Chronic kidney disease in adults with schizophrenia: A nationwide population-based study

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ABSTRACT

Objective: Several studies have recently reported an association between chronic kidney disease (CKD) and schizophrenia, yet this association has not been sufficiently established. The aim of this study was to examine the association between schizophrenia and CKD in a large dataset, as well as to assess the level of accessibility of these patients to common treatments for CKD.

Method: Patients diagnosed with schizophrenia (n = 27,516) and an equal number of age and sex frequency-matched controls were included in this nationwide population-based study. Logistic regressions and ROC curves were employed to assess the association between schizophrenia and CKD and the level of fit of the models.

Results: Schizophrenia was associated with CKD, after controlling for demographic, behavioral, and medical risk factors (OR = 1.62, CI 1.45–1.82, p < .0001). After adjusting for demographic and behavioral risk factors, CKD patients without schizophrenia were more likely to receive dialysis (OR = 1.70, 95% CI 1.18–2.44, p < .01) and kidney transplantation (OR = 5.43, 95% CI 2.84–10.38, p < .001) as compared to CKD patients with schizophrenia.

Conclusion: As CKD affects survival, quality of life, and medical and familial burden, additional thought should be given to detection of CKD, as well as to accessibility to treatment, among patients with schizophrenia.

1. Introduction

Chronic kidney disease (CKD) is considered to be a common and frequently under-recognized disorder [1], associated with adverse clinical outcomes, poor quality of life, and high health-care costs [2]. Defined as kidney damage (i.e. albuminuria) or a decreased glomerular filtration rate (GFR) of < 60 ml/min/1.73 m² for at least three months [3], CKD is ranked as the 19th highest cause of years of life lost overall [4], and accounts for 24% of the total Medicare budget in the US [5]. The estimated global prevalence of CKD at stages 1–5 in adults was found to be 10.4% in men and 11.8% in women, and 4.7% in men and 5.8% in women at stages 3–5 [6]. Thus, CKD is a global-health challenge which demands ongoing research and clinical efforts to improve interventions and reduce morbidity and mortality [6].

A potential group of patients presenting an elevated risk for CKD are patients with severe mental illness (SMI), particularly those suffering from schizophrenia. Studies indicate that diabetes and hypertension, two of the most common causes of CKD, are highly prevalent among patients with schizophrenia [7]. It has been suggested that behavioral factors such as smoking and obesity contribute to physical comorbidity among these patients [8]. Other comorbid medical conditions such as cardiovascular disease, which in and of itself is considered a significant risk factor for CKD [9], might also serve as facilitating factors for the development of CKD. Studies conducted in Taiwan [10] and England [11] have recently demonstrated an association between CKD and schizophrenia, with the effect of second-generation antipsychotics (SGAs) showing mixed findings. However, one study used population-based data with a relatively small number of patients with schizophrenia followed for up to three years, while the other assessed this association among patients with severe mental illness including schizophrenia, bipolar, and other organic psychotic illnesses. Therefore, additional evidence is needed in order to establish this association for discrete diagnostic populations, such as patients with schizophrenia.

An additional aspect of medical and psychiatric comorbidities is

related to patients' access to medical treatments. Cumulative evidence in recent years indicates substantial disparities in healthcare provision to patients with SMI, which in turn contribute to poor physical health outcomes [12–14]. These disparities have been associated with structural factors, such as the separation of mental health services from other medical services, as well as healthcare provider issues such as stigma associated with mental illness, and consequences of mental illness and side effects of its treatment. Studies assessing access to treatment for CKD among patients with schizophrenia have generally found lowered access to kidney transplantation [11], yet their access to more routine treatments such as dialysis has not been sufficiently assessed.

In this study we aimed to assess the association between schizophrenia and CKD. Specifically, we aimed to address the following research questions: (a) Is schizophrenia associated with CKD after controlling for demographic, behavioral, and medical risk factors? (b) Does a schizophrenia diagnosis affect CKD patients' accessibility to dialysis and kidney transplantation? In order to address these research questions, we employed a nationwide population-based study which included 27,516 patients diagnosed with schizophrenia and an equal number of age and sex frequency-matched controls, using the Clalit Health Services (CHS) databases.

