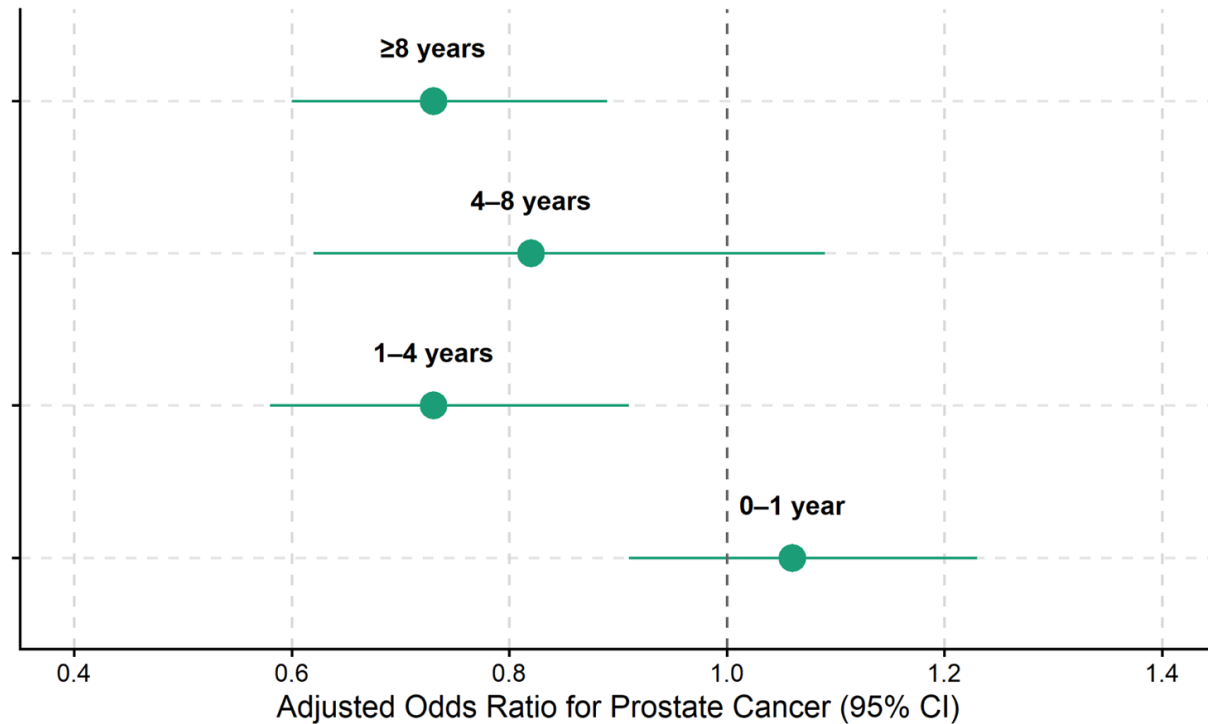
- 1,250 schizophrenia patients diagnosed with prostate cancer
- 6,250 controls matched for age, and SES.

