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Second-generation antipsychotics and the Risk of Chronic Kidney Disease: A Population-based Case-Control Study

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Abstract (279/300 words)

Objectives:
To examine the association between use of second-generation antipsychotics (SGA) and the risk of chronic kidney disease (CKD).

Design: Population-based case-control study

Setting: Routinely collected laboratory, prescription, and diagnostic information on all inhabitants with creatinine measurements residing on the island of Funen, Denmark (2001-2015).

Participants: 21,434 cases with incident CKD matched with 85,576 CKD-free population controls by risk-set sampling using age, sex, and calendar year.

Primary and secondary outcome measures:
CKD was defined as an eGFR below 60 ml/min/1.73m^2 in a period longer than three months. Information on drug exposure and comorbidities were obtained from the Danish National Prescription Register and the Danish National Patient Register. We calculated odds ratios (OR) for the association between SGA use and CKD using conditional logistic regression.

Results:
Use of SGAs was associated with increased risk of CKD among ever-users (OR 1.24, 95%CI: 1.12-1.37) and current users (OR 1.26, 95%CI: 1.12-1.42). We found no clear evidence of dose-response-relationship. Both short duration (1-2 antipsychotic prescriptions; OR 1.22, 95%CI: 1.01-1.48), as well as long-term use (>30 prescriptions; OR 1.45, 95%CI 1.19-1.76) were associated with an increased risk of CKD. Both use of SGAs with mild and high risk of metabolic disturbances was associated with increased risk of CKD (OR 1.21, 95%CI: 1.06-1.39 and 1.36, 95%CI: 1.11-1.68 respectively). Recent use of NSAIDs, prior use of lithium, hypertension, or prior AKI were not clearly associated with development of CKD in connection to SGA exposure. The highest risk of CKD was found for clozapine (OR 1.81, 95%CI: 1.22-2.69).

Conclusions:
Use of SGA is associated with a small-to-moderately increased risk of incident CKD. All investigated second-generation antipsychotics, except for aripiprazole, were associated with an increased risk of CKD.

Keywords:
Antipsychotics, chronic kidney disease, case-control study

Article summary:

Strengths and limitations of this study

- Improved outcome definition by incorporating creatinine levels to estimate glomerular filtration, which enabled us to include cases of chronic kidney disease who were not treated at hospitals or specialized nephrology departments.
- Inclusion of information on comorbidity and prescriptions with high validity from Danish National Health Registers.
- Population-based design in a population, which are considered representative for the general Danish population.
- Limited number of antipsychotic users among cases, and very few users of second-generation antipsychotics with low risk of metabolic disturbances, such as aripiprazole.
- Information on general risk factors for disease as overweight, smoking and lifestyle were not available.

INTRODUCTION

Antipsychotics are primarily used for maintenance treatment in schizophrenia and some cases of bipolar affective disorder. Such maintenance treatment is often year- or life-long, which makes tolerability an important concern in choosing and adhering to treatment. Second generation antipsychotics (SGA) are associated with a number of adverse effects including weight gain, metabolic syndrome, diabetes, and cardiovascular disease[1,2]. Observational studies have linked SGAs to an increased risk of acute kidney injury (AKI)[3,4] and chronic kidney disease (CKD)[5,6].

CKD can develop in several ways: Following AKI, as a complication to metabolic syndrome and diabetes (diabetic nephropathy), or as a complication to cardiovascular disease, either hypertension (hypertensive nephropathy) or arteriosclerosis[7]. Use of SGAs has been associated with all these conditions. Therefore, maintenance treatment with antipsychotics might contribute to the development of CKD, which is important as the mortality of patients with end-stage renal disease is comparable to patients with coronary heart disease[8].

Prior studies on the association of SGAs and CKD have used hospital discharge diagnoses of CKD as outcome definitions[5,6]. In advanced stages, CKD will result in hospitalization, dialysis, kidney transplantation or death, but less severe stages of CKD are usually handled in primary care, which are not recorded in the administrative registers.

We aimed to investigate the association between use of SGAs and the subsequent risk of CKD by combining prescription information with laboratory data to substantiate the outcome definition.

METHODS

We undertook a population-based case-control study of incident CKD-cases among inhabitants residing on the island of Funen, Denmark who - between 2001 and 2015 - had at least two measurements of creatinine performed. We compared the use of SGAs among CKD-cases to that of a disease-free control population.

Data sources

We used information from the Funen Laboratory Cohort (FLaC). A more detailed description of FLaC has been published elsewhere[9]. In summary, FLaC contains information regarding all biochemistry and laboratory results of all Funen inhabitants who, within the study period, had at least one measurement of plasma creatinine performed. A total of 460,365 patients out of 693,843 Funen inhabitants, had their creatinine measured in this period, comprising a total of 7,742,124 creatinine samples. We linked this information to several nationwide Danish administrative registers: Danish Civil Registration System[10,11], The Danish National Patient Registry[12], Registers in Statistics Denmark recording education level[13], and The Danish National Prescription Registry[14]. As the Danish National Health Service provides universal tax-supported healthcare for the entire Danish population, and as all Danish inhabitants are assigned a unique personal 10-digit identified (Central Personal Register (CPR) number) at birth, it is possible to conduct true population-based register-linkage studies covering the entire population[10].

Population

All adults with two or more recorded creatinine values and living on Funen and the surrounding islands in the period January 2001 to December 2015 were eligible for inclusion in the study. Funen is a part of the Region of Southern Denmark, and is considered representative for the entire Danish population[15]. For each individual, an observation period was defined, starting at the first creatinine measurement during the study period and ending with the last creatinine measurement. Only individuals with normal kidney function were included. In case of emigration from the island of Funen, the observation period ended on the last date of creatinine measurement prior to emigration.

Cases

Cases were defined as individuals with incident CKD during the observation period. We defined CKD according to the KDIGO guidelines[16] as the first measurement of eGFR below 60 ml/min/1.73m^2. The date of this measurement defined the index date. In order to ensure that cases had CKD, the first eGFR measured three months after the index date also had to be below 60 ml/min/1.73m2, as well as all the measurements in the in-between period (from the index date to 3 months after). The eGFR was calculated according to the CKDepi formula[17]. Individuals with a discharge diagnosis of renal disease according to the definition of possible CKD, as proposed by Kessing et al.[18] prior to the date of biochemical CKD were excluded. (ICD-10: N18-N19.9 inclusive plus N00, N01, N03, N04, N05, N06, N8.8 plus N14.1, N14.2, N16.8, N17, N25.1, N26, and N27). Individuals with any eGFR measurement below 60 ml/min/1,73m^2 up to one year prior to the study start, were also excluded.

Controls

Four population controls were matched on age, sex, and calendar time to each case and assigned an index date corresponding to the case's date of diagnosis. We used risk-set sampling and excluded controls who fulfilled the same exclusion criteria as described for cases. To ensure that controls had not developed CKD since their last creatinine measurement, all controls were required to have a creatinine recorded at least one year after the index date. This measurement had to be above or equal to 60 ml/min/1.73m2. Cases could be selected as controls before they became cases, and we allowed the study population to be selected as controls more than once. Because of these criteria the generated odds ratio (OR) is considered an unbiased estimate of the incidence rate ratio. Please refer to figure 1 for a graphical depiction of the study design.

< figure 1 around here >

Drug exposure

We obtained information on all filled prescriptions of SGAs and used the defined daily dose (DDD), according to the WHO Collaborating Centre for Drug Statistics methodology[19]. We used the DDDs as a surrogate marker of the cumulative exposure but converted them into olanzapine equivalents[20]. For an overview of the ATC codes and the corresponding DDDs, please refer to the supplementary appendix. The DDDs, determined by the WHO, are based on doses in maintenance

treatment of schizophrenia. We used the number of filled prescriptions as a surrogate marker of duration of use, as many of the drugs are used off-label in lower doses than for treatment of schizophrenia.

Statistical analyses

We used conditional logistic regression to estimate odds ratios (OR) with 95% confidence interval (CI) for the association between SGA-use and the risk of CKD. Our primary outcome was risk of CKD in relation to ever use of SGA. Secondary outcomes were risk of CKD in relation to current use, cumulative exposure, and cumulative duration. We computed a crude and adjusted ORs (aOR), where the adjusted model included the following predefined clinically relevant potential confounders: prior use of lithium, recent use of NSAIDs, diabetes, hypertension, and highest achieved level of education. We conducted subgroup analyses by stratifying on metabolic risk of SGA as proposed by De Hert et al.[2], individual SGAs, diabetes, hypertension, and prior AKI. R version 3.5.1 (R Core Team, Vienna, Austria) was used for all analyses.

Patient and public involvement

No patients were involved in designing the study

Approval

This study was approved by the Danish Data Protection Agency (j.nr 2008-58-0034) and the Danish Patient Safety Authority (j.nr. 3-3013-809/1). According to Danish law, studies based solely on register data do not require approval from an ethics review board[21].

RESULTS

We identified 21.434 cases with incident CKD in Funen County between 2001 and 2016, with 48% males and a median age of 71 years (IQR 64-78 years). Using risk-set sampling, cases were matched by sex, age, and calendar year to 85.576 CKD-free population controls. Hypertension and diabetes were more prevalent among cases than controls at baseline (65 vs 55% and 14 vs 10% respectively). The most commonly used SGA among cases and controls was risperidone. See table 1 for further details.

< table 1 around here >

Main analysis:

Among cases, 557 (2.6%) were ever-users of SGAs, compared to 1731 (2.0%) of controls yielding an adjusted OR of 1.24 (95%CI: 1.12-1.37). The corresponding adjusted OR for current use was 1.26 (95%CI: 1.12-1.42). We did not find evidence of a dose-response-relationship, neither in relation to cumulative use nor in relation to duration of use (see table 2). Short duration measured as 1-2 antipsychotic prescriptions, as well as long-term use (>30 prescriptions) were both associated with increased risk (see table 2).

< table 2 around here >

Subgroup analysis:
The majority of cases and controls used SGAs with mild risk of metabolic disturbances (e.g. risperidone), followed by SGAs with high risk (e.g. clozapine and olanzapine), and moderate risk (e.g. quetiapine). Use of SGAs with mild and high risk of metabolic disturbances was associated with increased risk of CKD in the adjusted model ($OR_{mildrisk}$ 1.21, 95%CI: 1.06-1.39 and $OR_{highrisk}$ 1.36, 95%CI: 1.11-1.68) (see table 3).

Users of SGAs, who also had diabetes, had an 50% increased risk of developing CKD compared to controls, but due to the low number of exposed diabetics, the confidence interval overlapped unity ($aOR_{diabetes}$ 1.52, 95%CI: 0.90-2.54). Antipsychotic users in the low age category, had an increased risk of CKD compared to the higher age category ($aOR_{<65years}$ 1.50, 95%CI: 1.25-1.80). None of the other known risk factors for CKD (use of NSAIDs, hypertension, and prior AKI) were clearly associated with development of CKD in connection to SGA exposure (see table 3).

< table 3 around here >

Specific SGAs:
All SGAs, except for aripiprazole, were associated with increased risk of CKD. The risk was most pronounced for clozapine (aOR 1.81, 95%CI: 1.22-2.69) followed by olanzapine (aOR 1.41, 95%CI: 1.19-1.65) and quetiapine (aOR 1.28, 95%CI: 1.17-1.42).

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DISCUSSION

In this large population-based study using routinely collected eGFR to define CKD, we found that ever-users of SGAs had a higher risk of developing CKD compared to never-users. However, there was no clear evidence of a dose-response-relationship, and several known risk factors for CKD did not substantially increase the risk of developing CKD (e.g. NSAID use, prior lithium use, prior AKI [7]). We found a further increased risk of developing CKD among individuals with diabetes, and among those below 65 years of age at the time of CKD-diagnosis, although the risk among diabetics was not significant. For individual antipsychotics, the use of clozapine or olanzapine was associated with the highest risk of developing.

Regarding the overall risk of developing CKD in connection to treatment with SGAs, our main findings are in line with previous studies: Tzeng and colleagues[5] found a similar increased risk of CKD among individuals with schizophrenia during three years of follow-up. (HR 1.36, 95%CI: 1.13-1.63), and Wang and colleagues substantiated this finding by observing an increased risk of CKD among individuals with more than 90 and 1000 days of SGA exposure (OR 1.42 and 1.30 respectively)[6].
In our current study we observed a 52% increased risk of developing CKD for antipsychotic-users who also had diabetes compared to non-diabetics, although not statistically significant. Development of CKD and later potentially end-stage renal

disease (ESRD) is a well-established complication of diabetes[22], and our finding might underscore the importance of regular monitoring of kidney-function in this population. CKD-prevalence is related to age, as nephron-loss and the prevalence of medical conditions generally increases with age[7]. Our finding of the highest risk among the younger age group might be explained by a higher proportion of long-term antipsychotic use for severe mental illness in this age category, whereas antipsychotic use in the older age category might represent short-term and/or low-dose use in conditions as dementia and delirium. Analysis of the individual SGAs in connection to CKD found the highest risk associated with olanzapine and clozapine, which was expected as these SGAs are associated with the highest risk of metabolic disturbances and diabetes[1].