2. Methods

2.1. Data source

The Israeli health care system provides ambulatory care via the Health Maintenance Organizations (HMOs) in Israel, which cover 98% of the Israeli population. All Israeli residents are required by law to be insured by one of four Israeli HMOs. Of these four, the Clalit Health Services (CHS) is the largest health care organization, providing health care services for 52% of Israel's population (4,400,000 enrollees) [15]. CHS has a comprehensive database with continuous real-time input from health care providers, pharmacies, medical care facilities, and administrative computerized operating systems. The diagnoses of chronic diseases are based on information derived from hospital and primary care physicians' reports, which then undergo a comprehensive validation process by systematic methodology. A process of validation of CHS registries is performed by CHS use of logistic checks such as comparisons of diagnoses from various sources, and by direct validation of the diagnoses by the treating physicians of each patient. The validity of the diagnoses in the current registry was previously shown to be high [16], with both psychiatric and medical diagnoses utilized and validated in many studies [17–19]. Prior to data analysis, we also ascertained the validity of the schizophrenia diagnosis by randomly sampling 10% of the cohort and evaluating their clinical files. This evaluation was performed by an expert senior psychiatrist (author IK), which reviewed the clinical files for the presence of symptoms that would meet ICD criteria for a diagnosis of schizophrenia.

Ninety-four percent of the selected sample was found to be accurately diagnosed with schizophrenia, with the remaining 6% having insufficient information to confirm the diagnosis, indicating that this dataset is indeed valid and reliable.

2.2. Study population and disease definition

The study included all individuals who were enrolled in CHS since the beginning of the utilization of computerized systems in CHS (2000) until October 2017. Patients were identified as having CKD if they were diagnosed by a community physician with the following ICD-9 codes: 40301 (malignant hypertensive renal disease with renal failure), 40311 (benign hypertensive disease with chronic renal failure), 40391 (unspecified hypertensive disease with chronic renal failure), 40402 (malignant hypertensive heart and renal disease with renal failure), 40403 (malignant hypertensive heart and renal disease with renal failure and chronic renal failure), 40412 (benign hypertensive heart and renal

disease with renal failure), 40413 (benign hypertensive heart and renal disease with renal failure and chronic renal failure), 40492 (unspecified hypertensive heart and renal disease with renal failure), 40493 (unspecified hypertensive heart and renal disease with renal failure and chronic renal failure), 585 (chronic renal failure), 586 (renal failure, unspecified), or if they presented with a creatinine level of above 2.5 mg/dl. Due to the possibility that a creatinine level of above 2.5 mg/dl might not represent chronic kidney failure, we omitted all patients (n = 280) who were included solely via this indication from the main analyses. The majority of the sample with available lab values (84.9%) had a decreased GFR of < 60 ml/min at the time of diagnosis, which corresponds to stages 3 and above. Patients were defined as having schizophrenia (n = 27,516) when there was an active diagnosis in the medical documentation registered by a community psychiatrist or if it was listed in the diagnoses of discharge letters from a mental health hospital. Both schizophrenia and CKD diagnoses were derived from the validated CHS registry. A control group (n = 27,516) was randomly sampled at a 1:1 ratio, selected from the list of CHS members. Sex and age were frequency-matched to random cases while excluding patients with a schizophrenia diagnosis. The study was approved by the CHS institutional review board (IRB) prior to data collection and analysis.

2.3. Definition of covariates

Baseline demographic characteristics were assessed in patients with and without schizophrenia, and included age, sex, and socioeconomic status (SES). Sociodemographic status was established by the calculation of an index score combining information from social services, as well as demographic variables such as district and current address [20], as commonly utilized in studies employing the CHS databases. Smoking and obesity were registered by the primary physician. Medical risk factors included diabetes mellitus, hypertension, congestive heart failure, cardiomyopathy, and hyperlipidemia, as registered in the medical file by the primary physician.

2.4. Statistical analysis

The distribution of sociodemographic and clinical factors between the schizophrenia- diagnosed group and the control group was assessed using the chi-square test for categorical variables and *t*-test for continuous variables. Odds ratios (OR) across strata were tested using chi-square tests. A hierarchical logistic regression was employed in order to assess the association between schizophrenia and CKD while controlling for demographic, medical, and behavioral variables. Variables were added to the model in four different blocks, as follows: Block 1 - demographic variables, including age, sex, and socioeconomic status; Block 2 - comorbid medical conditions, including diabetes, dyslipidemia, hypertension, and congestive heart failure; Block 3 - comorbid behavioral risk factors, including smoking and obesity; and Block 4 - schizophrenia diagnosis. Goodness of fit for the logistic regression models was assessed using the Hosmer-Lemeshow test. ROC curves were plotted in order to assess level of sensitivity and specificity, as well as to compare model fit using the area under the curve. Simultaneous logistic regressions were used to assess the association between having a schizophrenia diagnosis and the probability of receiving dialysis and kidney transplantation. Statistical analysis was performed using SPSS software, version 25 (SPSS, Chicago, IL, U.S.A.), using $p < .05$ threshold for statistical significance.

