ORIGINAL ARTICLE

Risk factors for new-onset diabetes mellitus after kidney transplantation: A systematic review and meta-analysis

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ABSTRACT
Aims/Introduction: To systematically review the risk factors for new-onset diabetes mellitus after kidney transplantation, and to provide a theoretical basis for the prevention and management of new-onset diabetes mellitus after kidney transplantation.

Materials and Methods: We searched PubMed, Web of Science, Embase, the Cochrane Library databases and other databases for case–control studies related to risk factors for new-onset diabetes mellitus after kidney transplantation published between January 2005 and July 2019. A meta-analysis of data on risk factors for new-onset diabetes mellitus after kidney transplantation from the included studies was carried out. A narrative review of risk factors for new-onset diabetes mellitus after kidney transplantation was also carried out.

Results: A total of 24 case–control studies were included in the meta-analysis, with a total of 7,140 patients. There were 1,598 patients with new-onset diabetes mellitus after kidney transplantation, and 5,542 patients without new-onset diabetes mellitus after kidney transplantation. The meta-analysis results showed that age, polycystic kidney disease, family history of diabetes, body mass index, acute rejection, tacrolimus use, hepatitis B virus infection, hepatitis C virus infection and hypertension were associated with new-onset diabetes mellitus after kidney transplantation, whereas sex, sirolimus use, cyclosporin A use, steroid use and cytomegalovirus infection were not associated with new-onset diabetes mellitus after kidney transplantation.

Conclusions: Older age, body mass index, family history of diabetes, tacrolimus use, history of hypertension, polycystic kidney disease, acute rejection, hepatitis B virus infection and hepatitis C virus infection are risk factors for new-onset diabetes mellitus after kidney transplantation. Therefore, the clinical implications of these factors warrant attention.

INTRODUCTION

New-onset diabetes mellitus after transplantation (NODAT) refers to the detection of diabetes after a successful organ transplantation in patients who had not previously shown abnormal blood glucose levels before surgery. With the continuous developments and improvements in the field of organ transplantation, kidney transplantation has been carried out in an increasing number of patients; however, NODAT often occurs after kidney transplantation, with an incidence rate of 2–50%[1–3]. NODAT can lead to related complications, such as kidney transplant failure, cardiovascular disease and infection[4], seriously endangering the quality of life and prognosis of patients with a kidney transplant, and increasing their economic burden. Some studies have shown that the occurrence and development of NODAT after renal transplantation are affected by age, body mass index (BMI), hepatitis C virus (HCV) infection, cytomegalovirus (CMV) infection, use of immunosuppressive drugs, polycystic kidney disease, acute rejection, family history of diabetes mellitus and other risk factors[5–11]; however, there are still controversies. Therefore, a comprehensive and accurate understanding of NODAT-related risk factors after renal transplantation is necessary to prevent and clinically manage NODAT in renal transplant recipients.

METHODS

All analyses were based on previously published studies; therefore, ethical approval and patient consent were not required.

Inclusion and exclusion criteria

The inclusion criteria were as follows: (i) type of study: case–control study; (ii) participants: patients aged >18 years and undergoing kidney transplantation for the first time; (iii) exposure factors: risk factors for NODAT in kidney transplant recipients; and (iv) outcome indicators: NODAT after kidney transplantation, diagnosed according to the diagnostic criteria of the World Health Organization or the American Diabetes Association.

The exclusion criteria were as follows: (i) repeated publications; (ii) too few risk factors or too few cases; and (iii) unavailable full text, incomplete data, unconvertible data or no control group.

Search strategy

PubMed, Web of Science, Embase, the Cochrane Library databases and other databases were searched by computer to collect case–control studies on the risk factors for NODAT after kidney transplantation. The retrieval period was from the establishment of the database through July 2019. In addition, references cited in the articles were traced to supplement the relevant literature. For retrieval, a combination of subject words and free words were used. The search terms included "kidney transplantation," "renal transplantation," "renal transplantations," "kidney grafting,'" "kidney transplantations," "diabetes mellitus," "diabetes insipidus," "prediabetic state," "scleredema adultorum," "glucose tolerance" and 'gastroparesis.'

Literature selection and data extraction

Two researchers independently screened, extracted and cross-checked the literature. Any differences were resolved through discussion and consultation with a third researcher. When selecting documents, the titles were read first. After excluding obviously irrelevant documents, the abstract and full text were read to determine their eligibility for inclusion. If necessary, the authors of the original study were contacted by email or phone to obtain any uncertain, but essential, information for the present study. The following data were extracted: (i) basic information including title, author, publication date, study type, publication area and follow-up time; (ii) baseline characteristics of the study participants, such as sample content and basic information, as well as exposure of risk factors in the case group and control group; (iii) number of cases and controls, and exposure and non-exposure in each study; (iv) key elements of bias risk assessment; and (v) outcome indicators and outcome measurement data.