The primary strength of the present study is the improved outcome definition. By using creatinine levels to estimate glomerular filtration, we can include CKD-cases who are not treated at hospitals and specialized nephrology departments. A considerable proportion of CKD-cases might be handled in general practice until severe or ESRD is present. These cases would be missed if our outcome definition only relied on hospital diagnoses. Secondly, the linkage to Danish registers allowed us to obtain high quality information on comorbidity and prescriptions. Lastly, the population of Funen is considered representative for the general Danish population[15].

However, some limitations must be acknowledged: The number of antipsychotic users among CKD-cases was generally low, and most users had very short duration of antipsychotic use (i.e. ≤2 prescriptions). Our population included few users with high cumulative doses (i.e. >3650 mg olanzapine-equivalents), as well as very few users of SGAs with low risk of metabolic disturbances, such as aripiprazole. This means that our dose-response analysis is likely to underestimate the cumulative dose and an associated risk in this sub-population. Also, information on general risk factors for disease as overweight, smoking and lifestyle are not included in our data sources.

In conclusion, we found a small-to-moderately increased risk of incident CKD among individuals using second-generation antipsychotics. All investigated second-generation antipsychotics, except for aripiprazole, were associated with an increased risk of CKD.

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LEGENDS TO FIGURES

Figure 1: Graphical representation of time periods, case definition, control selection and covariate assessment

Figure 2: Association between exposure to second-generation antipsychotics and the risk of chronic kidney disease by individual drugs

Table 1: Characteristics of cases and controls

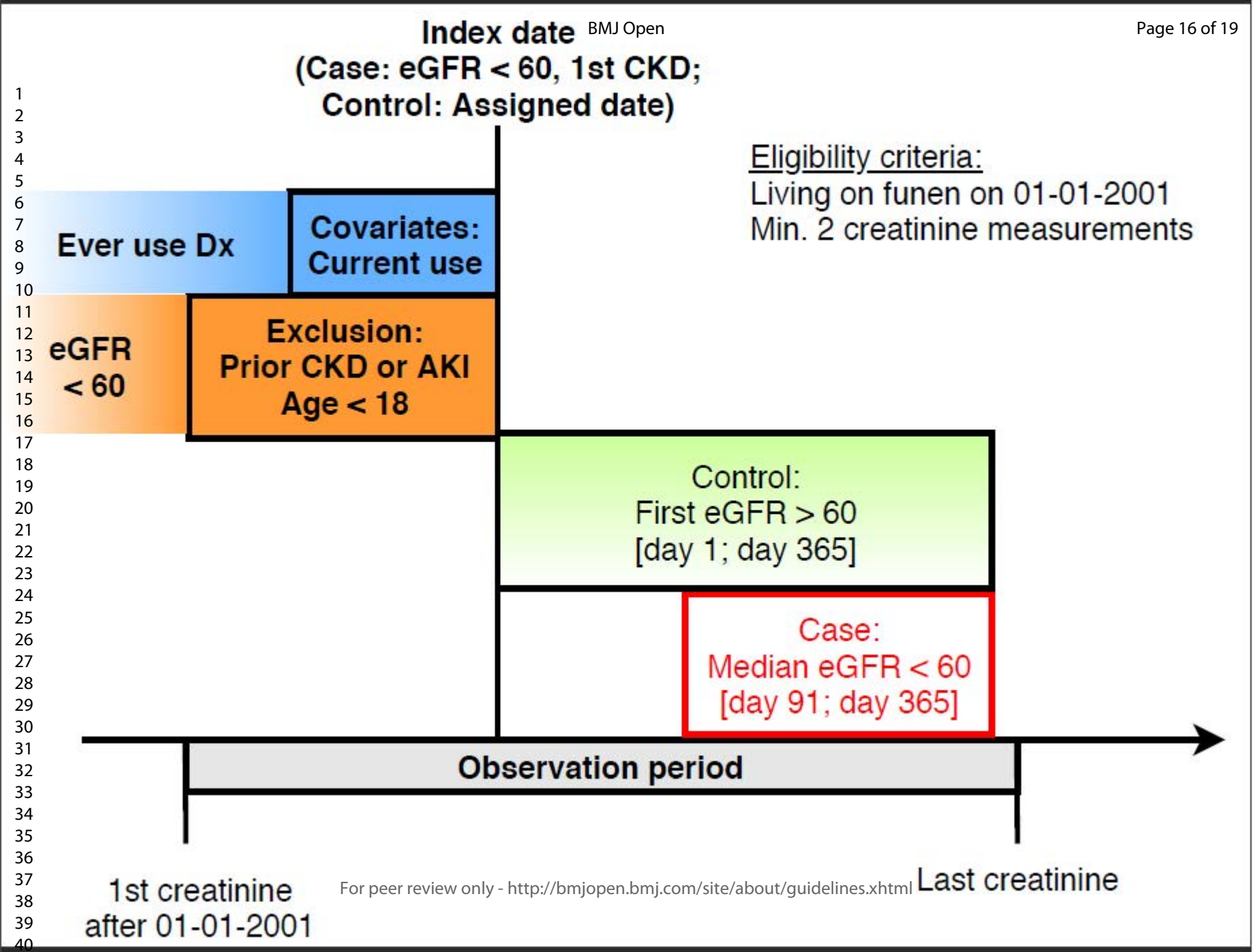
Characteristic	Cases, N (%)	Controls, N (%)
Total	21,434	85,576
Male sex	10,277 (48)	41,010 (48)
Age, median (IQR)	71 (64-78)	71 (64-78)
Mental disorders		
Schizophrenia	74 (<1)	217 (<1)
Bipolar disease	120 (1)	356 (<1)
Dementia	122 (1)	366 (<1)
Other co-morbidities		
Diabetes	3,057 (14)	8,138 (10)
Hypertension	13,962 (65)	47,095 (55)
Antipsychotic exposure		
Second-generation antipsychotics	557 (3)	1731 (2)
Quetiapine	173 (1)	504 (1)
Aripiprazole	8 (<1)	41 (<1)
Risperidone	299 (1)	967 (1)
Olanzapine	220 (1)	593 (1)
Clozapine	37 (<1)	82 (<1)
Exposure to other medications		
Prior use of Lithium	210 (1)	563 (1)
Recent use of NSAIDs	5,610 (26)	20,081 (23)
Highest achieved level of education		
Level 1	10,250 (48)	38,385 (45)
Level 2	6,785 (32)	27,778 (32)
Level 3	2,687 (13)	12,727 (15)

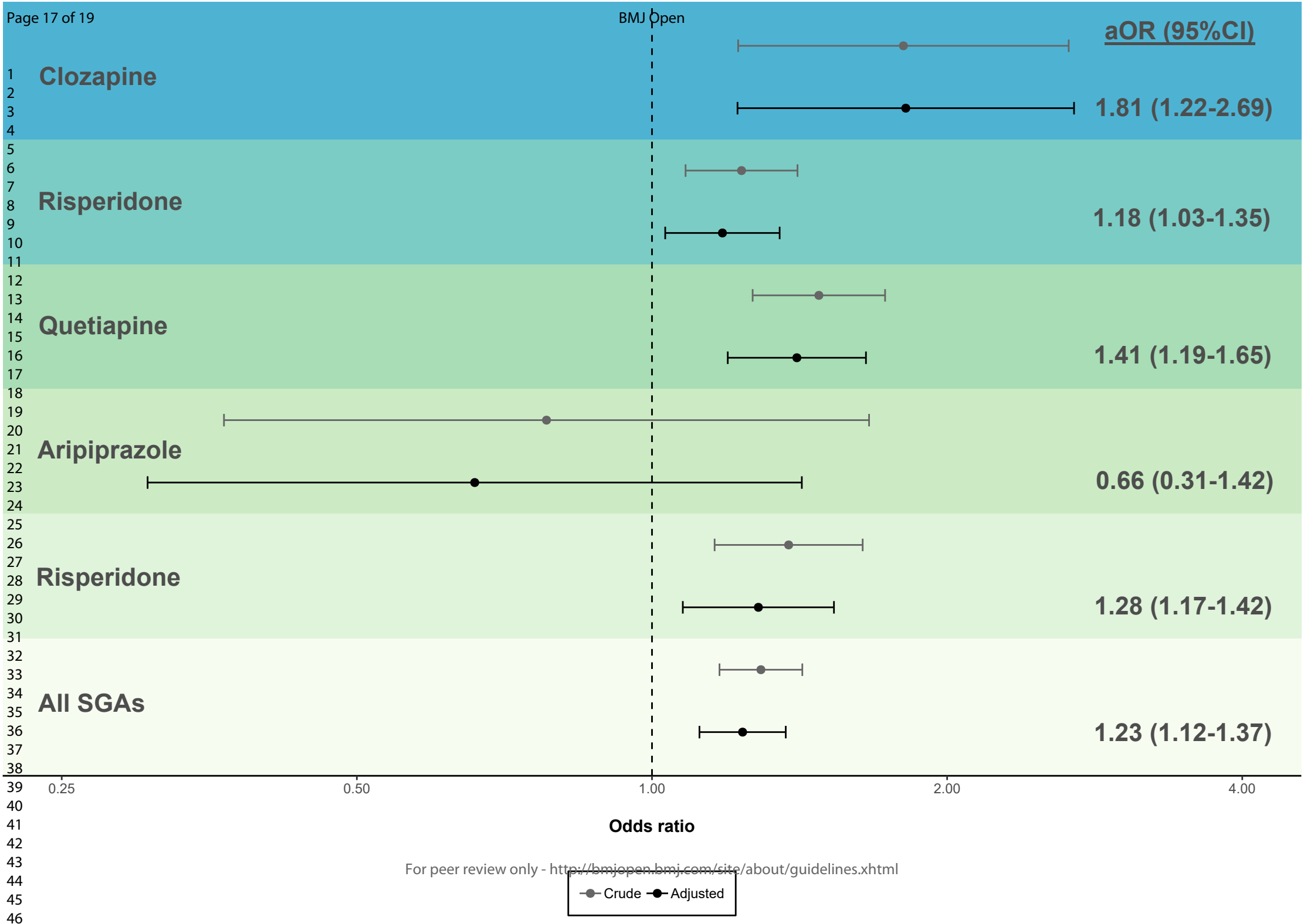
Table 2: Odds ratios (OR) for chronic kidney disease with use of second-generation antipsychotics

Exposure	Cases, N (%) (N = 21434)	Controls, N (%) (N = 85576)	Crude OR	Adjusted OR
Never use	20877	83845	1 (ref)	1 (ref)
Ever use	557 (3)	1731 (2)	1.29 (1.17-1.42)	1.24 (1.12-1.37)
Current use	399 (2)	1206 (1)	1.32 (1.18-1.49)	1.26 (1.12-1.42)
Cumulative use (olanzapine eq.)				
0-899mg	380 (2)	1246 (1)	1.22 (1.09-1.37)	1.17 (1.04-1.32)
900-1799mg	52 (<1)	124 (<1)	1.70 (1.23-2.36)	1.60 (1.15-2.23)
1800-3649mg	29 (<1)	121 (<1)	0.96 (0.64-1.43)	0.91 (0.60-1.38)
>3650mg	96 (<1)	240 (<1)	1.60 (1.26-2.03)	1.46 (1.14-1.86)
Number of prescriptions				
1-2	144 (1)	450 (1)	1.28 (1.06-1.54)	1.22 (1.01-1.48)
3-4	76 (<1)	236 (<1)	1.28 (0.98-1.66)	1.24 (0.95-1.62)
5-10	68 (<1)	240 (<1)	1.14 (0.87-1.50)	1.06 (0.80-1.39)
11-30	115 (1)	409 (<1)	1.12 (0.91-1.38)	1.10 (0.89-1.36)
>30	154 (1)	396 (<1)	1.57 (1.30-1.89)	1.45 (1.19-1.76)

Table 3: Association between exposure to second-generation antipsychotics and the risk of chronic kidney disease by subgroups (risk of metabolic disturbances, recent use of NSAIDs, pre-existing diabetes, hypertension, prior acute kidney injury (AKI), and age)

Exposure		Cases, N (%)	Controls, N (%)	Crude OR (95% CI)	Adjusted OR (95% CI)
		N = 21434	N = 85576		
SGA	Low risk	8 (1)	41 (2)	0.85 (0.39-1.82)	0.71 (0.32-1.54)
	Mild risk	298 (54)	947 (55)	1.26 (1.10-1.44)	1.21 (1.06-1.39)
	Moderate risk	118 (21)	372 (21)	1.28 (1.04-1.58)	1.19 (0.96-1.48)
	High risk	133 (24)	371 (21)	1.43 (1.17-1.74)	1.36 (1.11-1.68)
NSAID	No	15824 (74)	65495 (77)	1.29 (1.15-1.45)	1.22 (1.08-1.38)
	Yes	5610 (26)	20081 (23)	1.13 (0.84-1.51)	1.10 (0.81-1.49)
Diabetes	No	18377 (86)	77438 (90)	1.27 (1.14-1.41)	1.24 (1.11-1.39)
	Yes	3057 (14)	8138 (10)	1.56 (0.96-2.53)	1.52 (0.90-2.54)
Hypertension	No	7472 (35)	38481 (45)	1.43 (1.19-1.72)	1.33 (1.10-1.60)
	Yes	13962 (65)	47095 (55)	1.21 (1.05-1.39)	1.14 (0.98-1.32)
Prior AKI	No	18998 (89)	83099 (97)	1.31 (1.18-1.47)	1.27 (1.14-1.42)
	Yes	2436 (11)	2477 (3)	1.24 (0.59-2.58)	0.96 (0.45-2.07)
Age group	<65	5847 (27)	23423 (27)	1.66 (1.40-1.97)	1.50 (1.25-1.80)
	65+	15587 (73)	62153 (73)	1.15 (1.02-1.30)	1.13 (1.00-1.28)