# Antipsychotic and Risk for Prostate Cancer Data from Sweden and Israel

Risk for Prostate Cancer by Duration of AP Exposure - Sweden

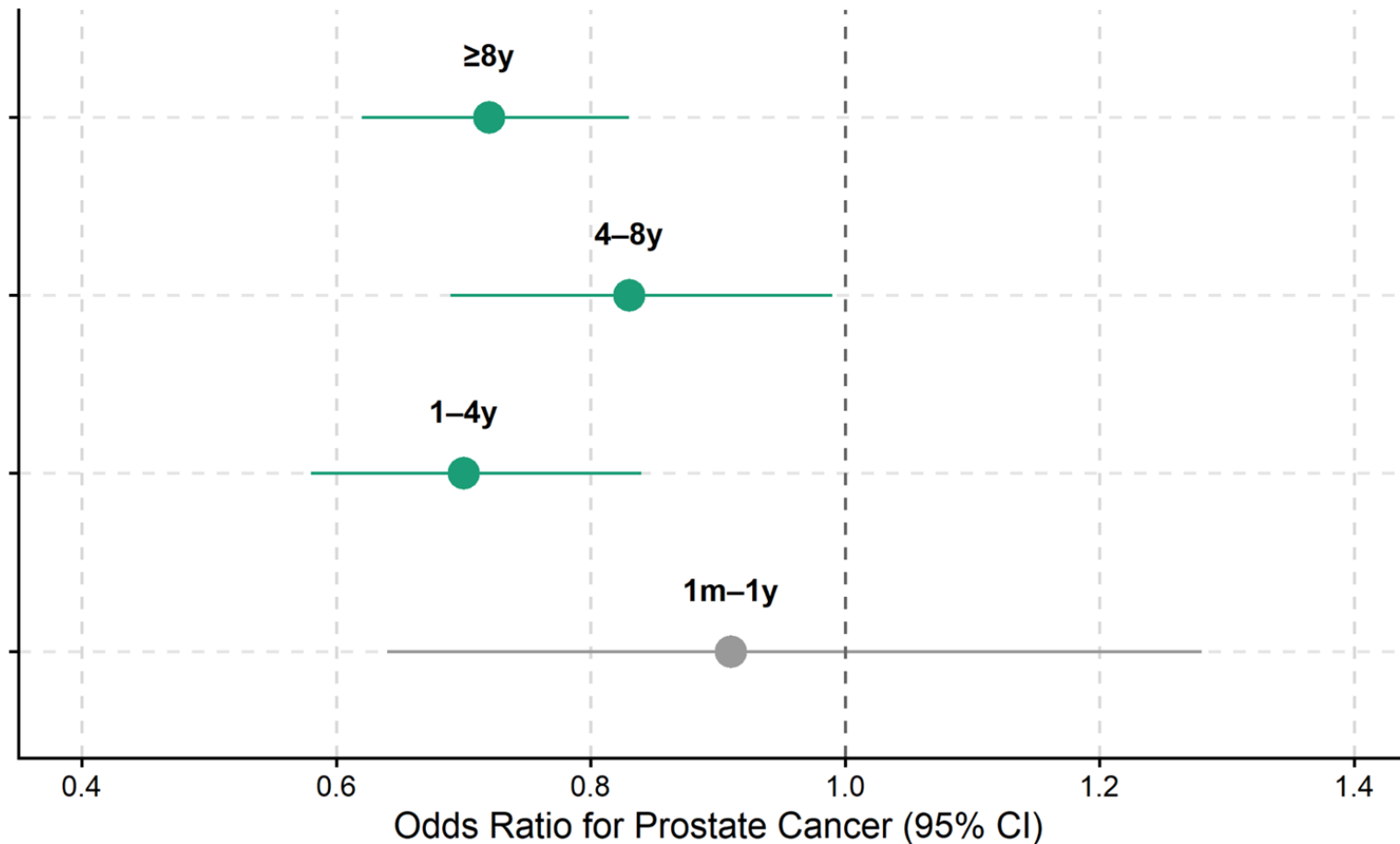


Risk for Prostate Cancer by Duration of AP Exposure - Israel



# Antipsychotic and Risk for Prostate Cancer Combined Data from Sweden and Israel: Meta-Analysis

Risk for Prostate Cancer by Duration of AP Exposure - Combined



# Replication

**Prostate Cancer and Schizophrenia.**

Torrey, E. F. (2006)