Risk assessment of the included studies

Two researchers independently evaluated the risk of bias in the study according to the Newcastle–Ottawa Scale (NOS). In the case of disagreement, a third reviewer made the final decision.

Statistical analysis

Revman 5.3 software (Cochrane Collaboration, Oxford, UK) was used for meta-analysis. The mean difference was used as the effect index in measurement data and the odds ratio (OR) was used as the effect index in counting data. The point estimates and 95% confidence intervals (CIs) were calculated for each effect quantity. The heterogeneity among the results was analyzed using the χ^2-test (test level $\alpha = 0.1$), and the degree of heterogeneity was determined by the I^2 statistic. If there was no statistical heterogeneity between the results of each study, the fixed effects model was used for meta-analysis; however, if there was statistical heterogeneity between the results of each study, the source of heterogeneity was further analyzed. After excluding the influence of obvious clinical heterogeneity, the random effects model was used for meta-analysis. The inspection level of the meta-analysis was set as $\alpha = 0.05$. Obvious clinical heterogeneities were subjected to subgroup analysis or sensitivity analysis, or only descriptive analysis. Funnel plot analysis was used to assess publication bias.

RESULTS

Literature screening process and results

A total of 1,054 related articles were collected in the initial examination. After the layer-by-layer screening, 24 articles were finally included[1–3,6,9–28]. The 24 studies involved 7,140 patients, including 1,598 with NODAT after kidney transplantation and 5,542 without NODAT after kidney transplantation. The process and results of the literature screening are shown in Figure 1.

Basic characteristics of the included studies and results of bias risk assessment

Table 1 shows the basic characteristics of the included studies and the results of bias risk assessment according to the NOS. Tables 2 and 3 summarize relevant information on meta-analysis of modifiable risk factors and non-modifiable risk factors, respectively.

Meta-analysis results

Non-modifiable factors
1. Age: 17 studies[1,9–18,20,21,24,25,27,28] were included, with 1,105 patients in the NODAT group and 3,530 patients in the non-NODAT group. After the heterogeneity test ($P < 0.00001$, $I^2 = 78\%$), the random effects model was used, and the results showed that age was a risk factor for NODAT after kidney transplantation (mean difference = 6.05, 95% CI 4.33–7.78, $P < 0.00001$; Figure 2).
2. Sex: 21 studies[1–3,6,9–15,17–22,24,25,27,28] were included, with 1,512 patients in the NODAT group and 5,337 patients in the non-NODAT group. After the heterogeneity test ($P = 0.42$, $I^2 = 3\%$), the fixed effects model was used, and the results showed that sex was not a risk factor for NODAT after kidney transplantation (OR 1.00, 95% CI 0.88–1.13, $P = 0.97$; Figure 3).
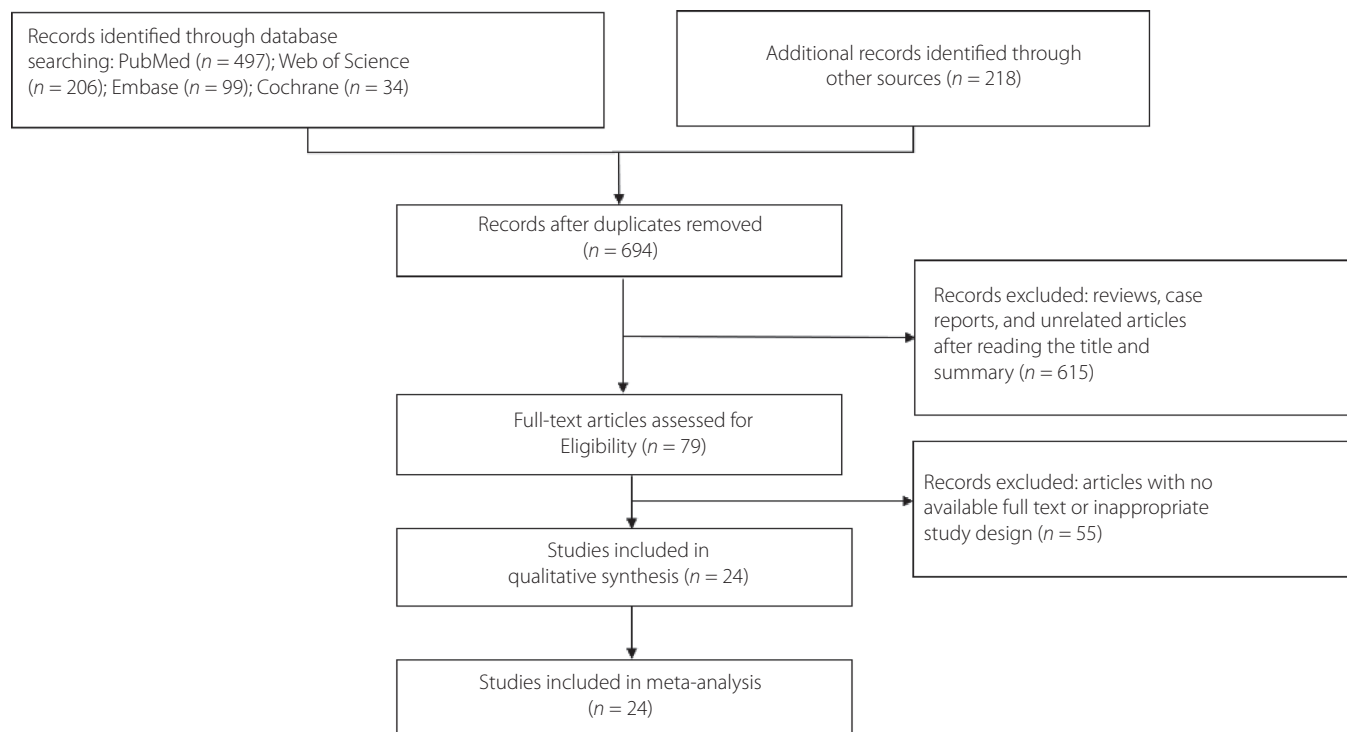
Figure 1 | Flow diagram showing the study selection process.