3. Results

Characteristics of the study population are presented in Table 1. Schizophrenia was significantly associated with low SES. Schizophrenia was associated with a higher prevalence of smoking and obesity and with a higher prevalence of diabetes and dyslipidemia. Of the total

Table 1
Descriptive characteristics of the study population (n = 55,032).

	Schizophrenia (n = 27,516)	Control (n = 27,516)	OR	p
Age	49.52 (16.01)	49.52 (16.01)		N/A
Sex				
Male[a]	16,687 (60.6%)	16,687 (60.6%)		N/A
Female	10,829 (39.4%)	10,829 (39.4%)		
SES				
Medium-high	14,600 (53.1%)	16,138 (58.6%)	Ref.	
Low	12,730 (46.3%)	11,277 (41.0%)	1.24 [1.20;1.29]	< 0.0001
Smoking[b]	14,262 (51.8%)	10,892 (39.6%)	1.64 [1.58;1.69]	< 0.0001
Obesity[b]	8985 (32.7%)	6326 (23.0%)	1.62 [1.56;1.68]	< 0.0001
Diabetes[b]	6034 (21.9%)	4046 (14.7%)	1.62 [1.55;1.70]	< 0.0001
Hypertension[b]	6040 (22.0%)	6001 (21.8%)	1.00 [0.96;1.05]	0.85
Hyperlipidemia[b]	13,403 (48.7%)	11,134 (40.5%)	1.39 [1.35;1.44]	< 0.0001

SES = socioeconomic status.
[a] Reference group is female.
[b] Reference group in these categories is not having the condition/disease.

schizophrenia group, 1124 individuals had CKD, which corresponds to 4.1% of the entire group. In the control group, 671 of the patients were diagnosed with CKD, which corresponds to 2.4% of the control group.

In order to assess the contribution of a schizophrenia diagnosis to the likelihood of having CKD after controlling for the effects of known risk factors, we employed a hierarchical logistic regression. Results of the hierarchical logistic regression are presented in Table 2. As can be seen, age and sex significantly predicted the probability of having CKD, with males having a higher probability for CKD compared to females (OR 0.53), and a higher age associated with a higher probability for CKD (OR 1.04). All medical condition related variables were highly predictive of CKD after controlling for demographic variables. The presence of congestive heart failure significantly predicted the probability of CKD (OR 3.13), followed by hypertension (OR 3.02), dyslipidemia (OR 2.04), and diabetes mellitus (OR 1.52). Of the behavioral variables, smoking was not significantly predictive of CKD, but obesity was (OR 1.25). Finally, schizophrenia was entered into the regression, and was found to be predictive of CKD above and beyond all other risk factors (OR 1.62).

Fig. 1 presents the plots of the ROC curve analyses. As can be seen, in the basic model which included only demographic variables, the Hosmer-Lemeshow test for model fit was 15.62 (p = .04). The area under the curve for this model was 0.79 (SE 0.005, 95% CI 0.78–0.81, p < .001). In the final model, the Hosmer-Lemeshow test for model fit was 13.72 (p = .08). The area under the curve for this model was 0.85 (SE 0.00, 95% CI 0.84–0.86, p < .001).

Finally, we aimed to examine the association between a comorbid schizophrenia diagnosis in CKD patients and the likelihood of their receiving dialysis treatment or kidney transplantation. In order to assess possible bias stemming from differential CKD stage among schizophrenia and controls, we first conducted a chi square test comparing stages of diagnosis, where stages 1–2 were considered as early stages and 3–5 later stages. The analyses indicated no significant differences in CKD stages, χ^2 (1 = 1.88, p = .27. Results of the simultaneous logistic regression are presented in Table 3.

Dialysis treatment was more commonly received among patients with CKD who did not have a comorbid schizophrenia diagnosis (11.1%) as compared to CKD patients who did have the diagnosis (8.5%). After adjusting for demographic (age, sex) and behavioral (smoking, obesity) risk factors, CKD patients without schizophrenia were significantly more likely to receive dialysis as compared to CKD patients with schizophrenia (OR = 1.70, 95% CI 1.18–2.44, p < .01). Age, sex, smoking, and obesity made no significant contribution to the prediction of receiving dialysis. CKD patients with no schizophrenia diagnosis were also significantly more likely to receive kidney transplantation treatment (5.9%) as compared to CKD patients with a schizophrenia diagnosis (1.6%), (OR = 5.43, 95% CI 2.84–10.38, p < .001). Only age was found to be an additional significant predictor, with lower age indicating less likelihood of receiving kidney transplantation (OR = 0.94, 95% CI 0.92–0.96, p < .001).