Appendix 1: Definitions

Study drugs (Second-generation antipsychotics)	ATC code	DDD (mg)	Equivalent to 1mg olanzapine (mg)	Risk of metabolic disturbances
Aripiprazole	N05AX12	15	1.5	Low
Clozapine	N05AH02	300	30	High
Olanzapine	N05AH03	10	-	High
Risperidone	N05AX08	5	0.5	Mild
Quetiapine	N05AH04	400	40	Moderate
Other medications				
Non-steroidal anti-inflammatory drugs (NSAIDs)	M01A, excl. M01AX01			
Lithium	N05AN01			
Comorbidities	Definition			
Diabetes	Use of ATC-group A10			
Hypertension	Use of ATC-group C03A, C08C, C09A, C09C			
Possible CKD	ICD-10: N00, 01, 03-06, 08.8, 14.1, 14.2, 16.8, 17-19, 25.1, 26-27			
Schizophrenia	ICD-10: F20			
Bipolar affective disorder	ICD-10: F30-31			
Dementia	ICD-10: F00-03 and G30-31			

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *case-control studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4-5
Participants	6	*(*a) Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls	5
		(*b*) For matched studies, give matching criteria and the number of controls per case	5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*4-6*
Bias	9	Describe any efforts to address potential sources of bias	6
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5-6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6
		(*b*) Describe any methods used to examine subgroups and interactions	6
		(*c*) Explain how missing data were addressed	-
		(*d*) If applicable, explain how matching of cases and controls was addressed	5
		(*e*) Describe any sensitivity analyses	-
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6
		(b) Give reasons for non-participation at each stage	-
		(c) Consider use of a flow diagram	-
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	6, table 1
		(b) Indicate number of participants with missing data for each variable of interest	-
Outcome data	15*	Report numbers in each exposure category, or summary measures of exposure	6
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	6-7, table 2+3
		(*b*) Report category boundaries when continuous variables were categorized	-
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	-
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	7, table 2+3
Discussion			
Key results	18	Summarise key results with reference to study objectives	7
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	8
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	7-8
Generalisability	21	Discuss the generalisability (external validity) of the study results	8
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	8

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Second-generation antipsychotics and the Risk of Chronic Kidney Disease: A Population-based Case-Control Study

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Abstract (279/300 words)

Objectives:
To examine the association between use of second-generation antipsychotics (SGA) and the risk of chronic kidney disease (CKD).

Design: Population-based case-control study

Setting: Routinely collected laboratory, prescription, and diagnostic information on all inhabitants with creatinine measurements residing on the island of Funen, Denmark (2001-2015).

Participants: 21,434 cases with incident CKD matched with 85,576 CKD-free population controls by risk-set sampling using age, sex, and calendar year.

Primary and secondary outcome measures:
CKD was defined as an eGFR below 60 ml/min/1.73m^2 in a period longer than three months. Information on drug exposure and comorbidities were obtained from the Danish National Prescription Register and the Danish National Patient Register. We calculated odds ratios (OR) for the association between SGA use and CKD using conditional logistic regression.

Results:
Use of SGAs was associated with increased risk of CKD among ever-users (OR 1.24, 95%CI: 1.12-1.37) and current users (OR 1.26, 95%CI: 1.12-1.42). We found no clear evidence of dose-response-relationship. Both short duration (1-2 antipsychotic prescriptions; OR 1.22, 95%CI: 1.01-1.48), as well as long-term use (>30 prescriptions; OR 1.45, 95%CI 1.19-1.76) were associated with an increased risk of CKD. Both use of SGAs with mild and high risk of metabolic disturbances was associated with increased risk of CKD (OR 1.21, 95%CI: 1.06-1.39 and 1.36, 95%CI: 1.11-1.68 respectively). Recent use of NSAIDs, prior use of lithium, hypertension, or prior AKI were not clearly associated with development of CKD in connection to SGA exposure. The highest risk of CKD was found for clozapine (OR 1.81, 95%CI: 1.22-2.69).

Conclusions:
Use of SGA is associated with a small-to-moderately increased risk of incident CKD. All investigated second-generation antipsychotics, except for aripiprazole, were associated with an increased risk of CKD.

Keywords:
Antipsychotics, chronic kidney disease, case-control study

Article summary:

Strengths and limitations of this study

- Improved outcome definition by incorporating creatinine levels to estimate glomerular filtration, which enabled us to include cases of chronic kidney disease who were not treated at hospitals or specialized nephrology departments.
- Inclusion of information on comorbidity and prescriptions with high validity from Danish National Health Registers.
- Population-based design in a population, which are considered representative for the general Danish population.
- Limited number of antipsychotic users among cases, and very few users of second-generation antipsychotics with low risk of metabolic disturbances, such as aripiprazole.
- Information on general risk factors for disease as overweight, smoking and lifestyle were not available.

INTRODUCTION

Antipsychotics are primarily labelled for maintenance treatment in schizophrenia, bipolar affective disorder, and insufficiently responding unipolar depression, but are also used commonly in a number of other psychiatric conditions[1]. Maintenance treatment in chronic conditions is often year- or life-long, which makes tolerability an important concern in choosing and adhering to treatment. Furthermore, the risk of acute adverse events associated with antipsychotics are relevant to both long-term treatment and to episodic treatment. Second generation antipsychotics (SGA) are associated with a number of adverse effects including weight gain, metabolic syndrome, diabetes, and cardiovascular disease[2,3]. Observational studies have linked SGAs to an increased risk of both acute kidney injury (AKI)[4,5] and chronic kidney disease (CKD)[6,7].

CKD can develop in several ways: Following AKI, as a complication to metabolic syndrome and diabetes (diabetic nephropathy), or as a complication to cardiovascular disease, either hypertension (hypertensive nephropathy) or arteriosclerosis[8]. Use of SGAs has been associated with all these conditions. For example, case reports have described clozapine, olanzapine, and quetiapine to be associated with interstitial nephritis and AKI[9,10]. Therefore, maintenance treatment with antipsychotics might contribute to the development of CKD, which is important as the mortality of patients with end-stage renal disease is comparable to patients with coronary heart disease[11].

Prior studies on the association of SGAs and CKD have used hospital discharge diagnoses of CKD as outcome definitions[6,7]. In advanced stages, CKD will result in hospitalization, dialysis, kidney transplantation or death, but less severe stages of CKD are usually handled in primary care, which are not recorded in the administrative registers.

We aimed to investigate the association between use of SGAs and the subsequent risk of CKD by combining prescription information with laboratory data to substantiate the outcome definition.

METHODS

We undertook a population-based case-control study of incident CKD-cases among inhabitants residing on the island of Funen, Denmark who - between 2001 and 2015 - had at least two measurements of creatinine performed. We compared the use of SGAs among CKD-cases to that of a disease-free control population.

Data sources

We used information from the Funen Laboratory Cohort (FLaC). A more detailed description of FLaC has been published elsewhere[12]. In summary, FLaC contains information regarding all biochemistry and laboratory results of all Funen inhabitants who, within the study period, had at least one measurement of plasma creatinine performed. A total of 460,365 patients out of 693,843 Funen inhabitants, had their creatinine measured in this period, comprising a total of 7,742,124 creatinine samples. We linked this information to several nationwide Danish administrative registers: Danish Civil Registration System[13,14], The Danish National Patient Registry[15], Registers in Statistics Denmark recording education level[16], and The Danish National Prescription Registry[17]. As the Danish National Health Service provides universal tax-supported healthcare for the entire Danish population, and as all Danish inhabitants are assigned a unique personal 10-digit identified (Central Personal Register (CPR) number) at birth, it is possible to conduct true population-based register-linkage studies covering the entire population[13].

Population

All adults with two or more recorded creatinine values and living on Funen and the surrounding islands in the period January 2001 to December 2015 were eligible for inclusion in the study. Funen is a part of the Region of Southern Denmark, and is considered representative for the entire Danish population[18]. For each individual, an observation period was defined, starting at the first creatinine measurement during the study period and ending with the last creatinine measurement. Only individuals with normal kidney function were included. In case of emigration from the island of Funen, the observation period ended on the last date of creatinine measurement prior to emigration.

Cases

Cases were defined as individuals with incident CKD during the observation period. We defined CKD according to the KDIGO guidelines[19] as the first measurement of eGFR below 60 ml/min/1.73m^2. The date of this measurement defined the index date. In order to ensure that cases had CKD, the first eGFR measured three months after the index date also had to be below 60 ml/min/1.73m2, as well as all the measurements in the in-between period (from the index date to 3 months after). The eGFR was calculated according to the CKDepi formula[20]. Individuals with a discharge diagnosis of renal disease according to the definition of possible CKD, as proposed by Kessing et al.[21] prior to the date of biochemical CKD were excluded. (ICD-10: N18-N19.9 inclusive plus N00, N01, N03, N04, N05, N06, N8.8 plus N14.1, N14.2, N16.8, N17, N25.1, N26, and N27). Individuals with any eGFR measurement below 60 ml/min/1,73m^2 up to one year prior to the study start, were also excluded.

Controls

Four population controls were matched on age, sex, and calendar time to each case and assigned an index date corresponding to the case's date of diagnosis. We used risk-set sampling and excluded controls who fulfilled the same exclusion criteria as described for cases. To ensure that controls had not developed CKD since their last creatinine measurement, all controls were required to have at least one creatinine recorded in the year after the index date. This measurement had to be above or equal to 60 ml/min/1.73m2. Cases could be selected as controls before they became cases, and we allowed the study population to be selected as controls more than once. Because of these criteria, the generated odds ratio (OR) is considered an unbiased estimate of the incidence rate ratio. Please refer to figure 1 for a graphical depiction of the study design.

< figure 1 around here >

Drug exposure

We obtained information on all filled prescriptions of SGAs and used the defined daily dose (DDD), according to the WHO Collaborating Centre for Drug Statistics methodology[22]. We used the DDDs as a surrogate marker of the cumulative exposure but converted them into olanzapine equivalents[23]. For an overview of the ATC codes and the corresponding DDDs, please refer to appendix 1. The DDDs, determined by the WHO, are based on doses in maintenance treatment of schizophrenia. We used the number of filled prescriptions as a surrogate marker of duration of use, as many of the drugs are used off-label in lower doses than for treatment of schizophrenia.

Covariates

We included the following potential confounders in our analysis: i) Age, sex and calendar time (accounted for by sampling procedure), ii) use of other drugs known to affect renal function (lithium, NSAIDs), iii) history of hypertension and diabetes, and iv) highest achieved level of education as a proxy for socioeconomic status. Use of lithium was defined as any filling of prescriptions for lithium before the index date. Recent use of NSAIDs was defined as filling of prescriptions within one year before the index date. Relevant ICD-10 diagnoses and ATC-codes are listed in appendix 1.

Statistical analyses

We used conditional logistic regression to estimate odds ratios (OR) with 95% confidence interval (CI) for the association between SGA-use and the risk of CKD. Our primary outcome was risk of CKD in relation to ever use of SGA. Secondary outcomes were risk of CKD in relation to current use, cumulative exposure, and cumulative duration. We computed a crude and adjusted ORs (aOR), where the adjusted model included the following predefined clinically relevant potential confounders: prior use of lithium, recent use of NSAIDs, diabetes, hypertension, and highest achieved level of education. We conducted subgroup analyses by stratifying on metabolic risk of SGA as proposed by De Hert et al.[3], cumulative dose, individual SGAs, diabetes, hypertension, and prior AKI. To explore a potential dose response relation, we performed a supplementary analysis, using conditional logistic regression amongst all users of SGA and restricted cubic splines with knots placed at the value for the 10th, 50th and 90th percentile for cumulative doses. We conducted

a sensitivity analysis where eligible controls where not required to have normal eGFR measurement(s) in the year following the index date to assess the potential of selection bias with this criterion. Furthermore, we conducted control analyses to assess the association between CKD and known risk factors (history of diabetes or hypertension, and use of lithium or NSAIDs), and between a negative control exposure and CKD (topical ocular antibiotics – not considered associated with CKD). R version 3.5.1 (R Core Team, Vienna, Austria) was used for all analyses.

Patient and public involvement

No patients were involved in designing the study

Approval

This study was approved by the Danish Data Protection Agency (j.nr 2008-58-0034) and the Danish Patient Safety Authority (j.nr. 3-3013-809/1). According to Danish law, studies based solely on register data do not require approval from an ethics review board[24].

RESULTS

We identified 21.434 cases with incident CKD in Funen County between 2001 and 2016, with 48% males and a median age of 71 years (IQR 64-78 years). Using risk-set sampling, cases were matched by sex, age, and calendar year to 85.576 CKD-free population controls. Hypertension and diabetes were more prevalent among cases than controls at baseline (65 vs 55% and 14 vs 10% respectively). ORs for the association between risk factors and CKD presented in appendix 2. The most commonly used SGA among cases and controls was risperidone. See table 1 for further details.