*Urology, 68(6), 1280-1283.*

# Antipsychotic Treatment, Schizophrenia and Major Adverse Cardiovascular Events (MACE)



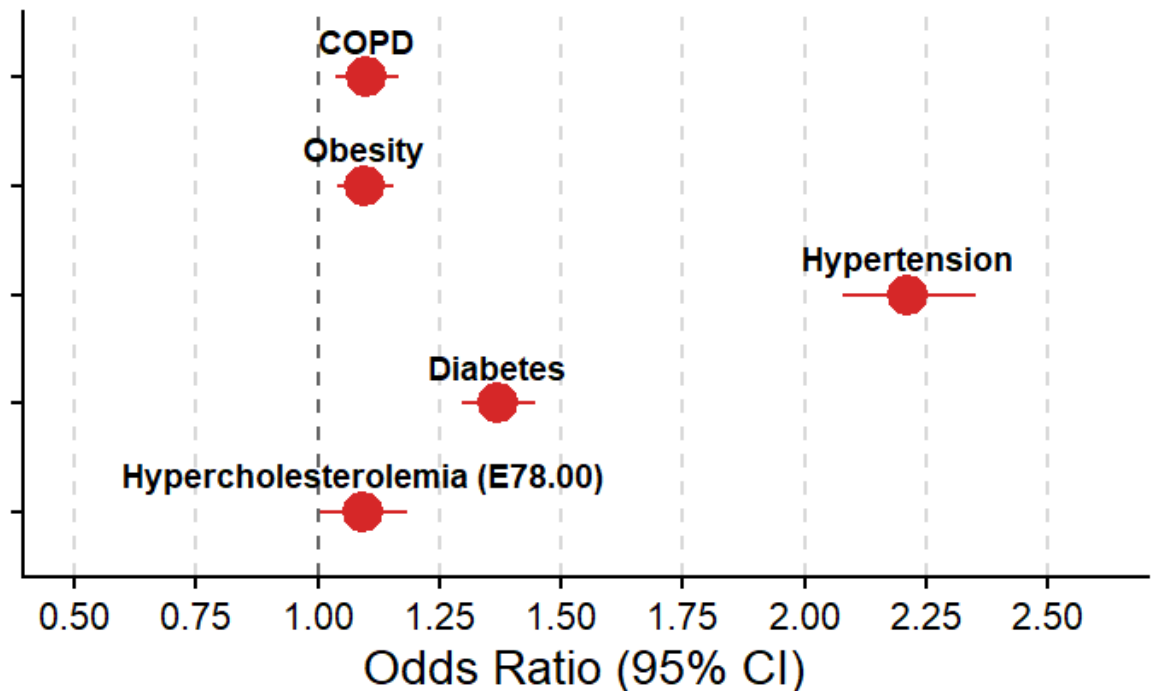
**Rationale:** Antipsychotic increase the risk of diabetes, obesity, hypertension, and hyperlipidemia, do they increase risk for MACE?

Retrospective nested case-control design

**Population:**

- 9,025 schizophrenia patients diagnosed with MACE
- 18,050 controls matched without MACE

