Sex difference in the association between antipsychotic use and acute ischemic heart disease: a retrospective cohort study of one million primary care patients

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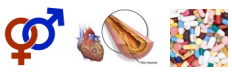
BACKGROUND

- Antipsychotics are believed to heighten the risk of ischemic heart disease (IHD) [1]
- However, mixed findings are reported by existing meta-analyses [2, 3]
- This association may only exist in certain subpopulations
- Sex differences of this association have been little examined



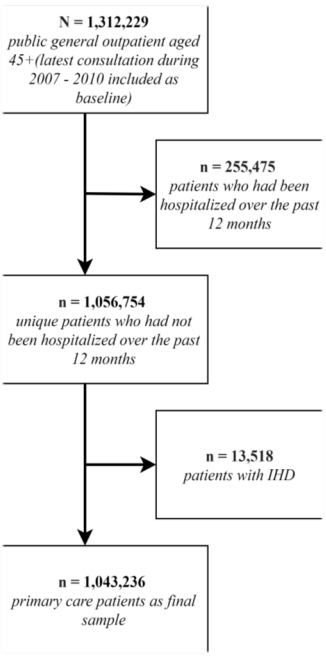


Figure 1. Flow chart showing the procedures of the sample selection for this study

METHODS

Design

- Multicenter retrospective cohort study
- Records of all public General Outpatient Clinic (Hospital Authority) patients aged 45+ who visited during 2007—2010 were examined
- The last visit was taken as the baseline
- Those who had an International Classification of Primary Care (ICPC) codes of IHD (K74, K75, and K76) or any hospitalization in the past 12 months were excluded
- Follow-up until hospitalization through accident & emergency units for IHD or any other acute reasons or four years after baseline
- Ethics approval by Survey and Behavioral Research Ethics Committee of the Chinese University of Hong Kong (Date: 25th August 2015)

Outcome and Exposures

- Outcome: time to acute IHD hospitalization
- Main exposure: prescription of any of 16 antipsychotic medications in the past 12 months (prior to the baseline)
- Effect modifier: biological sex
- Confounders: age, schizophrenia (ICPC code P72), dementia (ICPC code P70), depression (ICPC codes P03, P76, and P77), bipolar disorder (ICPC code P73), diabetes (ICPC codes T89 and T90), hypertension (ICPC codes K86 and K87), atrial fibrillation (ICPC code K78), stroke (ICPC codes: K89 and K90), lipid disorder (ICPC code T93), tobacco abuse (ICPC code P17), antidepressant and statin prescriptions

Statistical analysis

- Mixed-effects Cox regression (random intercept across 74 clinics)

Table 1. Descriptive statistics of the sample (N = 1,043,236)

	Without antipsychotic prescriptions		With antipsychotic prescriptions	
n	1,025,456		17,780	
Sex (%)				
Men	436623	(42.6)	7110	(40.0)
Women	588,833	(57.4)	10,670	(60.0)
Age (%)				
45-54	341,743	(33.3)	6,614	(37.2)
55-64	306,180	(29.9)	5,037	(28.3)
65-74	200,401	(19.5)	2,421	(13.6)
75-84	138,672	(13.5)	2,354	(13.2)
85+	38,460	(3.8)	1,354	(7.6)
International Classification of Primary Care Diagnoses (%)				
Schizophrenia	69	(0.0)	156	(0.9)
Depression	1,845	(0.2)	36	(0.2)
Bipolar disorder	5	(0.0)	3	(0.0)
Dementia	1,338	(0.1)	326	(1.8)
Tobacco abuse	6,209	(0.6)	116	(0.7)
Diabetes	147,949	(14.4)	3,160	(17.8)
Hypertension	378,476	(36.9)	5,663	(31.9)
Atrial fibrillation	3,738	(0.4)	78	(0.4)
Stroke	12,388	(1.2)	384	(2.2)
Lipid disorder	101,192	(9.9)	1,285	(7.2)
Statin prescription (%)	77,410	(7.6)	1,169	(6.6)
Antidepressant prescription (%)	29,166	(2.8)	4,905	(27.6)
Acute IHD hospitalization within four years (%)				
Not hospitalized	1,017,251	(99.2)	17,643	(99.2)
Hospitalized	8205	(0.8)	137	(0.8)

*P-value of chi-square tests/Fisher's exact tests for the difference between patients on antipsychotics and t who were not

RESULTS

- Among 1,043,236 included patients, 17,780 (1.7%) were prescribed antipsychotics, and 8,342 (0.8%) developed IHD (please see Table 1)
- Kaplan Meier curve in Figure 2 shows a possible interaction between antipsychotic use and sex, with a greater increase of risk associated with antipsychotics among women than men
- In sex-specific analyses, antipsychotic prescription was associated with a 32% increased hazard rate of acute IHD among women (95% CI: 1.05 – 1.67) but not among men (please see Table 2)
- In the sex-combined model, the adjusted hazard ratio for the interaction between antipsychotics and being women was 1.46 (95% CI: 1.04 – 2.05) (please see Table 2)
- This moderation effect attenuated and became non-significant when either haloperidol or quetiapine was omitted from the operationalization of antipsychotic use (please see Figure 3)