< table 1 around here >

Main analysis:

Among cases, 557 (2.6%) were ever-users of SGAs, compared to 1731 (2.0%) of controls yielding an adjusted OR of 1.24 (95%CI: 1.12-1.37). The corresponding adjusted OR for current use was 1.26 (95%CI: 1.12-1.42). We did not find evidence of a dose-response-relationship, using predefined categories neither in relation to cumulative use nor in relation to duration of use (see table 2). Short duration measured as 1-2 antipsychotic prescriptions, as well as long-term use (>30 prescriptions) were both associated with increased risk (see table 2).

< table 2 around here >

Subgroup analysis:

The majority of cases and controls used SGAs with mild risk of metabolic disturbances (e.g. risperidone), followed by SGAs with high risk (e.g. clozapine and olanzapine), and moderate risk (e.g. quetiapine). Use of SGAs with mild and high risk of metabolic disturbances was associated with increased risk of CKD in the adjusted model ($OR_{mildrisk}$ 1.21, 95%CI: 1.06-1.39 and $OR_{highrisk}$ 1.36, 95%CI: 1.11-1.68) (see table 3).

Users of SGAs, who also had diabetes, had an 50% increased risk of developing CKD compared to controls, but due to the low number of exposed diabetics, the confidence interval overlapped unity ($aOR_{diabetes}$ 1.52, 95%CI: 0.90-2.54). Antipsychotic users in the low age category, had an increased risk of CKD compared to the higher age category ($aOR_{<65years}$ 1.50, 95%CI: 1.25-1.80). None of the other known risk factors for CKD (use of NSAIDs, hypertension, and prior AKI) were clearly associated with development of CKD in connection to SGA exposure (see table 3). The absolute risk of CKD in this population was 3.4% for individuals <65 years, 16% for individuals ≥65 years. For individuals with prior AKI the absolute risk was 40.8% versus 4.6% for individuals without prior AKI.

< table 3 around here >

Specific SGAs:

All SGAs, except for aripiprazole, were associated with increased risk of CKD (see figure 2). The risk was most pronounced for clozapine (aOR 1.81, 95%CI: 1.22-2.69)

followed by olanzapine (aOR 1.41, 95%CI: 1.19-1.65) and quetiapine (aOR 1.28, 95%CI: 1.17-1.42).

< figure 2 around here >

Supplementary and sensitivity analyses:
Additional analysis of the association between cumulative dose of SGAs and the risk of CKD, yielded a somewhat uniform dose-response relationship, with risk of CKD increasing slightly with increasing cumulative dose of SGA until approximately 900-1000mg olanzapine equivalents (appendix 3).
The risk of CKD in relation SGA exposure was largely unchanged, when including controls who were not required normal eGFR measurements in the year following their assigned index date (appendix 4).

DISCUSSION

In this large population-based study using routinely collected eGFR to define CKD, we found that ever-users of SGAs had a higher risk of developing CKD compared to never-users. However, there was no clear evidence of a dose-response-relationship, and several known risk factors for CKD did not substantially increase the risk of developing CKD (e.g. NSAID use, prior lithium use, prior AKI[8]). We found a further increased risk of developing CKD among individuals with diabetes, and among those below 65 years of age at the time of CKD-diagnosis, although the risk among diabetics was not significant. For individual antipsychotics, the use of clozapine or olanzapine was associated with the highest risk of developing.

Regarding the overall risk of developing CKD in connection to treatment with SGAs, our main findings are in line with previous studies: Tzeng and colleagues[6] found a similar increased risk of CKD among individuals with schizophrenia during three years of follow-up. (HR 1.36, 95%CI: 1.13-1.63), and Wang and colleagues substantiated this finding by observing an increased risk of CKD among individuals with more than 90 and 1000 days of SGA exposure (OR 1.42 and 1.30 respectively)[7].

In our current study we observed a 52% increased risk of developing CKD for antipsychotic-users who also had diabetes compared to non-diabetics, although not statistically significant. Development of CKD and later potentially end-stage renal disease (ESRD) is a well-established complication of diabetes[25], and our finding might underscore the importance of regular monitoring of kidney-function in this population. CKD-prevalence is related to age, as nephron-loss and the prevalence of medical conditions generally increases with age[8]. Our finding of the highest risk among the younger age group (table 3) might be explained by the low absolute risk observed in this age group, resulting in greater increases in relative risk, when exposed to SGAs. Another potential explanation for this finding might be a higher proportion of long-term antipsychotic use for severe mental illness in this age category, whereas antipsychotic use in the older age category might represent short-term and/or low-dose use in conditions as dementia and delirium. Furthermore, the observed increase in risk associated with use of few prescriptions is suggestive of some degree of residual confounding. Analysis of the individual SGAs in connection to CKD (see figure 2) found the highest risk associated with olanzapine and clozapine, which was expected as these SGAs are associated with the highest risk of metabolic disturbances and diabetes[2].

The primary strength of the present study is the improved outcome definition. By using creatinine levels to estimate glomerular filtration, we can include CKD-cases who are not treated at hospitals and specialized nephrology departments. A considerable proportion of CKD-cases might be handled in general practice until severe or ESRD is present. These cases would be missed if our outcome definition only relied on hospital diagnoses. Secondly, the linkage to Danish registers allowed us to obtain high quality information on comorbidity and prescriptions. Lastly, the population of Funen is considered representative for the general Danish population[18].

However, several limitations must be acknowledged: Firstly, the number of antipsychotic users among CKD-cases was generally low, and most users had very short duration of antipsychotic use (i.e. ≤2 prescriptions). Our population included few users with high cumulative doses (i.e. >3650 mg olanzapine-equivalents). This means that our dose-response analysis is likely to underestimate the associated risk among this sub-population with high cumulative doses. The population also includes very few users of SGAs with low risk of metabolic disturbances, such as aripiprazole, which makes us unable to conclude if this group is associated with increased risk of CKD or not. Secondly, we were not able to adjust for use of other potentially nephrotoxic drugs[26] (besides lithium and NSAIDs), as these are primarily used in hospitals (i.e., aminoglycosides, chemotherapy, or x-ray contrast) or dispensed from out-patient clinics (i.e., antiretrovirals, or calcineurin-inhibitors), and thus not captured in our data sources. Thirdly, information on general risk factors for disease as overweight, smoking and lifestyle are not included in our data sources.

Our finding of modest increases in risk of CKD with SGAs, does not suggest any clear association between these. Furthermore, the presence of an increased risk with few antipsychotic prescriptions is indicative of some degree of residual confounding. Therefore, we do not believe that SGAs by themselves increases the risk of CKD, but rather contribute to metabolic disturbances which in the end result in kidney damage. The increased risk among SGA users with diabetes adds to this interpretation. This underscores the importance of frequent monitoring of metabolic status in patients treated with antipsychotics, which could include monitoring of kidney function as standard practice.

In conclusion, we found a small-to-moderately increased risk of incident CKD among individuals using second-generation antipsychotics. All investigated second-generation antipsychotics, except for aripiprazole, were associated with an increased risk of CKD.

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Author contributions: LCL, JLEH, MH and DPH initiated and designed the study. LCL analysed the data. MH and DPH drafted the manuscript. All authors critically revised the manuscript and approved the submission.
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LEGENDS TO FIGURES

Figure 1: Graphical representation of time periods, case definition, control selection and covariate assessment

Figure 2: Association between exposure to second-generation antipsychotics and the risk of chronic kidney disease by individual drugs (aOR: Adjusted odds ratio)

Table 1: Characteristics of cases and controls

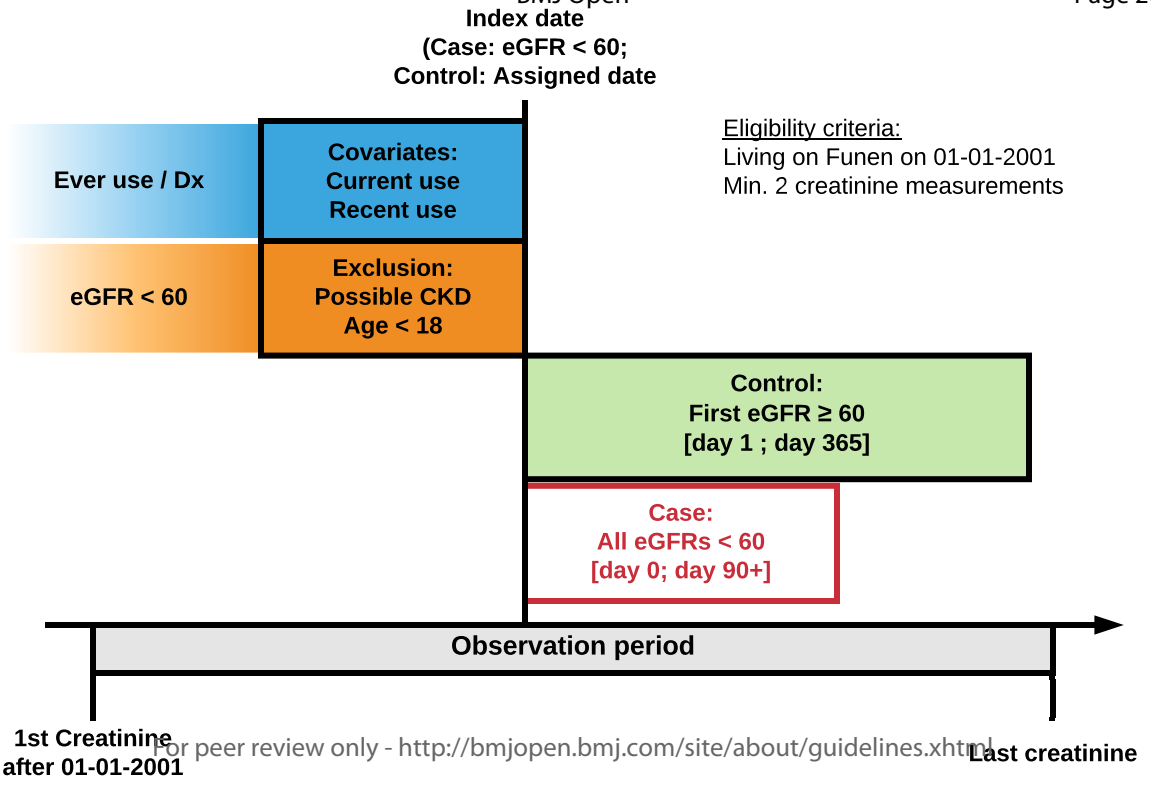
Characteristic	Cases, N (%)	Controls, N (%)
All	21,434	85,576
Demographics		
Male sex (%)	10,277 (48)	41,010 (48)
Age, median [IQR]	71 [64, 78]	71 [64, 78]
History of mental disorders		
Any psychiatric disease (%)	1,549 (7)	4,828 (6)
Schizophrena (%)	74 (<1)	217 (<1)
Bipolar disease (%)	120 (1)	356 (<1)
Moderate to severe depression (%)	549 (3)	1,742 (2)
Dementia (%)	122 (1)	366 (<1)
Other co-morbidities		
Acute kidney injury (%)	2,436 (11)	2,477 (3)
Diabetes (%)	3,057 (14)	8,138 (10)
Hypertension (%)	13,962 (65)	47,095 (55)
Antipsychotic exposure		
Second-generation antipsychotics (%)	557 (3)	1,731 (2)
Quetiapine (%)	173 (1)	504 (1)
Aripiprazole (%)	8 (<1)	41 (<1)
Risperidone (%)	299 (1)	967 (1)
Olanzapine (%)	220 (1)	593 (1)
Clozapine (%)	37 (<1)	82 (<1)
Exposure to other medications		
Prior use of lithium (%)	210 (1)	563 (1)
Recent use of NSAIDs (%)	5,610 (26)	20,081 (23)
Highest achieved level of education (%)		
Level 1	10,250 (48)	38,385 (45)
Level 2	6,785 (32)	27,778 (32)
Level 3	2,687 (13)	12,727 (15)
Unknown	1,712 (8)	6,686 (8)