4. Discussion

This study employed a nationwide population-based cohort design

Table 2
Results of hierarchical logistic regression predicting CKD.

		OR	95% CI	p	Hosmer-Lemeshow		AUC		
					Value	p	AUC	95% CI	p
Model 1: demographic baseline variables	Age	1.04	1.04–1.05	< 0.0001	15.62	0.04	0.79	0.78–0.81	< 0.0001
	Sex[a]	0.53	0.47–0.59	< 0.0001					
	SES-medium[b]	1.00	0.89–1.13	0.89					
	SES-high[b]	0.97	0.82–1.14	0.97					
Model 2: comorbid medical condition	Congestive heart failure[c]	3.13	2.64–3.71	< 0.0001	13.17	0.10	0.85	0.84–0.86	< 0.0001
	Hyperlipidemia[c]	2.04	1.74–2.40	< 0.0001					
	Diabetes[c]	1.52	1.35–1.72	< 0.0001					
	Hypertension[c]	3.02	2.64–3.45	< 0.0001					
Model 3: behavioral risk factors	Smoking[c]	0.95	0.85–1.07	0.46	9.87	0.27	0.85	0.84–0.86	< 0.0001
	Obesity[c]	1.25	1.12–1.41	< 0.0001					
Model 4: schizophrenia	Schizophrenia[c]	1.62	1.45–1.82	< 0.0001	13.72	0.08	0.85	0.84–0.86	< 0.0001

Abbreviations: SES = socioeconomic status, OR = odds ratio, CI = confidence interval, AUC = area under the curve.
[a] Reference group is male.
[b] Reference group is low.
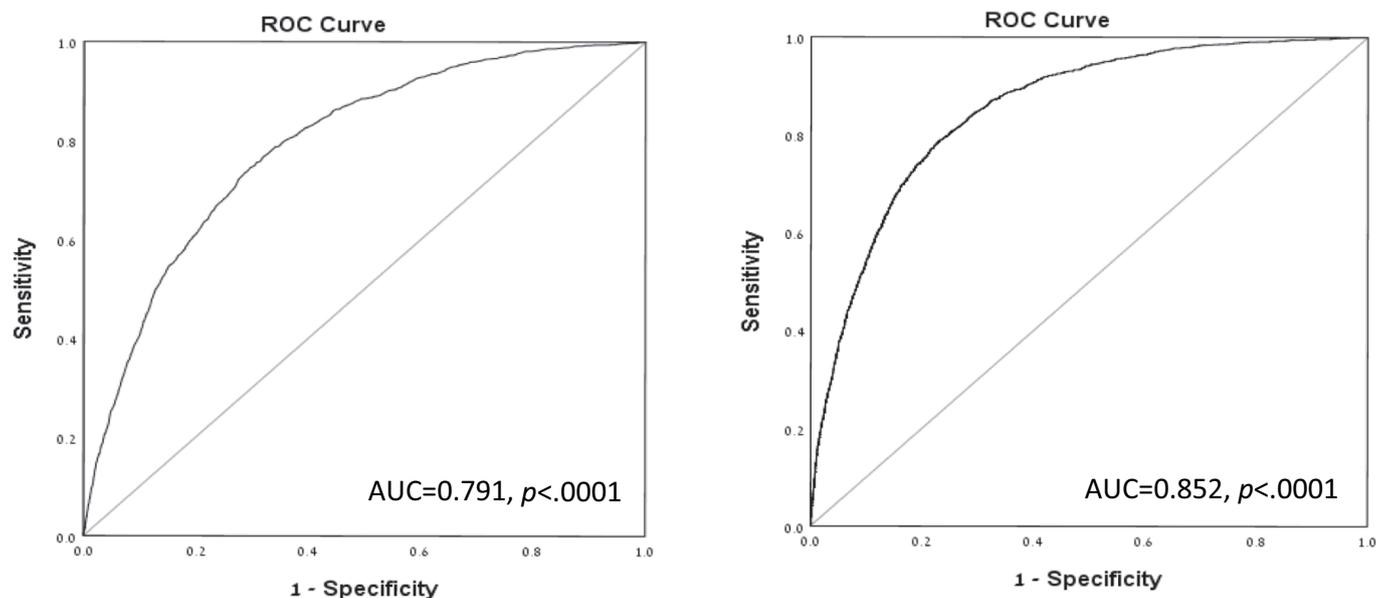[c] Reference group is not having the condition/disease.