3. Polycystic kidney disease: 10 studies[1,9,13,14,17,18,20,23,26,27] were included, with 638 patients in the NODAT group and 1,824 patients in the non-NODAT group. After the heterogeneity test ($P = 0.17$, $I^2 = 30\%$), the fixed effects model was used, and the results showed that polycystic kidney disease was a risk factor for NODAT after kidney transplantation (OR 1.69, 95% CI 1.22–2.34, $P = 0.002$; Figure 4).

4. Family history of diabetes mellitus: 14 studies[1,3,9–13,15,17,22,23,25–27] were included, with 829 patients in the NODAT group and 3,113 patients in the non-NODAT group. According to the heterogeneity test ($P < 0.00001$, $I^2 = 83\%$) and the random-effect model, family history of diabetes was a risk factor for NODAT after kidney transplantation (OR 3.14, 95% CI 1.87–5.27, $P < 0.0001$; Figure 5).

Modifiable risk factors

1. BMI: 14 studies[1,6,9,11,13–18,21,25–27] were included, with 990 patients in the NODAT group and 2,466 patients in the non-NODAT group. After the heterogeneity test ($P = 0.0006$, $I^2 = 64\%$), the random effects model was used, and BMI was found to be a risk factor for NODAT after kidney transplantation (mean difference = 1.82, 95% CI 1.35–2.30, $P < 0.00001$; Figure 6).

2. Tacrolimus use: 12 studies[6,9–11,13,14,19,20,23,25,27,28] were included, with 1,011 patients in the NODAT group and

3,398 patients in the non-NODAT group. After the heterogeneity test ($P = 0.009$, $I^2 = 56\%$), the fixed effects model was used, and the results showed that tacrolimus use was a risk factor for NODAT after kidney transplantation (OR 1.20, 95% CI 1.02–1.41, $P = 0.03$; Figure 7).

3. Sirolimus use: five studies[10,11,14,19,28] were included, with 558 patients in the NODAT group and 1,814 patients in the non-NODAT group. After the heterogeneity test ($P < 0.00001$, $I^2 = 86\%$), the random effects model was used, and the results showed that sirolimus use was not a risk factor for NODAT after kidney transplantation (OR 2.21, 95% CI 0.96–5.09, $P = 0.06$; Figure 8).

4. Cyclosporin A use: seven studies[3,6,9,13,14,19,28] were included, with 659 patients in the NODAT group and 2,268 patients in the non-NODAT group. After the heterogeneity test ($P = 0.003$, $I^2 = 70\%$), the random effects model was used, and the results showed that cyclosporin A use was not a risk factor for NODAT after kidney transplantation (OR 0.91, 95% CI 0.63–1.31, $P = 0.61$; Figure 9).

5. Steroid use: eight studies[3,6,9,12–14,17,18] were included, with 630 patients in the NODAT group and 1,750 patients in the non-NODAT group. After the heterogeneity test ($P = 0.82$, $I^2 = 0\%$), the fixed effects model was used, and the results showed that steroid use was not a risk factor for NODAT after kidney transplantation (OR 1.42, 95% CI 0.97–2.08, $P = 0.07$; Figure 10).