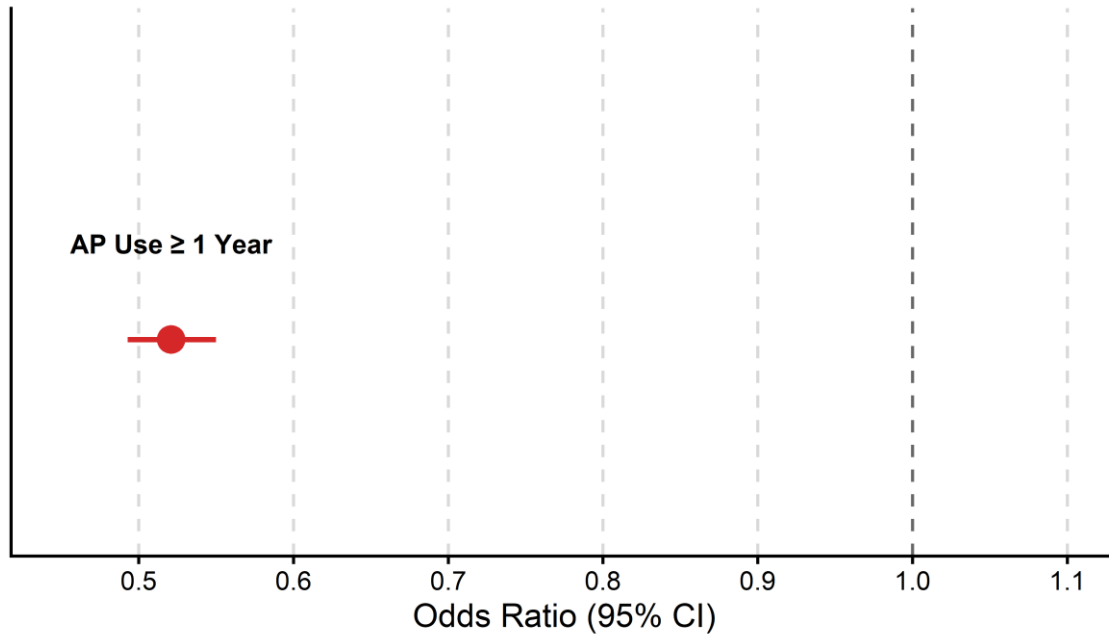
## Clinical Risk Factors for MACE



# Antipsychotic Treatment, Schizophrenia and Major Adverse Cardiovascular Events (MACE)

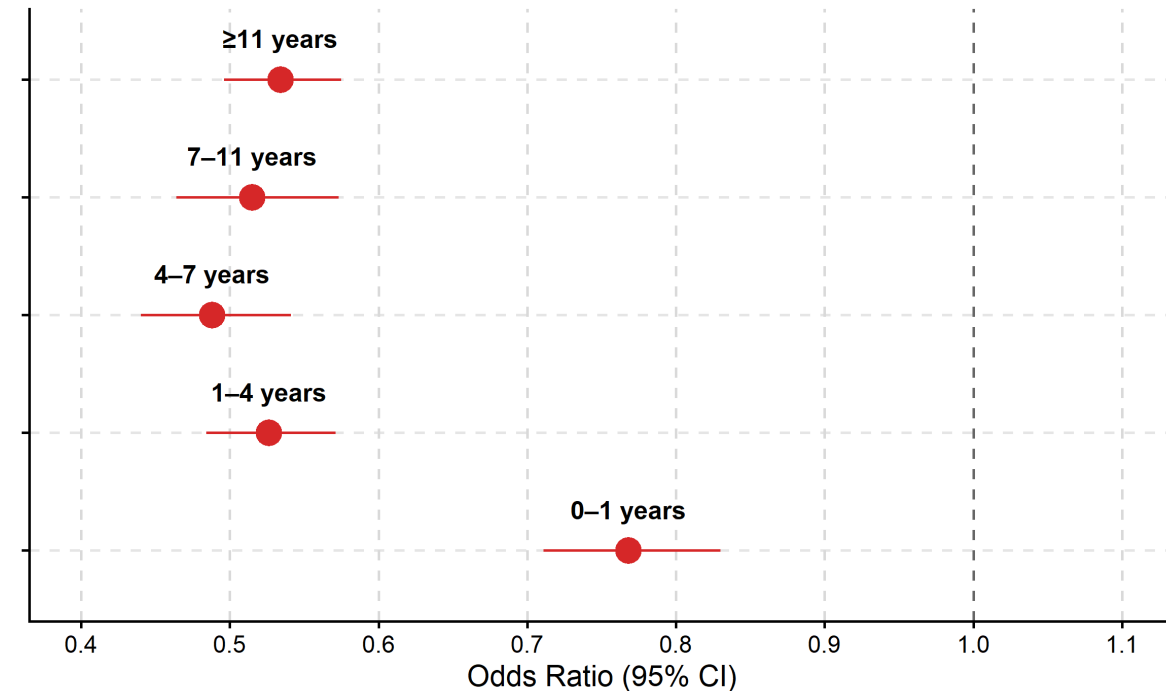


**Risk for MACE**  
Antipsychotic Use  $\geq$  1 Year



Analyses were adjusted for clinical covariates (COPD, obesity, hypertension, diabetes, hypercholesterolemia).