Fig. 1. ROC curves for the prediction of CKD with model 1 (demographic factors only) as compared to the final model including risk factors and schizophrenia diagnosis.

to assess the association between CKD and schizophrenia, as well as the extent to which a schizophrenia diagnosis affects CKD patients' accessibility to treatment. Using the highly validated diagnostic data derived from the nationwide databases of CHS, we found that a schizophrenia diagnosis was associated with a higher risk for CKD, even when controlling for known risk factors. Our findings indicate that patients with schizophrenia and CKD were less likely to receive treatments for CKD, such as dialysis and kidney transplantation. These results confirm previous reports from other countries demonstrating an association between CKD and schizophrenia, as well as raise important questions regarding the reasons for the lowered accessibility of patients with schizophrenia to common treatments for CKD.

The association between CKD and severe mental illness has been primarily assessed in bipolar disorder, schizophrenia, and other non-organic psychotic disorders. Some studies employed a more restrictive approach to diagnosis, whereas others combined all diagnoses to address SMI in general. In a matched cohort study conducted in Taiwan, Tzeng et al. [10] examined the association between schizophrenia and CKD using a group of 2338 patients with schizophrenia matched to 7014 controls. They found that patients with schizophrenia were more likely to develop CKD (HR = 1.36), after adjusting for sex, age group, hypertension, diabetes mellitus, dyslipidemia, heart disease, and non-steroidal anti-inflammatory drugs (NSAIDs) usage, with a hazard ratio of 1.25 for patients with schizophrenia. They found that neither typical nor atypical antipsychotics were associated with an increased risk of CKD. Using a non-matched design encompassing schizophrenia, bipolar disorder, and other non-organic psychoses, Iwagami et al. [11] recently found the adjusted OR for CKD to be 1.45 for patients with SMI and no history of lithium prescription. Thus, this study supports and extends these findings, using a larger matched sample of patients with

schizophrenia with highly validated diagnoses, showing an OR of 1.75 after adjusting for demographic, behavioral, and medical risk factors.

In line with Iwagami et al. [11] who found a lower probability for kidney transplantation among patients with SMI, our study demonstrated that this differential accessibility is also evident specifically in patients with schizophrenia. Our findings also extend the understanding regarding the scope of the problem, by indicating that these patients are less likely to receive dialysis treatment, even though health policy in Israel mandates that every patient with CKD be afforded dialysis regardless of his/her mental or general health status [21]. These results converge with previous reports indicating that patients with schizophrenia receive suboptimal pre-dialysis renal care. For example, they are less likely to visit nephrologists and receive fewer erythropoietin prescriptions [22]. Taken together, it seems that the well-known medical disparities among patients with mental health problems [23] also affect the medical management of CKD among these patients, which in turn affects financial burden, social inclusion, and survival.

It should be noted that a severe psychiatric disease is considered to be a relative contraindication for renal transplantation [24]. The reasons for this contraindication are potential drug interactions, fear of low compliance with medication and medical follow-up after transplant, poor social support needed to handle post-transplant rehabilitation, and assumed emotional and cognitive disabilities which might affect the management of the medical issues associated with the transplant. Nonetheless, the results of our study indicate that possible behavioral risk factors such as smoking and obesity are not significant predictors of receiving renal transplantation. Studies assessing the outcome of renal transplantation among patients with schizophrenia indeed found that nearly half of them were reported to suffer from a psychotic relapse after transplantation, which was subsequently associated with graft loss

Table 3

Frequency of dialysis and kidney transplantation among CKD patients with or without schizophrenia.

	CKD and schizophrenia		CKD without schizophrenia		OR[b]	95% CI	p
	Treated	Not treated	Treated	Not treated			
Dialysis[a]	78 (8.5%)	844 (91.5%)	66 (11.1%)	527 (88.9%)	1.70	1.18–2.44	< 0.01
Kidney transplantation[a]	15 (1.6%)	907 (98.4%)	35 (5.9%)	558 (94.1%)	5.43	2.84–10.38	< 0.001

[a] Reference group is patients with schizophrenia and CKD.
[b] The odds of receiving treatment after adjusting for age, sex, obesity, and smoking.

and mortality [25]. Nonetheless, as kidney transplantation is associated with better quality of life and longer survival [26], the inequality in likelihood of renal transplant following these current guidelines should be further addressed and possibly reconsidered.