Table 1 | Characteristics and Newcastle–Ottawa Scale quality score of included studies

Author	Year	Study type	NOS	Country	NODAT (*n*)	Sample (*n*)	Period	Risk factors
Choudhury *et al.*	2019	Case–control study	7	India	43	133	NA	Age, BMI
Jahromi *et al.*	2019	Case–control study	7	Kuwait	154	309	2015–2016	Sex, BMI, HCV, CMV, tacrolimus, cyclosporine A, hypertension, steroid
Lima *et al.*	2018	Case–control study	6	Brazil	80	258	2015.7–2015.12	Sex, CMV, hypertension
Xu *et al.*	2018	Case–control study	7	China	110	358	2010.1.1–2014.12.31	Polycystic kidney, HCV, CMV, tacrolimus, family history of diabetes mellitus, sex, BMI, age
Sinangil *et al.*	2017	Case–control study	6	Turkey	70	420	2005.2–2014.2	Sirolimus, HCV, HBV, tacrolimus, acute rejection, family history of diabetes mellitus, age, BMI, sex
Yang *et al.*	2017	Case–control study	8	China	71	365	2004.12–2014.12	Polycystic kidney, HBV, CMV, acute rejection, family history of diabetes mellitus, hypertension, age, BMI, sex, steroid
Yu *et al.*	2016	Case–control study	6	South Korea	85	418	2009.1–2012.4	Age, BMI, sex, polycystic kidney, tacrolimus, cyclosporine A, acute rejection, family history of diabetes mellitus, hypertension
Xie *et al.*	2016	Case–control study	7	China	37	397	2007.1–2010.5	Cyclosporine A, family history of diabetes mellitus, hypertension, sex, steroid
Dedinská *et al.*	2015	Case–control study	7	Slovak Republic	64	167	2003–2012	Polycystic kidney, HCV, CMV, family history of diabetes mellitus, hypertension, age, BMI, sex, steroid
Augusto *et al.*	2014	Case–control study	7	France	28	154	2005–2010	Polycystic kidney, polycystic kidney, tacrolimus, acute rejection, family history of diabetes mellitus, hypertension, age, BMI, sex, steroid
Buarque *et al.*	2014	Case–control study	7	Brazil	61	307	2006.1–2010.12	HCV, CMV, acute rejection, family history of diabetes mellitus, hypertension, sex
Cotovio *et al.*	2013	Case–control study	7	Portugal	47	94	2005–2009	Polycystic kidney, HCV, hypertension, age, BMI, sex, steroid
Chen *et al.*	2012	Case–control study	6	Spain	162	319	NA	Polycystic kidney, sirolimus, tacrolimus, cyclosporine A, acute rejection, age, BMI, sex, steroid
Kurzawski *et al.*	2012	Case–control study	7	Poland	67	235	2000–2009	HCV, HBV, CMV, acute rejection, age, BMI, sex
Prakash *et al.*	2012	Case–control study	6	India	13	68	1998.1–2012.4	Polycystic kidney, HCV, tacrolimus, family history of diabetes mellitus
Santos *et al.*	2012	Case–control study	6	Spain	37	303	NA	HCV, tacrolimus, acute rejection, family history of diabetes mellitus, age, BMI, sex
Yang *et al.*	2011	Case–control study	6	Spain	133	303	NA	HCV, tacrolimus, sirolimus, acute rejection, family history of diabetes mellitus, hypertension, age, sex
Razeghi *et al.*	2010	Case–control study	6	Iran	30	90	2003.6–2004.5	Polycystic kidney, family history of diabetes mellitus, hypertension, BMI
Ghisdal *et al.*	2009	Case–control study	7	France	118	1076	NA	Tacrolimus, sirolimus, cyclosporine A, acute rejection, sex
Laecke *et al.*	2009	Case–control study	6	Belgium	75	254	2002–2008	Tacrolimus, sirolimus, cyclosporine A, acute rejection, sex
Chakkera *et al.*	2009	Case–control study	6	America	22	91	2003–2006	HCV, family history of diabetes mellitus, age, BMI, sex
Hamer *et al.*	2007	Case–control study	8	England	28	429	1990–2004	Polycystic kidney, tacrolimus, acute rejection, age, sex
Andrade-Sierra *et al.*	2006	Case–control study	7	Mexico	53	522	1994.1–2002.12	HCV, acute rejection, family history of diabetes mellitus, age, sex, steroid
Numakura *et al.*	2005	Case–control study	6	Japan	10	70	1998.2–2004.3	CMV, acute rejection, age, sex

NA, not available; NODAT, new-onset diabetes mellitus after transplantation; NOS, Newcastle–Ottawa Scale.

Table 2 | Summary of meta-analysis results of non-modifiable factors for new-onset diabetes mellitus after renal transplantation

Factors	No. study	Sample (n)	Heterogeneity test		Effects model	OR/MD (95% CI)	P-value
			P-value	I² (%)			
Age	17	4,635	<0.00001	78	Random effects model	6.05 (4.33–7.78)	<0.00001
Sex	21	6,849	0.42	3	Fixed effects model	1.00 (0.88–1.13)	0.97
Polycystic kidney disease	10	2,462	0.17	30	Fixed effects model	1.69 (1.22–2.34)	0.002
Family history of diabetes mellitus	14	3,942	<0.00001	83	Random effects model	3.14 (1.87–5.27)	<0.0001

CI, confidence interval; MD, mean difference; NODAT, new-onset diabetes mellitus after transplantation; OR, odds ratio.