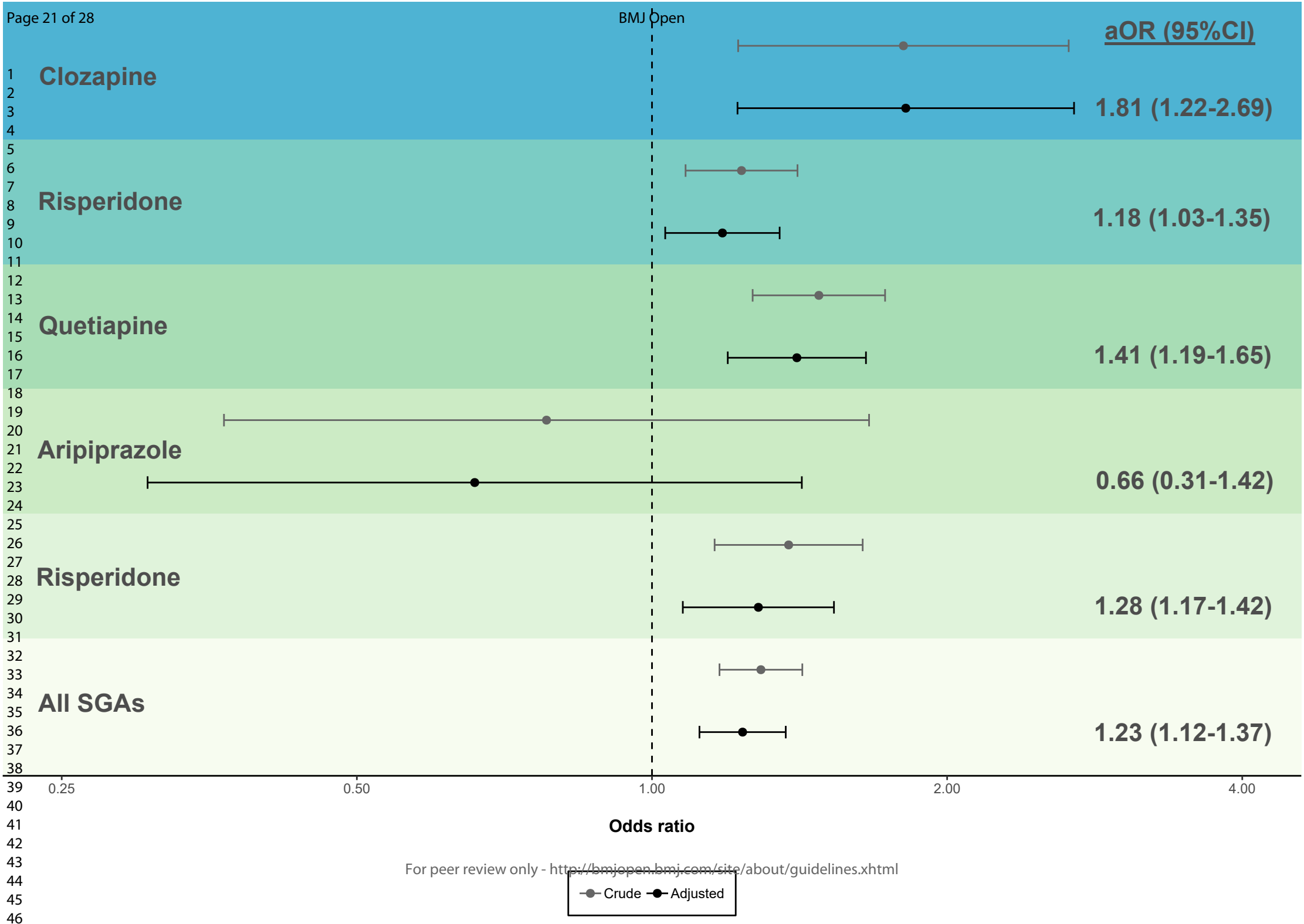
Table 2: Odds ratios (OR) for chronic kidney disease with use of second-generation antipsychotics

Exposure	Cases, N (%) (N = 21434)	Controls, N (%) (N = 85576)	Crude OR (95% CI)	Adjusted OR (95% CI)
Never use	20877	83845	1 (ref)	1 (ref)
Ever use	557	1731	1.29 (1.17-1.42)	1.24 (1.12-1.37)
Current use	399	1206	1.32 (1.18-1.49)	1.26 (1.12-1.42)
Cumulative use (olanzapine eq.)				
0-899mg	380	1246	1.22 (1.09-1.37)	1.17 (1.04-1.32)
900-1799mg	52	124	1.70 (1.23-2.36)	1.60 (1.15-2.23)
1800-3649mg	29	121	0.96 (0.64-1.43)	0.91 (0.60-1.38)
>3650mg	96	240	1.60 (1.26-2.03)	1.46 (1.14-1.86)
Number of prescriptions				
1-2	144	450	1.28 (1.06-1.54)	1.22 (1.01-1.48)
3-4	76	236	1.28 (0.98-1.66)	1.24 (0.95-1.62)
5-10	68	240	1.14 (0.87-1.50)	1.06 (0.80-1.39)
11-30	115	409	1.12 (0.91-1.38)	1.10 (0.89-1.36)
>30	154	396	1.57 (1.30-1.89)	1.45 (1.19-1.76)

Table 3: Association between exposure to second-generation antipsychotics and the risk of chronic kidney disease by subgroups (risk of metabolic disturbances, recent use of NSAIDs, pre-existing diabetes, hypertension, prior acute kidney injury (AKI), and age)

Exposure		Cases, N	Controls, N	Crude OR (95% CI)	Adjusted OR (95% CI)
All		N = 21434	N = 85576		
SGA	Low risk	8	41	0.85 (0.39-1.82)	0.71 (0.32-1.54)
	Mild risk	298	947	1.26 (1.10-1.44)	1.21 (1.06-1.39)
	Moderate risk	118	372	1.28 (1.04-1.58)	1.19 (0.96-1.48)
	High risk	133	371	1.43 (1.17-1.74)	1.36 (1.11-1.68)
NSAID	No	15824	947	1.29 (1.15-1.45)	1.22 (1.08-1.38)
	Yes	5610	20081	1.13 (0.84-1.51)	1.10 (0.81-1.49)
Diabetes	No	18377	77438	1.27 (1.14-1.41)	1.24 (1.11-1.39)
	Yes	3057	8138	1.56 (0.96-2.53)	1.52 (0.90-2.54)
Hypertension	No	7472	38481	1.43 (1.19-1.72)	1.33 (1.10-1.60)
	Yes	13962	47095	1.21 (1.05-1.39)	1.14 (0.98-1.32)
Prior AKI	No	18998	83099	1.31 (1.18-1.47)	1.27 (1.14-1.42)
	Yes	2436	2477	1.24 (0.59-2.58)	0.96 (0.45-2.07)
Age group	<65	5847	23423	1.66 (1.40-1.97)	1.50 (1.25-1.80)
	65+	15587	62153	1.15 (1.02-1.30)	1.13 (1.00-1.28)





SUPPLEMENTARY MATERIAL
Second-generation antipsychotics and the Risk of Chronic Kidney Disease: A Population-based Case-Control Study

Højlund M, Lund LC, Herping JLE, Haastrup MB, Damkier P, Henriksen DP
2020

Contents

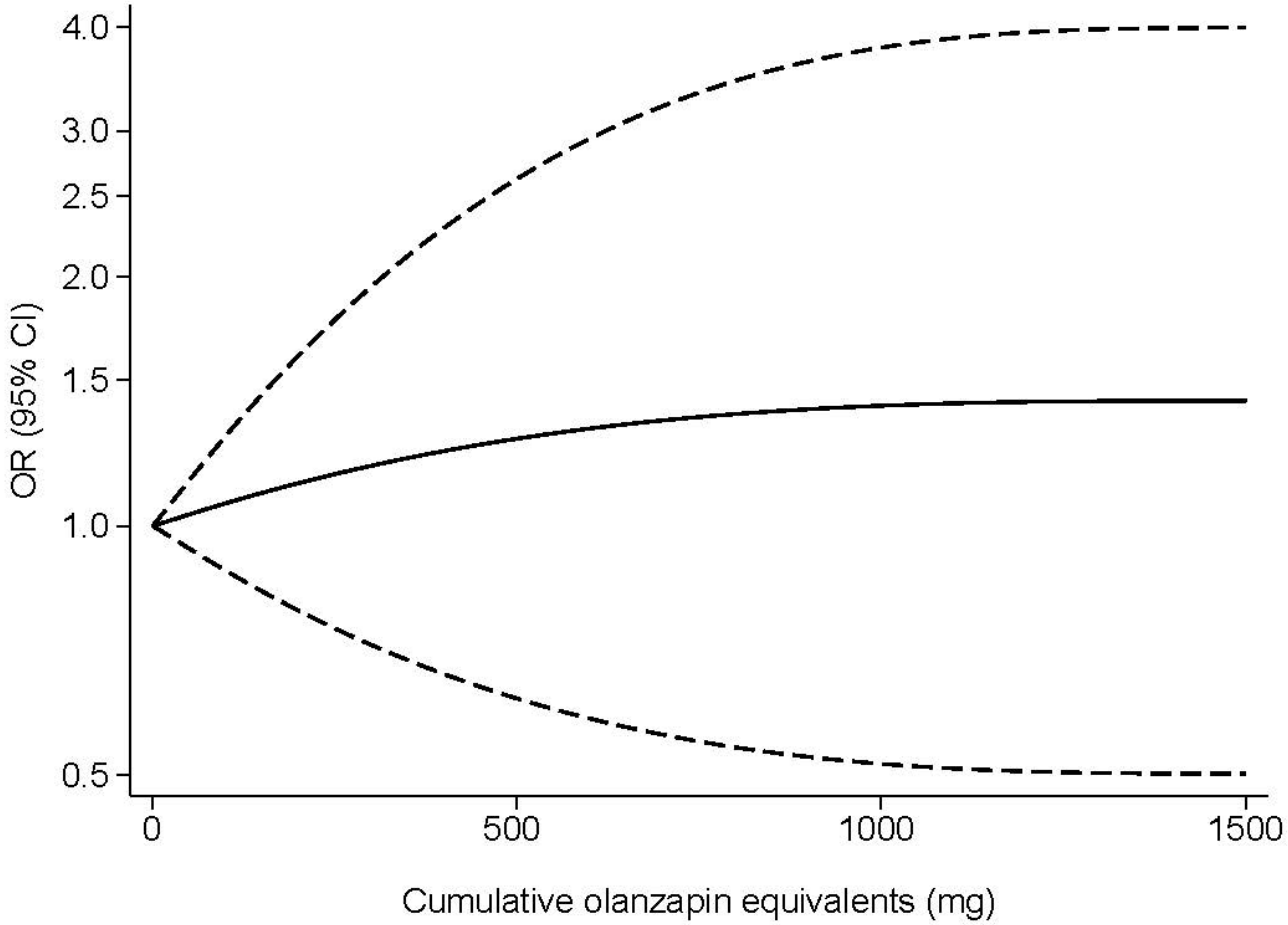
Appendix 1: Definitions for exposures, outcomes and confounders

Study drugs (Second-generation antipsychotics)	ATC code	DDD (mg)	Equivalent to 1mg olanzapine (mg)	Risk of metabolic disturbances (1)
Aripiprazole	N05AX12	15	1.5	Low
Clozapine	N05AH02	300	30	High
Olanzapine	N05AH03	10	-	High
Risperidone	N05AX08	5	0.5	Mild
Quetiapine	N05AH04	400	40	Moderate
Other medications				
Non-steroidal anti-inflammatory drugs (NSAIDs)	M01A, excl. M01AX01			
Lithium	N05AN01			
Comorbidities	**Definition**			
Diabetes	Use of ATC-group A10			
Hypertension	Use of ATC-group C03A, C08C, C09A, C09C			
Possible CKD (2)	ICD-10: N00, 01, 03-06, 08.8, 14.1, 14.2, 16.8, 17-19, 25.1, 26-27			
Schizophrenia	ICD-10: F20			
Bipolar affective disorder	ICD-10: F30-31			
Dementia	ICD-10: F00-03 and G30-31			
Prior AKI	Defined using creatinine measurements according to Kidney Disease Improving Global Outcomes (3)			

Appendix 2: Supplementary analysis of association between risk factors, negative control exposure and CKD

	Crude OR (95% CI)	Adjusted OR (95% CI)
Positive control exposures		
History of diabetes	1.59 (1.52-1.67)	1.45 (1.38-1.52)
History of hypertension	1.56 (1.51-1.61)	1.50 (1.45-1.55)
Prior use of lithium	1.50 (1.28-1.76)	1.60 (1.36-1.87)
Recent use of NSAID	1.16 (1.12-1.20)	1.14 (1.10-1.18)
Negative control exposure		
Use of ocular topical antibiotics	0.95 (0.90-1.00)	0.93 (0.88-0.98)

Appendix 3: Association between CKD and cumulated dose of SGA modeled using restricted cubic splines



Appendix 4: Sensitivity analysis with modified eligibility criteria for controls

	Cases (N=21434)	Controls (N=85654)	Crude OR (95% CI)	Adjusted OR (95% CI)
Ever use	557	1654	1.36 (1.23-1.49)	1.27 (1.14-1.40)
Current use	399	1153	1.39 (1.24-1.56)	1.32 (1.17-1.49)
Cumulative use				
0-899mg	380	1223	1.25 (1.12-1.41)	1.17 (1.03-1.32)
900-1799mg	52	121	1.71 (1.23-2.36)	1.58 (1.13-2.21)
1800-3649mg	29	100	1.18 (0.78-1.78)	1.19 (0.78-1.83)
>3650mg	96	210	1.83 (1.44-2.34)	1.61 (1.25-2.08)
Number of prescriptions				
1-2	144	384	1.50 (1.24-1.82)	1.38 (1.13-1.69)
3-4	76	229	1.31 (1.01-1.70)	1.21 (0.93-1.59)
5-10	68	228	1.19 (0.91-1.56)	1.09 (0.83-1.45)
11-30	115	444	1.05 (0.85-1.29)	0.99 (0.80-1.22)
>30	154	369	1.69 (1.40-2.05)	1.55 (1.27-1.88)

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STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *case-control studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	*(*a) Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls	5
		(*b*) For matched studies, give matching criteria and the number of controls per case	5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*4-6*
Bias	9	Describe any efforts to address potential sources of bias	6-7
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5-6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6-7
		(*b*) Describe any methods used to examine subgroups and interactions	6-7
		(*c*) Explain how missing data were addressed	-
		(*d*) If applicable, explain how matching of cases and controls was addressed	5
		(*e*) Describe any sensitivity analyses	-
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	-
		(c) Consider use of a flow diagram	-
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8, table 1
		(b) Indicate number of participants with missing data for each variable of interest	-
Outcome data	15*	Report numbers in each exposure category, or summary measures of exposure	8
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8-9, table 2+3
		(*b*) Report category boundaries when continuous variables were categorized	-
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	-
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	8-9, table 2+3
Discussion			
Key results	18	Summarise key results with reference to study objectives	10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	11
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10-11
Generalisability	21	Discuss the generalisability (external validity) of the study results	11
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	11

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Second-generation antipsychotics and the risk of chronic kidney disease: a population-based case-control study

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Keywords:	CLINICAL PHARMACOLOGY, EPIDEMIOLOGY, Nephrology < INTERNAL MEDICINE, Chronic renal failure < NEPHROLOGY, PSYCHIATRY

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Second-generation antipsychotics and the Risk of Chronic Kidney Disease: A Population-based Case-Control Study

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Word count: 2716, **Tables:** 3, **Figures:** 2, **References:** 26

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Abstract (279/300 words)

Objectives:
To examine the association between use of second-generation antipsychotics (SGA) and the risk of chronic kidney disease (CKD).