The high comorbidity between CKD and schizophrenia has several important clinical implications. Tonelli and colleagues evaluated 530,771 patients with CKD and found comorbid schizophrenia to be associated with frequent non-psychiatric hospitalizations and greater lengths of stay [27]. As patients with schizophrenia who are hospitalized for medical or surgical problems have increased risk for adverse events following hospitalization (including sepsis, deep vein thrombosis, pulmonary embolism, and decubitus ulcers) [28], the prevention of comorbid medical conditions in this population is critically important and can minimize additional risk. Current guidelines for routine blood tests in patients with schizophrenia include monitoring of blood pressure, glucose or glycosylated hemoglobin (HbA1c), body mass index and lipid profile [29], while little attention is given to creatinine levels and albuminuria. As routine monitoring of renal function might facilitate early identification of patients with renal damage, the inclusion of renal monitoring in routine clinical practice can possibly minimize these long-term adverse outcomes.

4.1. Limitations

This study has several limitations. First, the study design was cross-sectional; therefore, causal direction cannot be ascertained. For example, it could be argued that non-psychiatric drugs such as aspirin, antibiotics, and steroids can cause psychiatric symptoms such as confusion, insomnia, and psychosis [30], and therefore the causal association would be reversed. Although longitudinal studies do not support such a hypothesis [8], the causal trajectories remain to be further validated. As identification of behavioral risk factors such as obesity and smoking was made by the treating physicians, there is a possible bias concerning the timing and motives of the reports. For example, it is possible that patients only declare smoking to their physician if they have a medical problem associated with smoking, or that the physician decides to document smoking when a smoking-related illness has developed. Although most epidemiological studies utilizing chronic illness registries suffer from this methodological flaw of possible biased self-report, this limitation should be taken under consideration. The current study did not assess the usage of antipsychotic medications as a possible predictor of CKD. Although Tzeng et al. [10] found no association between typical and atypical medication usage and CKD, there are some indications that lithium is associated with an elevated risk for CKD among patients with SMI [31]. Even though lithium is a relatively uncommon treatment for patients with schizophrenia, we cannot disprove the option that this medication is a possible causal explanation for the association between schizophrenia and CKD. For example, lithium can serve as a potential treatment in patients with schizoaffective disorders. This possible causal pattern remains to be examined in future studies. As we have no access to the clinical criteria used to determine the provision of transplantation across different medical cites, future studies are needed to assess reasons for the low transplantation rates among patients with schizophrenia, seeing that these disparities have substantial implications for the well-being of patients with schizophrenia. Finally, as SMI is usually detected by early adulthood [32], whereas CKD starts to increase at later stages in life, it can be claimed that patients with diagnosed SMI are tested more frequently, and are therefore more frequently diagnosed with CKD. Nonetheless, studies indicate that patients with schizophrenia have significantly fewer visits in all general and preventative medical services, including office, emergency, dental, and vision visits, as well as lowered access to preventative routine examinations such as pap screen and Mammogram tests [33]. The results of our analyses further indicated that patients with schizophrenia were not diagnosed at early stages compared to the control group. Thus, although findings do not currently support such an

explanation, this possibility should be further evaluated.

4.2. Conclusions

Patients with schizophrenia are more likely to have comorbid CKD and are less likely to receive dialysis or kidney transplantation than patients without schizophrenia. As comorbid CKD and schizophrenia has negative long-term effects which in turn affect survival, quality of life, and medical and familial burden, attention should be given to the prevention and early detection of renal dysfunction among this population.

Ethics approval and informed consent

The study was approved by the institutional review board of Clalit Health Services (Version 001/2015 - November 12, 2015).

Consent for publication

There are no details, images, or videos relating to individual participants that require the obtaining of informed consent.

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Conflicts of interest

Prof. Arnon Cohen received research grants from Janssen, Novartis, AbbVie, Janssen and Sanofi. Prof. Arnon Cohen served as a consultant, advisor or speaker to AbbVie, Amgen, Boehringer Ingelheim, Dexcel pharma, Janssen, Kamedis, Lilly, Neopharm, Novartis, Perrigo, Pfizer, Rafa, Samsung Bioepis, Sanofi, Sirbal and Taro.

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