Table 3 | Summary of meta-analysis results of modifiable factors for new-onset diabetes mellitus after renal transplantation

Factors	No. study	Sample (n)	Heterogeneity test		Effects model	OR/MD (95% CI)	P-value
			P-value	I² (%)			
BMI	14	3,456	0.0006	64	Random effects model	1.82 (1.35, 2.30)	<0.00001
Tacrolimus use	12	4,409	0.009	56	Fixed effects model	1.2 (1.02, 1.41)	0.03
Sirolimus use	5	2,372	<0.00001	86	Random effects model	2.21 (0.96, 5.09)	0.06
Cyclosporin A use	7	2,927	0.003	70	Random effects model	0.91 (0.63, 1.31)	0.61
Steroid use	8	2,380	0.82	0	Fixed effects model	1.42 (0.97, 2.08)	0.07
Acute rejection	13	4,921	0.05	42	Fixed effects model	1.97 (1.61, 2.41)	<0.00001
HBV	3	1,020	0.05	67	Random effects model	3.53 (1.12, 11.13)	0.03
HCV	12	3,177	0.4	5	Fixed effects model	1.51 (1.01, 2.24)	0.04
CMV	8	2,069	0.21	27	Fixed effects model	1.11 (0.81, 1.53)	0.51
Hypertension	11	2,841	0.4	4	Fixed effects model	1.48 (1.19, 1.85)	0.0004

CI, confidence interval; MD, mean difference; NODAT, new-onset diabetes mellitus after transplantation; OR, odds ratio.

Figure 2 | Forest plots (random effects model) of meta-analysis on the association between age and the risk of new-onset diabetes mellitus after renal transplantation.

Figure 3 | Forest plots (fixed effects model) of meta-analysis on the association between sex and the risk of new-onset diabetes mellitus after renal transplantation.

Figure 4 | Forest plots (fixed effects model) of meta-analysis on the association between polycystic kidney disease and the risk of new-onset diabetes mellitus after renal transplantation.

6. Acute rejection: 13 studies[1,9–14,19–22,24,25] were included, with 923 patients in the NODAT group and 3,998 patients in the non-NODAT group. After the heterogeneity test ($P = 0.05$, $I^2 = 42\%$), the fixed effects model was used, and the results showed that acute rejection was a risk factor for NODAT after kidney transplantation [OR 1.97, 95% CI 1.61–2.41, $P < 0.00001$; Figure 11].

7. Hepatitis B virus (HBV) infection: three studies were included[1,11,21], with 208 patients in the NODAT group and 812 patients in the non-NODAT group. After the

Figure 5 | Forest plots (random effects model) of meta-analysis on the association between family history of diabetes and the risk of new-onset diabetes mellitus after renal transplantation.

heterogeneity test ($P = 0.05$, $I^2 = 67\%$), the random effects model was used, and the results showed that HBV infection was a risk factor for NODAT after kidney transplantation (OR 3.53, 95% CI 1.12–11.13, $P = 0.03$; Figure 12).

8. HCV infection: 12 studies[6,10–12,15,17,18,21–23,25,27] were included, with 831 patients in the NODAT group and 2,346 patients in the non-NODAT group. After the heterogeneity test ($P = 0.40$, $I^2 = 5\%$), the fixed effects model was used, and the results showed that HCV infection was a risk factor for NODAT after kidney transplantation (OR 1.51, 95% CI 1.01–2.24, $P = 0.04$; Figure 13).

9. CMV infection: eight studies[1,2,6,17,21,22,24,27] were included, with 617 patients in the NODAT group and 1,452 patients in the non-NODAT group. After the heterogeneity test ($P = 0.21$, $I^2 = 27\%$), the fixed effects model was used, and the results showed that CMV infection was not a risk factor for NODAT after kidney transplantation (OR 1.11, 95% CI 0.81–1.53, $P = 0.51$; Figure 14).

10. Hypertension: 11 studies[1–3,6,9,10,13,17,18,22,26] were included, with 805 patients in the NODAT group and 2,036 patients in the non-NODAT group. After the heterogeneity test ($P = 0.40$, $I^2 = 4\%$), the fixed effects model was used, and the results showed that hypertension was a risk factor for NODAT after kidney transplantation (OR 1.48, 95% CI 1.19–1.85, $P = 0.0004$; Figure 15).

Results of publication bias assessment

Two funnel plots were drawn based on age and HCV infection. The scatter plots were roughly symmetrical, suggesting a low likelihood of publication bias (Figures 16,17).