Design: Population-based case-control study

Setting: Routinely collected laboratory, prescription, and diagnostic information on all inhabitants with creatinine measurements residing on the island of Funen, Denmark (2001-2015).

Participants: 21,434 cases with incident CKD matched with 85,576 CKD-free population controls by risk-set sampling using age, sex, and calendar year.

Primary and secondary outcome measures:
CKD was defined as an eGFR below 60 ml/min/1.73m^2 in a period longer than three months. Information on drug exposure and comorbidities were obtained from the Danish National Prescription Register and the Danish National Patient Register. We calculated odds ratios (OR) for the association between SGA use and CKD using conditional logistic regression.

Results:
Use of SGAs was associated with increased risk of CKD among ever-users (OR 1.24, 95%CI: 1.12-1.37) and current users (OR 1.26, 95%CI: 1.12-1.42). We found no clear evidence of dose-response-relationship. Both short duration (1-2 antipsychotic prescriptions; OR 1.22, 95%CI: 1.01-1.48), as well as long-term use (>30 prescriptions; OR 1.45, 95%CI 1.19-1.76) were associated with an increased risk of CKD. Both use of SGAs with mild and high risk of metabolic disturbances was associated with increased risk of CKD (OR 1.21, 95%CI: 1.06-1.39 and 1.36, 95%CI: 1.11-1.68 respectively). Recent use of NSAIDs, prior use of lithium, hypertension, or prior AKI were not clearly associated with development of CKD in connection to SGA exposure. The highest risk of CKD was found for clozapine (OR 1.81, 95%CI: 1.22-2.69).

Conclusions:
Use of SGA is associated with a small-to-moderately increased risk of incident CKD. All investigated second-generation antipsychotics, except for aripiprazole, were associated with an increased risk of CKD.

Keywords:
Antipsychotics, chronic kidney disease, case-control study

Article summary:

Strengths and limitations of this study

- Improved outcome definition by incorporating creatinine levels to estimate glomerular filtration, which enabled us to include cases of chronic kidney disease who were not treated at hospitals or specialized nephrology departments.
- Inclusion of information on comorbidity and prescriptions with high validity from Danish National Health Registers.
- Population-based design in a population, which are considered representative for the general Danish population.
- Limited number of antipsychotic users among cases, and very few users of second-generation antipsychotics with low risk of metabolic disturbances, such as aripiprazole.
- Information on general risk factors for disease as overweight, smoking and lifestyle were not available.

INTRODUCTION

Antipsychotics are primarily labelled for maintenance treatment in schizophrenia, bipolar affective disorder, and insufficiently responding unipolar depression, but are also used commonly in a number of other psychiatric conditions[1]. Maintenance treatment in chronic conditions is often year- or life-long, which makes tolerability an important concern in choosing and adhering to treatment. Furthermore, the risk of acute adverse events associated with antipsychotics are relevant to both long-term treatment and to episodic treatment. Second generation antipsychotics (SGA) are associated with a number of adverse effects including weight gain, metabolic syndrome, diabetes, and cardiovascular disease[2,3]. Observational studies have linked SGAs to an increased risk of both acute kidney injury (AKI)[4,5] and chronic kidney disease (CKD)[6,7].

CKD can develop in several ways: Following AKI, as a complication to metabolic syndrome and diabetes (diabetic nephropathy), or as a complication to cardiovascular disease, either hypertension (hypertensive nephropathy) or arteriosclerosis[8]. Use of SGAs has been associated with all these conditions. For example, case reports have described clozapine, olanzapine, and quetiapine to be associated with interstitial nephritis and AKI[9,10]. Therefore, maintenance treatment with antipsychotics might contribute to the development of CKD, which is important as the mortality of patients with end-stage renal disease is comparable to patients with coronary heart disease[11].

Prior studies on the association of SGAs and CKD have used hospital discharge diagnoses of CKD as outcome definitions[6,7]. In advanced stages, CKD will result in hospitalization, dialysis, kidney transplantation or death, but less severe stages of CKD are usually handled in primary care, which are not recorded in the administrative registers.

We aimed to investigate the association between use of SGAs and the subsequent risk of CKD by combining prescription information with laboratory data to substantiate the outcome definition.

METHODS

We undertook a population-based case-control study of incident CKD-cases among inhabitants residing on the island of Funen, Denmark who - between 2001 and 2015 - had at least two measurements of creatinine performed. We compared the use of SGAs among CKD-cases to that of a disease-free control population.

Data sources

We used information from the Funen Laboratory Cohort (FLaC). A more detailed description of FLaC has been published elsewhere[12]. In summary, FLaC contains information regarding all biochemistry and laboratory results of all Funen inhabitants who, within the study period, had at least one measurement of plasma creatinine performed. A total of 460,365 patients out of 693,843 Funen inhabitants, had their creatinine measured in this period, comprising a total of 7,742,124 creatinine samples. We linked this information to several nationwide Danish administrative registers: Danish Civil Registration System[13,14], The Danish National Patient Registry[15], Registers in Statistics Denmark recording education level[16], and The Danish National Prescription Registry[17]. As the Danish National Health Service provides universal tax-supported healthcare for the entire Danish population, and as all Danish inhabitants are assigned a unique personal 10-digit identified (Central Personal Register (CPR) number) at birth, it is possible to conduct true population-based register-linkage studies covering the entire population[13].

Population

All adults with two or more recorded creatinine values and living on Funen and the surrounding islands in the period January 2001 to December 2015 were eligible for inclusion in the study. Funen is a part of the Region of Southern Denmark, and is considered representative for the entire Danish population[18]. For each individual, an observation period was defined, starting at the first creatinine measurement during the study period and ending with the last creatinine measurement. Only individuals with normal kidney function were included. In case of emigration from the island of Funen, the observation period ended on the last date of creatinine measurement prior to emigration.

Cases

Cases were defined as individuals with incident CKD during the observation period. We defined CKD according to the KDIGO guidelines[19] as the first measurement of eGFR below 60 ml/min/1.73m^2. The date of this measurement defined the index date. In order to ensure that cases had CKD, the first eGFR measured three months after the index date also had to be below 60 ml/min/1.73m2, as well as all the measurements in the in-between period (from the index date to 3 months after). The eGFR was calculated according to the CKDepi formula[20]. Individuals with a discharge diagnosis of renal disease according to the definition of possible CKD, as proposed by Kessing et al.[21] prior to the date of biochemical CKD were excluded. (ICD-10: N18-N19.9 inclusive plus N00, N01, N03, N04, N05, N06, N8.8 plus N14.1, N14.2, N16.8, N17, N25.1, N26, and N27). Individuals with any eGFR measurement below 60 ml/min/1,73m^2 up to one year prior to the study start, were also excluded.

Controls

Four population controls were matched on age, sex, and calendar time to each case and assigned an index date corresponding to the case's date of diagnosis. We used risk-set sampling and excluded controls who fulfilled the same exclusion criteria as described for cases. To ensure that controls had not developed CKD since their last creatinine measurement, all controls were required to have at least one creatinine recorded in the year after the index date. This measurement had to be above or equal to 60 ml/min/1.73m2. Cases could be selected as controls before they became cases, and we allowed the study population to be selected as controls more than once. Because of these criteria, the generated odds ratio (OR) is considered an unbiased estimate of the incidence rate ratio. Please refer to figure 1 for a graphical depiction of the study design.

< figure 1 around here >

Drug exposure

We obtained information on all filled prescriptions of SGAs and used the defined daily dose (DDD), according to the WHO Collaborating Centre for Drug Statistics methodology[22]. We used the DDDs as a surrogate marker of the cumulative exposure but converted them into olanzapine equivalents[23]. For an overview of the ATC codes and the corresponding DDDs, please refer to appendix 1. The DDDs, determined by the WHO, are based on doses in maintenance treatment of schizophrenia. We used the number of filled prescriptions as a surrogate marker of duration of use, as many of the drugs are used off-label in lower doses than for treatment of schizophrenia.

Covariates

We included the following potential confounders in our analysis: i) Age, sex and calendar time (accounted for by sampling procedure), ii) use of other drugs known to affect renal function (lithium, NSAIDs), iii) history of hypertension and diabetes, and iv) highest achieved level of education as a proxy for socioeconomic status. Use of lithium was defined as any filling of prescriptions for lithium before the index date. Recent use of NSAIDs was defined as filling of prescriptions within one year before the index date. Relevant ICD-10 diagnoses and ATC-codes are listed in appendix 1.

Statistical analyses

We used conditional logistic regression to estimate odds ratios (OR) with 95% confidence interval (CI) for the association between SGA-use and the risk of CKD. Our primary outcome was risk of CKD in relation to ever use of SGA. Secondary outcomes were risk of CKD in relation to current use, cumulative exposure, and cumulative duration. We computed a crude and adjusted ORs (aOR), where the adjusted model included the following predefined clinically relevant potential confounders: prior use of lithium, recent use of NSAIDs, diabetes, hypertension, and highest achieved level of education. We conducted subgroup analyses by stratifying on metabolic risk of SGA as proposed by De Hert et al.[3], cumulative dose, individual SGAs, diabetes, hypertension, and prior AKI. To explore a potential dose response relation, we performed a supplementary analysis, using conditional logistic regression amongst all users of SGA and restricted cubic splines with knots placed at the value for the 10th, 50th and 90th percentile for cumulative doses among cases.

We conducted a sensitivity analysis where eligible controls where not required to have normal eGFR measurement(s) in the year following the index date to assess the potential of selection bias with this criterion. Furthermore, we conducted control analyses to assess the association between CKD and known risk factors (history of diabetes or hypertension, and use of lithium or NSAIDs), and between a negative control exposure and CKD (topical ocular antibiotics – not considered associated with CKD). R version 3.5.1 (R Core Team, Vienna, Austria) was used for all analyses.

Patient and public involvement

No patients were involved in designing the study

Approval

This study was approved by the Danish Data Protection Agency (j.nr 2008-58-0034) and the Danish Patient Safety Authority (j.nr. 3-3013-809/1). According to Danish law, studies based solely on register data do not require approval from an ethics review board[24].

RESULTS

We identified 21,434 cases with incident CKD in Funen County between 2001 and 2016, with 48% males and a median age of 71 years (IQR 64-78 years). Using risk-set sampling, cases were matched by sex, age, and calendar year to 85,576 CKD-free population controls. Hypertension and diabetes were more prevalent among cases than controls at baseline (65 vs 55% and 14 vs 10% respectively). The most commonly used SGA among cases and controls was risperidone. See table 1 for further details.

< table 1 around here >

Main analysis:

Among cases, 557 (2.6%) were ever-users of SGAs, compared to 1731 (2.0%) of controls yielding an adjusted OR of 1.24 (95%CI: 1.12-1.37). The corresponding adjusted OR for current use was 1.26 (95%CI: 1.12-1.42). Control analyses confirmed that each of the assumed risk factors included in the model was positively associated with increased risk of CKD and that a negative control exposure was not associated with increased risk of CKD (appendix 2). We did not find evidence of a dose-response-relationship, using predefined categories neither in relation to cumulative use nor in relation to duration of use (see table 2). Short duration measured as 1-2 antipsychotic prescriptions, as well as long-term use (>30 prescriptions) were both associated with increased risk (see table 2).

< table 2 around here >

Subgroup analysis:

The majority of cases and controls used SGAs with mild risk of metabolic disturbances (e.g. risperidone), followed by SGAs with high risk (e.g. clozapine and olanzapine), and moderate risk (e.g. quetiapine). Use of SGAs with mild and high risk of metabolic disturbances was associated with increased risk of CKD in the adjusted model ($OR_{mildrisk}$ 1.21, 95%CI: 1.06-1.39 and $OR_{highrisk}$ 1.36, 95%CI: 1.11-1.68) (see table 3).

Users of SGAs, who also had diabetes, had an 50% increased risk of developing CKD compared to controls, but due to the low number of exposed diabetics, the confidence interval overlapped unity ($aOR_{diabetes}$ 1.52, 95%CI: 0.90-2.54). Antipsychotic users in the low age category, had an increased risk of CKD compared to the higher age category ($aOR_{<65years}$ 1.50, 95%CI: 1.25-1.80). None of the other known risk factors for CKD (use of NSAIDs, hypertension, and prior AKI) were clearly associated with development of CKD in connection to SGA exposure (see table 3). The absolute risk of CKD in this population was 3.4% for individuals <65 years, 16% for individuals ≥65 years. For individuals with prior AKI the absolute risk was 40.8% versus 4.6% for individuals without prior AKI.