**Risk for MACE by Duration of AP Exposure**



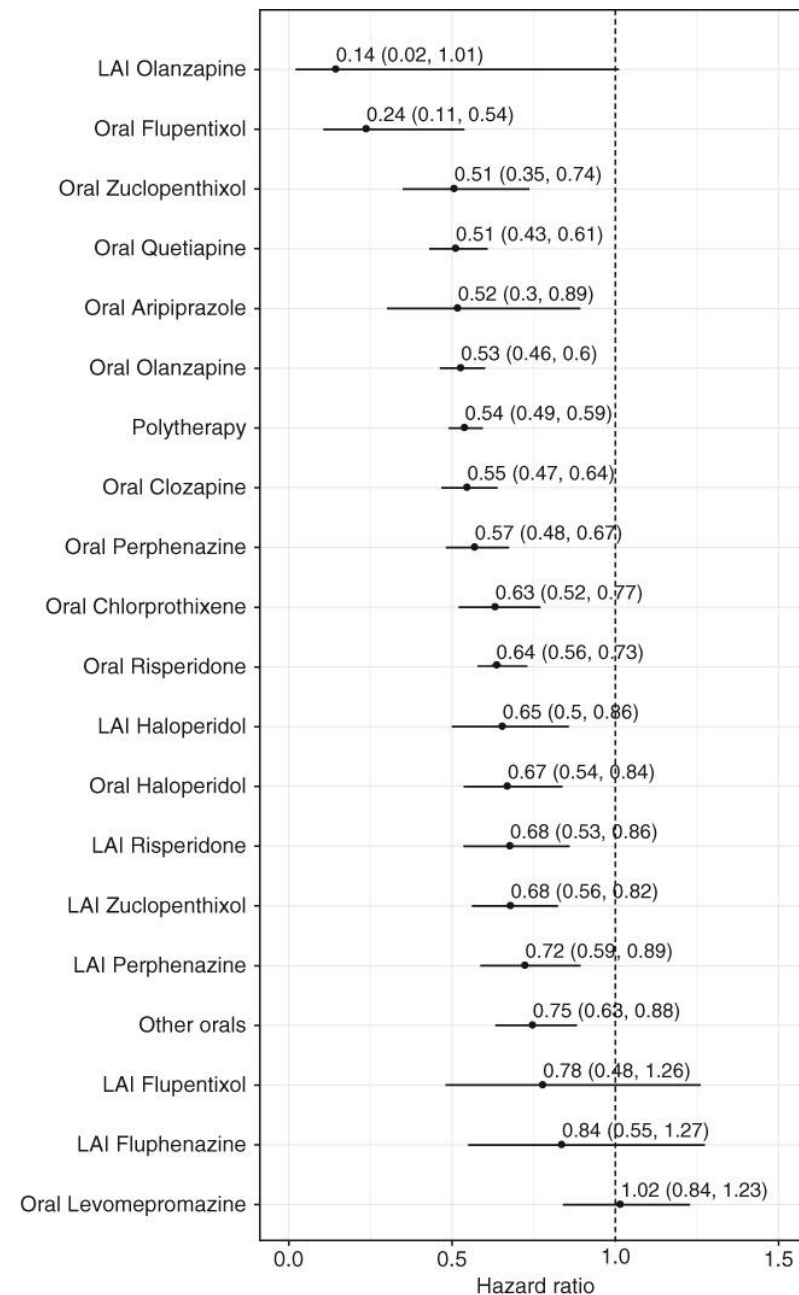
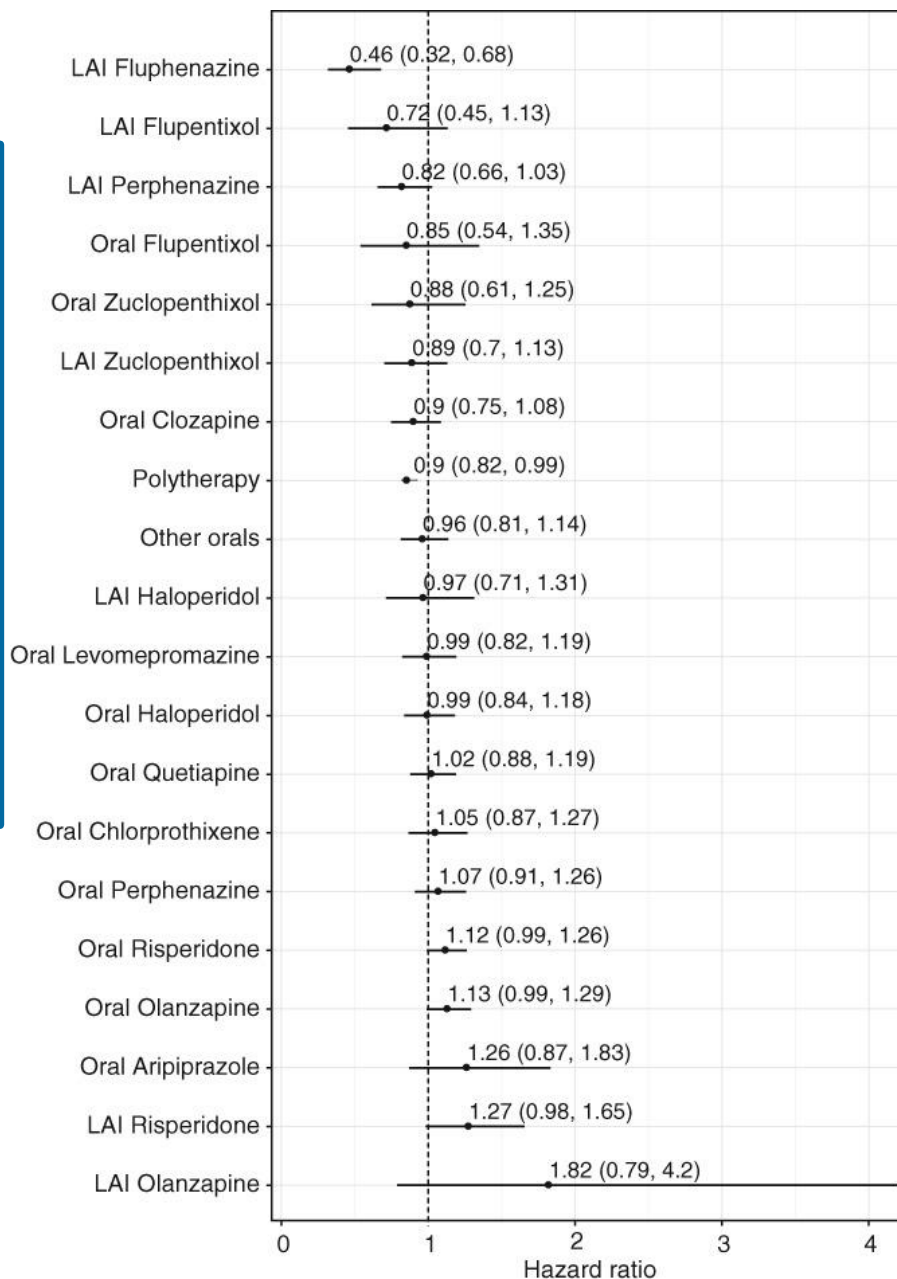
**Potential explanation:** Adherence to antipsychotics may reflect higher overall adherence to medications for hypertension, hypercholesterolemia, diabetes, and weight control.

# Replication

## Twenty-Year Follow-Up Study of Physical Morbidity and Mortality in Relation to Antipsychotic Treatment in a Nationwide Cohort of 62,250 Patients With Schizophrenia (FIN20).






Taipale, H., Tanskanen, A., Mehtälä, J., Vattulainen, P., Correll, C. U., & Tiihonen, J. (2020)

*World Psychiatry*, 19(1), 61–68.



# Clinical Outcomes

Long term antipsychotic use is associated with

-  Increased risk for hip fracture
-  Increased risk for breast cancer (for women population)
-  Increased risk for hematological malignancies (with long term clozapine use)
-  Decreased risk for prostate cancer
-  Decreased risk for major adverse cardiovascular events (MACE)

**This is the introduction to the  
symposium; the next speakers  
are going to talk about how this  
can all be fixed**

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