DISCUSSION

The occurrence and development of NODAT after renal transplantation are affected by many factors, including non-modifiable and modifiable factors. The non-modifiable factors include age, family history of diabetes, polycystic kidney disease, race and gene polymorphism[5,9,11], whereas the modifiable factors include BMI, acute rejection, immunosuppressant use, HBV infection, HCV infection, CMV infection, hypertension and dipeptidyl peptidase-4 inhibitor use[1,6,8,10,11]. In the present study, age, sex, family history of diabetes, hypertension, polycystic kidney disease, BMI, acute rejection, tacrolimus use, sirolimus use, cyclosporin A use, steroid use, HBV infection, HCV infection, CMV infection were included in the meta-analysis.

A number of studies have shown that age can affect the occurrence of NODAT[13–15]. The present study also found that age is a risk factor for the occurrence of NODAT after kidney transplantation, which might be related to the progressive decline of islet β-cell function with increasing age.

Family history of diabetes mellitus is an important risk factor for NODAT in transplant recipients[23,26]. It has been reported that the risk of NODAT in patients with a family history of type 2 diabetes is 6.4–8.6-fold higher than that in patients without a family history of type 2 diabetes[1,17]. The present study suggests that a family history of diabetes can increase the risk of NODAT in renal transplant recipients by up to 3.14-fold.