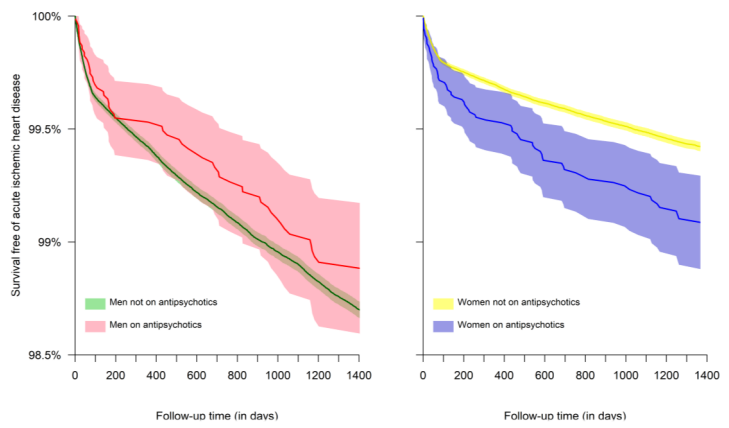


Figure 2. Patterns of survival free of acute hospitalization due to IHD by sex and prescription of antipsychotics. Shaded area represents 95% confidence intervals

Table 2. Adjusted hazard ratios [95% confidence intervals] of acute ischemic heart disease (IHD)

Sample used	Only men	Only Women	Men + Women without interaction between sex and antipsychotics	Men + Women with interaction between sex and antipsychotics
Antipsychotic prescription	***0.95 [0.73, 1.23]***	***1.32 [1.05, 1.67] ****	***1.19 [1.00, 1.41] ****	***0.98 [0.76, 1.27]***
Interaction (Antipsychotics : Women)				***1.46 [1.04, 2.05] ****
Age (in ten years)	1.55 [1.51, 1.59] ***	2.37 [2.30, 2.44] ***	1.86 [0.55, 6.32] **	1.86 [1.83, 1.90] ***
Women (men as referent)			0.46 [0.44, 0.48] ***	0.45 [0.43, 0.47] ***
Antidepressant prescription	1.14 [0.94, 1.39]	1.15 [0.96, 1.37]	1.16 [1.01, 1.32] *	1.15 [1.01, 1.32] *
International Classification of Primary Care Diagnoses as baseline [a]				
Dementia	0.99 [0.47, 2.08]	0.54 [0.30, 0.99] *	0.78 [0.49, 1.23]	0.76 [0.48, 1.22]
Tobacco abuse	1.55 [1.28, 1.88] ***	3.16 [1.83, 5.46] ***	1.68 [1.40, 2.01] ***	1.67 [1.40, 2.01] ***
Diabetes	1.29 [1.20, 1.38] ***	1.62 [1.49, 1.76] ***	1.43 [1.35, 1.50] ***	1.43 [1.35, 1.50] ***
Hypertension	1.60 [1.50, 1.70] ***	1.50 [1.39, 1.63] ***	1.55 [1.47, 1.62] ***	1.55 [1.47, 1.62] ***
Atrial fibrillation	1.20 [0.86, 1.67]	1.06 [0.72, 1.55]	1.16 [0.90, 1.49]	1.16 [0.90, 1.49]
Stroke	1.31 [1.11, 1.55] **	1.49 [1.23, 1.82] ***	1.37 [1.20, 1.55] ***	1.37 [1.20, 1.55] ***
Lipid disorder	1.12 [1.01, 1.24] *	1.15 [1.03, 1.28] *	1.14 [1.06, 1.23] ***	1.14 [1.06, 1.23] ***
Statin prescription	1.62 [1.46, 1.80] ***	1.59 [1.38, 1.82] ***	1.59 [1.47, 1.73] ***	1.59 [1.47, 1.73] ***
Interaction (Lipid disorder : Statin prescription)	0.40 [0.32, 0.50] ***	0.34 [0.26, 0.45] ***	0.38 [0.32, 0.45] ***	0.38 [0.32, 0.45] ***

*** $P < 0.001$, ** $P < 0.01$, * $P < 0.05$

[a] Hazard ratio for schizophrenia, depression and bipolar disorder are not shown because of extremely wide non-significant confidence intervals due to low prevalence

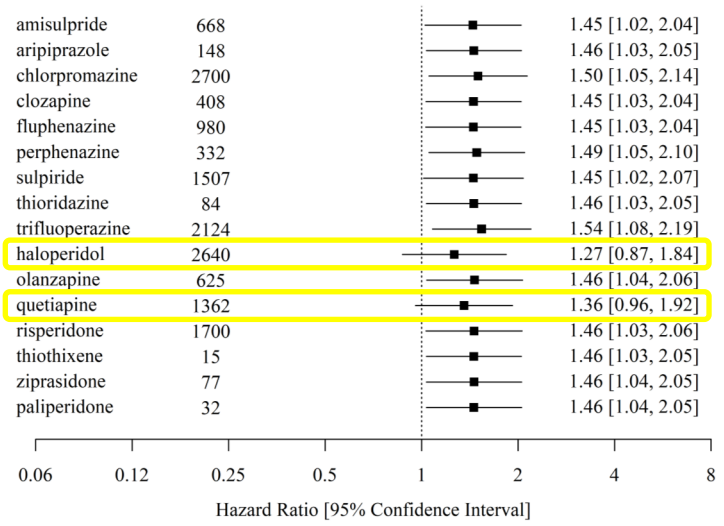


Figure 3. Forest plot showing the hazard ratios for the interaction between antipsychotics and sex (men as referent) from the replicated main analysis with each of the listed 16 antipsychotics omitted. Number of patients in the cohort who were prescribed the antipsychotic at least once in the past 12 months is also shown

DISCUSSION

- Antipsychotic prescription is associated with an increased risk of acute IHD among women in primary care and this relationship may be explained by specific antipsychotics
- Possible mechanisms include stronger physiological response among women [4], lower required antipsychotic dosage for women [5], and better medication compliance among women [6]
- Study limitations include the absence of randomization or propensity score matching (due to data unavailability), the lack of private sector data and data on deaths outside hospitals, lack of data on lifestyle and biometric parameters, under-recorded psychiatric diagnoses
- Caution is warranted when prescribing antipsychotics for women considering the associated cardiovascular risks

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