< table 3 around here >

Specific SGAs:

All SGAs, except for aripiprazole, were associated with increased risk of CKD (see figure 2). The risk was most pronounced for clozapine (aOR 1.81, 95%CI: 1.22-2.69) followed by olanzapine (aOR 1.41, 95%CI: 1.19-1.65) and quetiapine (aOR 1.28, 95%CI: 1.17-1.42).

< figure 2 around here >

Supplementary and sensitivity analyses:
Additional analysis of the association between cumulative dose of SGAs and the risk of CKD, yielded a somewhat uniform dose-response relationship, with risk of CKD increasing slightly with increasing cumulative dose of SGA until approximately 900-1000mg olanzapine equivalents (appendix 3).
The risk of CKD in relation SGA exposure was largely unchanged, when including controls who were not required normal eGFR measurements in the year following their assigned index date (appendix 4).

DISCUSSION

In this large population-based study using routinely collected eGFR to define CKD, we found that ever-users of SGAs had a higher risk of developing CKD compared to never-users. However, there was no clear evidence of a dose-response-relationship, and several known risk factors for CKD did not substantially increase the risk of developing CKD (e.g. NSAID use, prior lithium use, prior AKI[8]). We found a further increased risk of developing CKD among individuals with diabetes, and among those below 65 years of age at the time of CKD-diagnosis, although the risk among diabetics was not significant. For individual antipsychotics, the use of clozapine or olanzapine was associated with the highest risk of developing.

Regarding the overall risk of developing CKD in connection to treatment with SGAs, our main findings are in line with previous studies: Tzeng and colleagues[6] found a similar increased risk of CKD among individuals with schizophrenia during three years of follow-up. (HR 1.36, 95%CI: 1.13-1.63), and Wang and colleagues substantiated this finding by observing an increased risk of CKD among individuals with more than 90 and 1000 days of SGA exposure (OR 1.42 and 1.30 respectively)[7].

In our current study we observed a 52% increased risk of developing CKD for antipsychotic-users who also had diabetes compared to non-diabetics, although not statistically significant. Development of CKD and later potentially end-stage renal disease (ESRD) is a well-established complication of diabetes[25], and our finding might underscore the importance of regular monitoring of kidney-function in this population. CKD-prevalence is related to age, as nephron-loss and the prevalence of medical conditions generally increases with age[8]. Our finding of the highest risk among the younger age group (table 3) might be explained by the low absolute risk observed in this age group, resulting in greater increases in relative risk, when exposed to SGAs. Another potential explanation for this finding might be a higher proportion of long-term antipsychotic use for severe mental illness in this age category, whereas antipsychotic use in the older age category might represent short-term and/or low-dose use in conditions as dementia and delirium. Furthermore, the observed increase in risk associated with use of few prescriptions is suggestive of some degree of residual confounding. Analysis of the individual SGAs in connection to CKD (see figure 2) found the highest risk associated with olanzapine and clozapine, which was expected as these SGAs are associated with the highest risk of metabolic disturbances and diabetes[2].

The primary strength of the present study is the improved outcome definition. By using creatinine levels to estimate glomerular filtration, we can include CKD-cases who are not treated at hospitals and specialized nephrology departments. A considerable proportion of CKD-cases might be handled in general practice until severe or ESRD is present. These cases would be missed if our outcome definition only relied on hospital diagnoses. Secondly, the linkage to Danish registers allowed us to obtain high quality information on comorbidity and prescriptions. Lastly, the population of Funen is considered representative for the general Danish population[18].

However, several limitations must be acknowledged: Firstly, the number of antipsychotic users among CKD-cases was generally low, and most users had very short duration of antipsychotic use (i.e. ≤2 prescriptions). Our population included few users with high cumulative doses (i.e. >3650 mg olanzapine-equivalents). This means that our dose-response analysis is likely to underestimate the associated risk among this sub-population with high cumulative doses. The population also includes very few users of SGAs with low risk of metabolic disturbances, such as aripiprazole, which makes us unable to conclude if this group is associated with increased risk of CKD or not. Secondly, we were not able to adjust for use of other potentially nephrotoxic drugs[26] (besides lithium and NSAIDs), as these are primarily used in hospitals (i.e., aminoglycosides, chemotherapy, or x-ray contrast) or dispensed from out-patient clinics (i.e., antiretrovirals, or calcineurin-inhibitors), and thus not captured in our data sources. Thirdly, information on general risk factors for disease as overweight, smoking and lifestyle are not included in our data sources.

Our finding of modest increases in risk of CKD with SGAs, does not suggest any clear association between these. Furthermore, the presence of an increased risk with few antipsychotic prescriptions is indicative of some degree of residual confounding. Therefore, we do not believe that SGAs by themselves increases the risk of CKD, but rather contribute to metabolic disturbances which in the end result in kidney damage. The increased risk among SGA users with diabetes adds to this interpretation. This underscores the importance of frequent monitoring of metabolic status in patients treated with antipsychotics, which could include monitoring of kidney function as standard practice.

In conclusion, we found a small-to-moderately increased risk of incident CKD among individuals using second-generation antipsychotics. All investigated second-generation antipsychotics, except for aripiprazole, were associated with an increased risk of CKD.

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Author contributions: MH, LCL, JLEH, PD, and DPH initiated and designed the study. LCL analysed the data. MH, LCL, MBH, PD, and DPH interpreted the results. MH, PD, and DPH drafted the manuscript. All authors critically revised the manuscript and approved the final version for submission.
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LEGENDS TO FIGURES

Figure 1: Graphical representation of time periods, case definition, control selection and covariate assessment

Figure 2: Association between exposure to second-generation antipsychotics and the risk of chronic kidney disease by individual drugs (aOR: Adjusted odds ratio)

Table 1: Characteristics of cases and controls

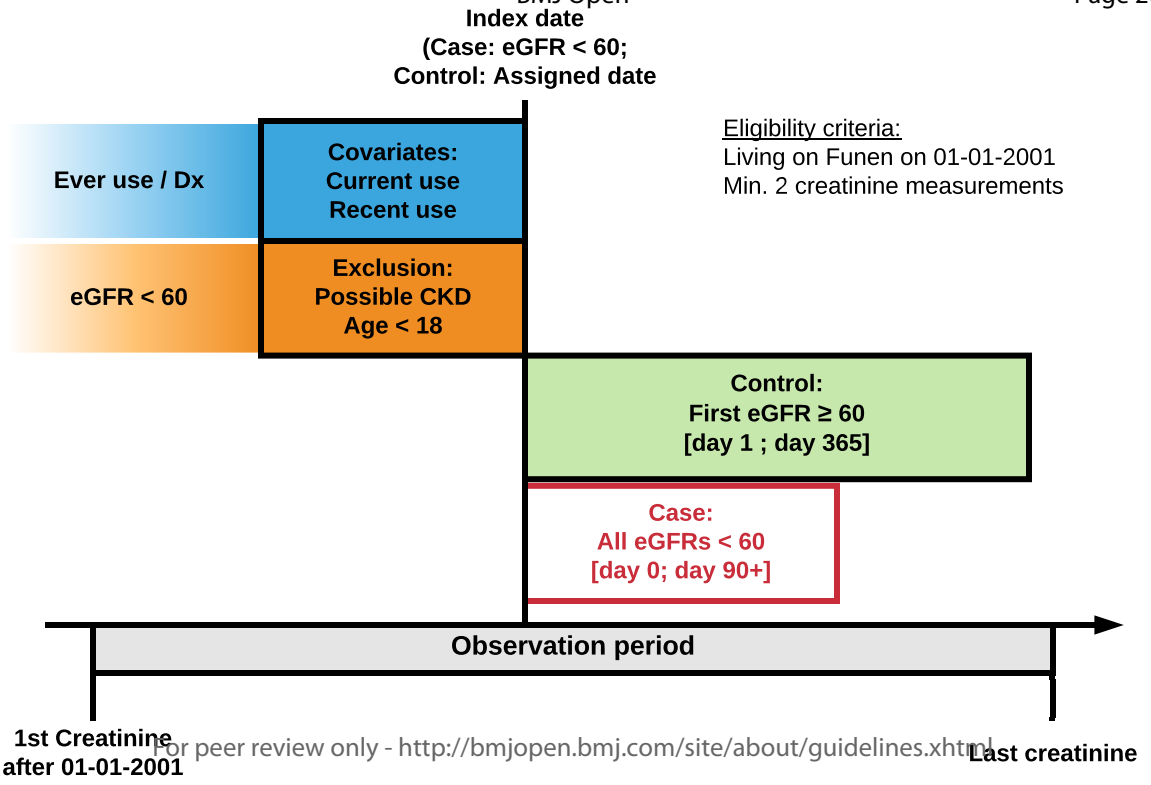
Characteristic	Cases, N (%)	Controls, N (%)
All	21,434	85,576
Demographics		
Male sex (%)	10,277 (48)	41,010 (48)
Age, median [IQR]	71 [64, 78]	71 [64, 78]
History of mental disorders		
Any psychiatric disease (%)	1,549 (7)	4,828 (6)
Schizophrena (%)	74 (<1)	217 (<1)
Bipolar disease (%)	120 (1)	356 (<1)
Moderate to severe depression (%)	549 (3)	1,742 (2)
Dementia (%)	122 (1)	366 (<1)
Other co-morbidities		
Acute kidney injury (%)	2,436 (11)	2,477 (3)
Diabetes (%)	3,057 (14)	8,138 (10)
Hypertension (%)	13,962 (65)	47,095 (55)
Antipsychotic exposure		
Second-generation antipsychotics (%)	557 (3)	1,731 (2)
Quetiapine (%)	173 (1)	504 (1)
Aripiprazole (%)	8 (<1)	41 (<1)
Risperidone (%)	299 (1)	967 (1)
Olanzapine (%)	220 (1)	593 (1)
Clozapine (%)	37 (<1)	82 (<1)
Exposure to other medications		
Prior use of lithium (%)	210 (1)	563 (1)
Recent use of NSAIDs (%)	5,610 (26)	20,081 (23)
Highest achieved level of education (%)		
Level 1	10,250 (48)	38,385 (45)
Level 2	6,785 (32)	27,778 (32)
Level 3	2,687 (13)	12,727 (15)
Unknown	1,712 (8)	6,686 (8)

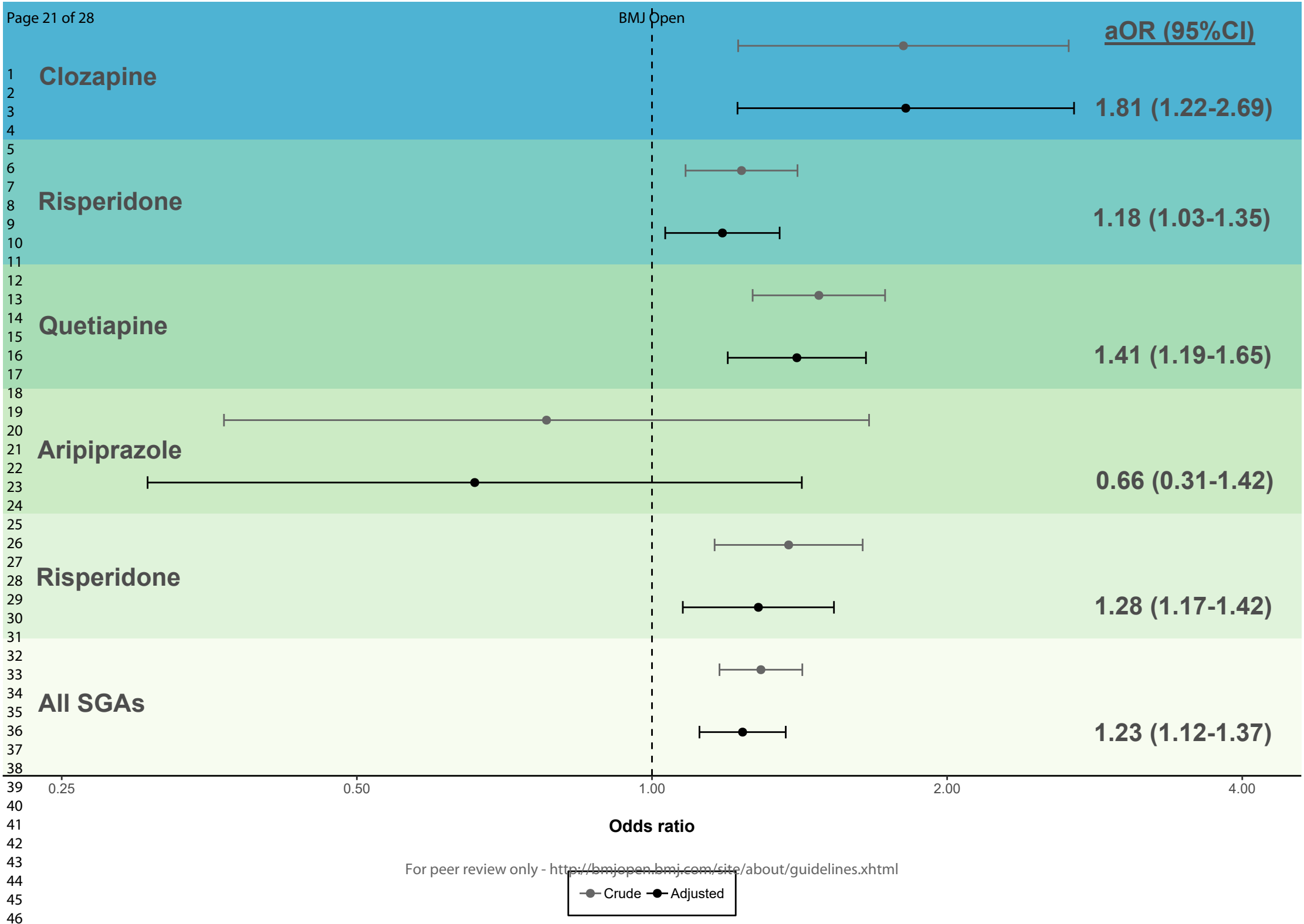
Table 2: Odds ratios (OR) for chronic kidney disease with use of second-generation antipsychotics