Whether polycystic kidney disease is a risk factor for NODAT after kidney transplantation remains controversial. Prakash et al.[23] and other researchers reported that polycystic kidney disease is a risk factor for NODAT after kidney transplantation, whereas Cotovio et al.[18] and other groups found that polycystic kidney disease is not a risk factor for NODAT
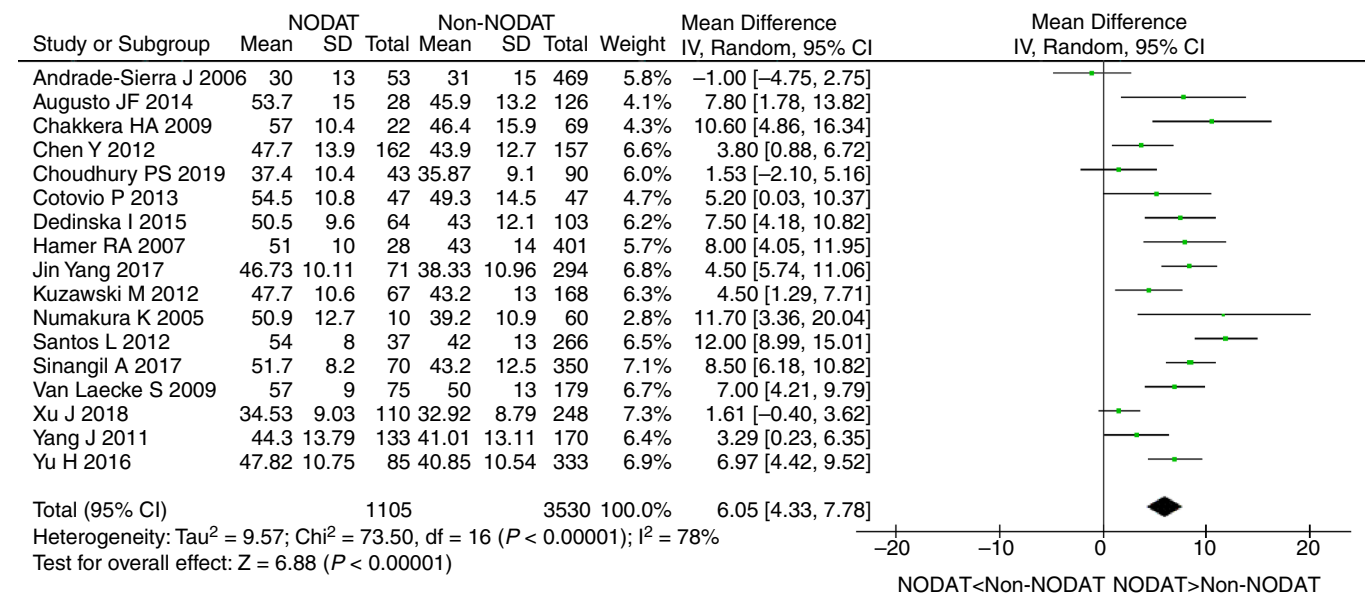
Figure 6 | Forest plots (random effects model) of meta-analysis on the association between BMI and the risk of new-onset diabetes mellitus after renal transplantation.
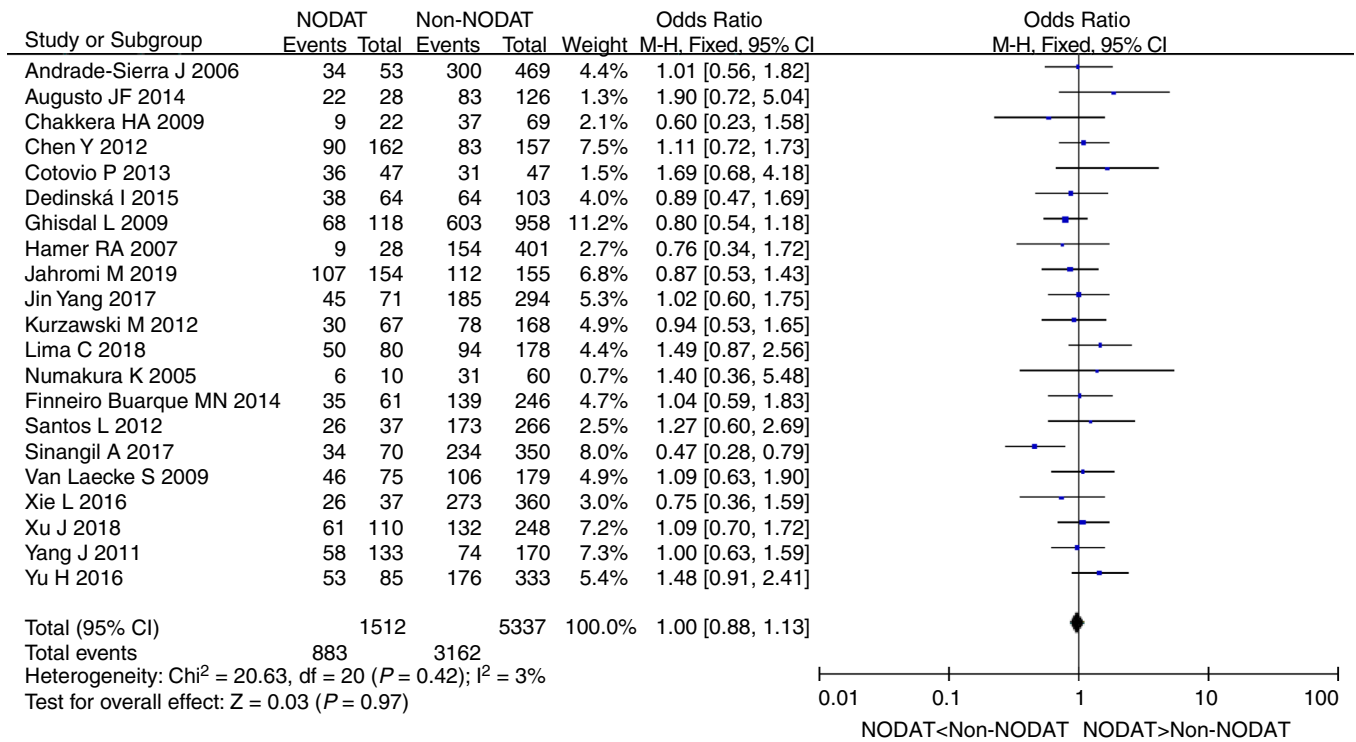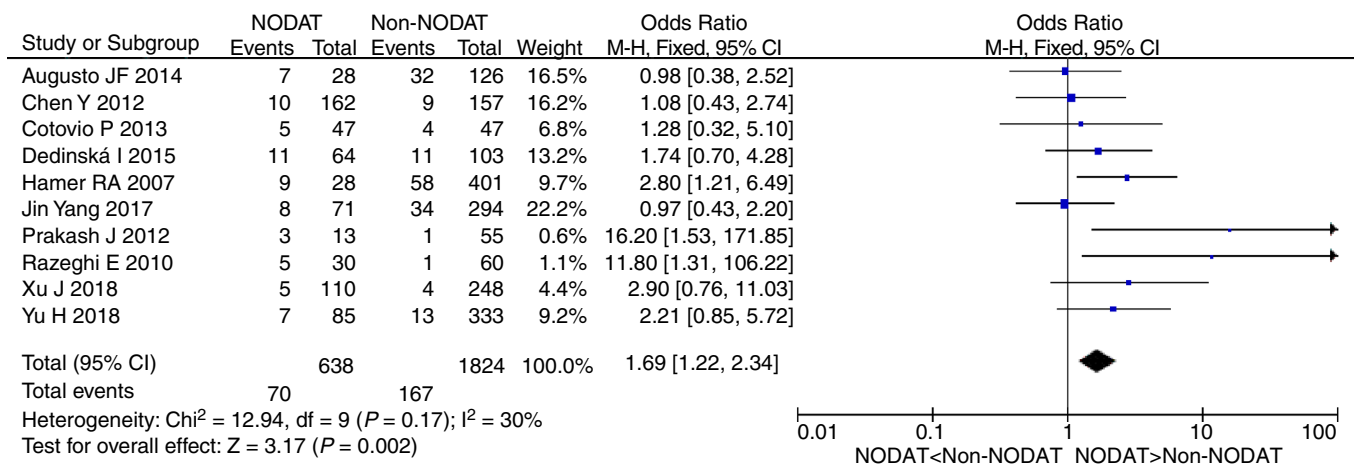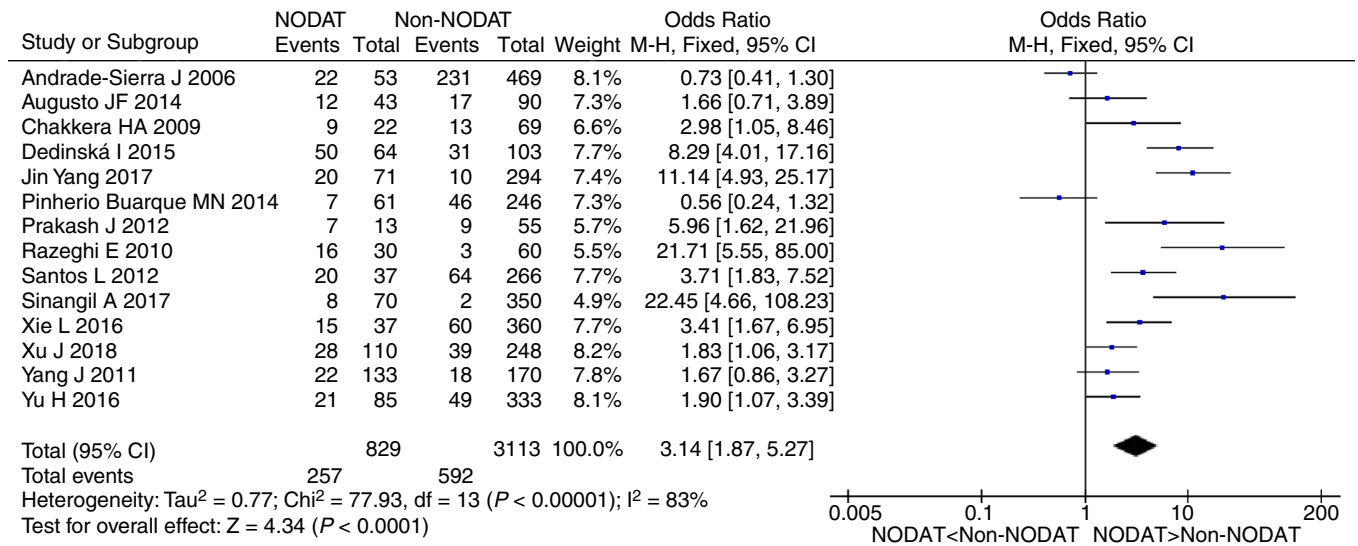