Exposure	Cases, N (%) (N = 21434)	Controls, N (%) (N = 85576)	Crude OR (95% CI)	Adjusted OR (95% CI)
Never use	20877	83845	1 (ref)	1 (ref)
Ever use	557	1731	1.29 (1.17-1.42)	1.24 (1.12-1.37)
Current use	399	1206	1.32 (1.18-1.49)	1.26 (1.12-1.42)
Cumulative use (olanzapine eq.)				
0-899mg	380	1246	1.22 (1.09-1.37)	1.17 (1.04-1.32)
900-1799mg	52	124	1.70 (1.23-2.36)	1.60 (1.15-2.23)
1800-3649mg	29	121	0.96 (0.64-1.43)	0.91 (0.60-1.38)
>3650mg	96	240	1.60 (1.26-2.03)	1.46 (1.14-1.86)
Number of prescriptions				
1-2	144	450	1.28 (1.06-1.54)	1.22 (1.01-1.48)
3-4	76	236	1.28 (0.98-1.66)	1.24 (0.95-1.62)
5-10	68	240	1.14 (0.87-1.50)	1.06 (0.80-1.39)
11-30	115	409	1.12 (0.91-1.38)	1.10 (0.89-1.36)
>30	154	396	1.57 (1.30-1.89)	1.45 (1.19-1.76)

Table 3: Association between exposure to second-generation antipsychotics and the risk of chronic kidney disease by subgroups (risk of metabolic disturbances, recent use of NSAIDs, pre-existing diabetes, hypertension, prior acute kidney injury (AKI), and age)

Exposure		Cases, N	Controls, N	Crude OR (95% CI)	Adjusted OR (95% CI)
All		N = 21434	N = 85576		
SGA	Low risk	8	41	0.85 (0.39-1.82)	0.71 (0.32-1.54)
	Mild risk	298	947	1.26 (1.10-1.44)	1.21 (1.06-1.39)
	Moderate risk	118	372	1.28 (1.04-1.58)	1.19 (0.96-1.48)
	High risk	133	371	1.43 (1.17-1.74)	1.36 (1.11-1.68)
NSAID	No	15824	947	1.29 (1.15-1.45)	1.22 (1.08-1.38)
	Yes	5610	20081	1.13 (0.84-1.51)	1.10 (0.81-1.49)
Diabetes	No	18377	77438	1.27 (1.14-1.41)	1.24 (1.11-1.39)
	Yes	3057	8138	1.56 (0.96-2.53)	1.52 (0.90-2.54)
Hypertension	No	7472	38481	1.43 (1.19-1.72)	1.33 (1.10-1.60)
	Yes	13962	47095	1.21 (1.05-1.39)	1.14 (0.98-1.32)
Prior AKI	No	18998	83099	1.31 (1.18-1.47)	1.27 (1.14-1.42)
	Yes	2436	2477	1.24 (0.59-2.58)	0.96 (0.45-2.07)
Age group	<65	5847	23423	1.66 (1.40-1.97)	1.50 (1.25-1.80)
	65+	15587	62153	1.15 (1.02-1.30)	1.13 (1.00-1.28)





SUPPLEMENTARY MATERIAL
Second-generation antipsychotics and the Risk of Chronic Kidney Disease: A Population-based Case-Control Study

Højlund M, Lund LC, Herping JLE, Haastrup MB, Damkier P, Henriksen DP
2020

Contents

Appendix 1: Definitions for exposures, outcomes and confounders

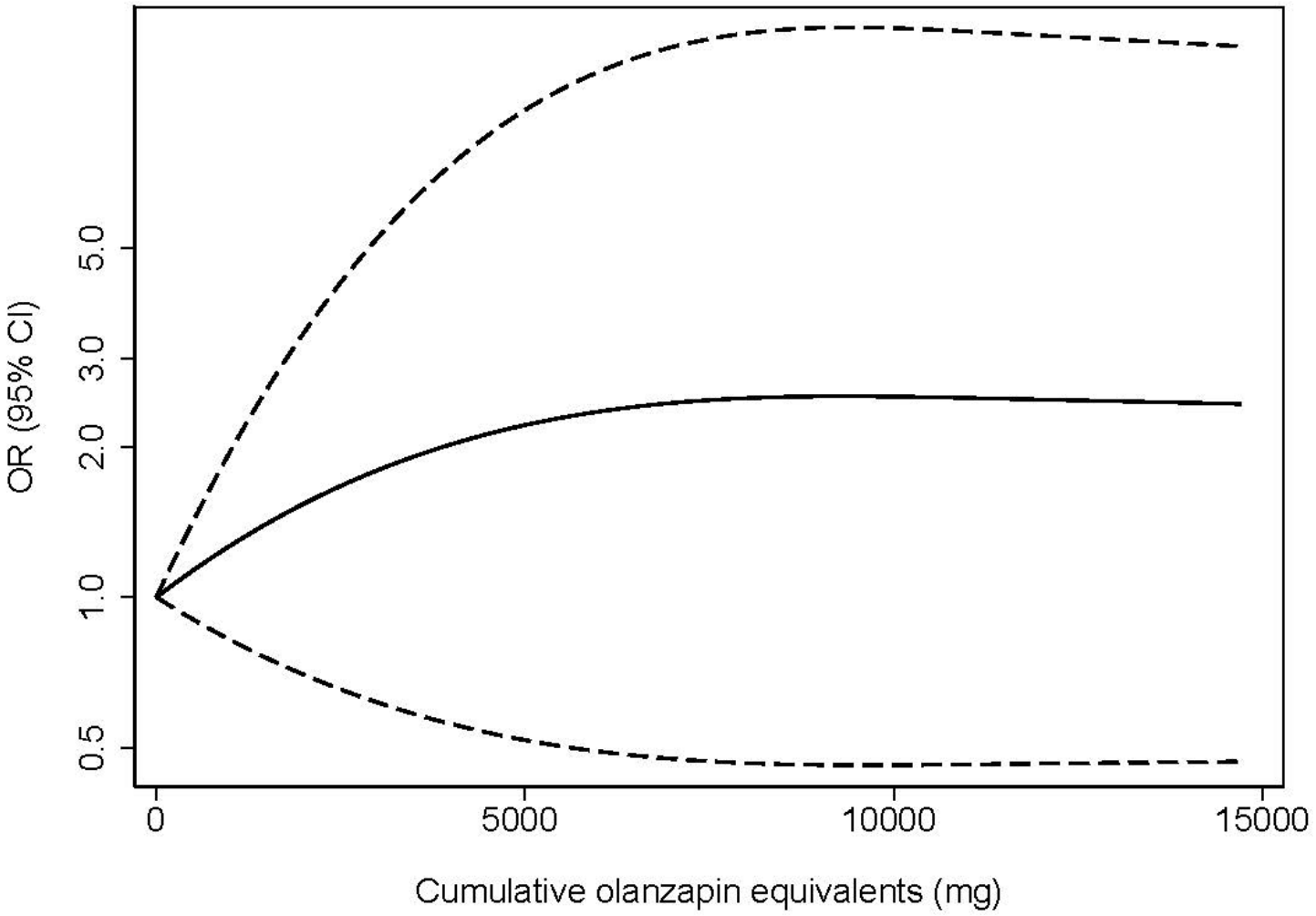
Study drugs (Second-generation antipsychotics)	ATC code	DDD (mg)	Equivalent to 1mg olanzapine (mg)	Risk of metabolic disturbances (1)
Aripiprazole	N05AX12	15	1.5	Low
Clozapine	N05AH02	300	30	High
Olanzapine	N05AH03	10	-	High
Risperidone	N05AX08	5	0.5	Mild
Quetiapine	N05AH04	400	40	Moderate
Other medications				
Non-steroidal anti-inflammatory drugs (NSAIDs)	M01A, excl. M01AX01			
Lithium	N05AN01			
Comorbidities	**Definition**			
Diabetes	Use of ATC-group A10			
Hypertension	Use of ATC-group C03A, C08C, C09A, C09C			
Possible CKD (2)	ICD-10: N00, 01, 03-06, 08.8, 14.1, 14.2, 16.8, 17-19, 25.1, 26-27			
Schizophrenia	ICD-10: F20			
Bipolar affective disorder	ICD-10: F30-31			
Dementia	ICD-10: F00-03 and G30-31			
Prior AKI	Defined using creatinine measurements according to Kidney Disease Improving Global Outcomes (3)			

Appendix 2: Supplementary analysis of association between risk factors, negative control exposure and CKD

	Crude OR (95% CI)	Adjusted OR (95% CI)
Positive control exposures		
History of diabetes	1.59 (1.52-1.67)	1.45 (1.38-1.52)
History of hypertension	1.56 (1.51-1.61)	1.50 (1.45-1.55)
Prior use of lithium	1.50 (1.28-1.76)	1.60 (1.36-1.87)
Recent use of NSAID	1.16 (1.12-1.20)	1.14 (1.10-1.18)
Negative control exposure		
Use of ocular topical antibiotics	0.95 (0.90-1.00)	0.93 (0.88-0.98)

Appendix 3: Association between CKD and cumulated dose of SGA modeled using restricted cubic splines

10%-percentile: 5 mg OLA eq, 50%-percentile: 250mg OLA eq, 90%-percentile: 11,200 mg OLA eq. Percentiles were derived from cumulative doses among cases. CI: Confidence interval, OLA eq: Olanzapine equivalents, OR: Odds ratio.



Appendix 4: Sensitivity analysis with modified eligibility criteria for controls

	Cases (N=21434)	Controls (N=85654)	Crude OR (95% CI)	Adjusted OR (95% CI)
Ever use	557	1654	1.36 (1.23-1.49)	1.27 (1.14-1.40)
Current use	399	1153	1.39 (1.24-1.56)	1.32 (1.17-1.49)
Cumulative use				
0-899mg	380	1223	1.25 (1.12-1.41)	1.17 (1.03-1.32)
900-1799mg	52	121	1.71 (1.23-2.36)	1.58 (1.13-2.21)
1800-3649mg	29	100	1.18 (0.78-1.78)	1.19 (0.78-1.83)
>3650mg	96	210	1.83 (1.44-2.34)	1.61 (1.25-2.08)
Number of prescriptions				
1-2	144	384	1.50 (1.24-1.82)	1.38 (1.13-1.69)
3-4	76	229	1.31 (1.01-1.70)	1.21 (0.93-1.59)
5-10	68	228	1.19 (0.91-1.56)	1.09 (0.83-1.45)
11-30	115	444	1.05 (0.85-1.29)	0.99 (0.80-1.22)
>30	154	369	1.69 (1.40-2.05)	1.55 (1.27-1.88)

References

1. De Hert M, Detraux J, van Winkel R, Yu W, Correll CU. Metabolic and cardiovascular adverse effects associated with antipsychotic drugs. Nat Rev Endocrinol. 2011;8:114–26.

2. Kessing LV, Gerds TA, Feldt-Rasmussen B, Andersen PK, Licht RW. Use of Lithium and Anticonvulsants and the Rate of Chronic Kidney Disease: A Nationwide Population-Based Study. JAMA Psychiatry. 2015;72:1182–91.

3. KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. KDIGO 2012 Clin Pract Guidel Eval Manag Chronic Kidney Dis. 2013;3:1–150.

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *case-control studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	*(*a) Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls	5
		(*b*) For matched studies, give matching criteria and the number of controls per case	5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*4-6*
Bias	9	Describe any efforts to address potential sources of bias	6-7
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5-6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6-7
		(*b*) Describe any methods used to examine subgroups and interactions	6-7
		(*c*) Explain how missing data were addressed	-
		(*d*) If applicable, explain how matching of cases and controls was addressed	5
		(*e*) Describe any sensitivity analyses	-
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	-
		(c) Consider use of a flow diagram	-
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8, table 1
		(b) Indicate number of participants with missing data for each variable of interest	-
Outcome data	15*	Report numbers in each exposure category, or summary measures of exposure	8
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8-9, table 2+3
		(*b*) Report category boundaries when continuous variables were categorized	-
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	-
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	8-9, table 2+3
Discussion			
Key results	18	Summarise key results with reference to study objectives	10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	11
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10-11
Generalisability	21	Discuss the generalisability (external validity) of the study results	11
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	11

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.