Figure 7 | Forest plots (fixed effects model) of meta-analysis on the association between tacrolimus use and the risk of new-onset diabetes mellitus after renal transplantation.

after kidney transplantation. Through the analysis of ten case–control studies, the present study found that preoperative polycystic kidney disease increases the risk of NODAT after kidney transplantation by 1.69-fold, which might be related to insulin resistance and hyperinsulinemia in some polycystic kidney disease patients[20,26,29].

A number of studies have shown that BMI is a risk factor for NODAT after kidney transplantation[6,25,30]. The mechanism of NODAT is related to the fact that obesity stimulates β-cells

of islets of Langerhans to induce insulin resistance, thereby weakening the ability of blood glucose clearance[3,11,22,31]. In the present study, the analysis of 14 case–control studies showed that BMI is a risk factor for NODAT after kidney transplantation, which is consistent with previous studies.

Acute rejection is a type of stress reaction that has been recognized as a risk factor for NODAT in kidney transplant recipients[1,10,19]. The mechanism of NODAT after kidney transplantation might be related to glucocorticoid shock therapy

Study or Subgroup	NODAT Events	Total	Non-NODAT Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Chen Y 2012	59	162	21	157	21.2%	3.71 [2.12, 6.49]
Ghisdal L 2009	8	118	29	958	19.2%	2.33 [1.04, 5.22]
Sinangil A 2017	9	70	32	350	19.3%	1.47 [0.67, 3.23]
Van Laecke S 2009	9	75	36	179	19.4%	0.54 [0.25, 1.19]
Yang J 2011	61	133	19	170	21.0%	6.73 [3.75, 12.10]
Total (95% CI)		558		1814	100.0%	2.21 [0.96, 5.09]
Total events	146		137			

Heterogeneity: Tau2 = 0.77; Chi^2 = 29.02, df = 4 (P < 0.00001); I^2 = 86%
Test for overall effect: Z = 1.87 (P = 0.06)

Figure 8 | Forest plots (random effects model) of meta-analysis on the association between sirolimus use and the risk of new-onset diabetes mellitus after renal transplantation.

Study or Subgroup	NODAT Events	Total	Non-NODAT Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Augusto JF 2014	6	28	30	126	8.3%	0.87 [0.32, 2.35]
Chen Y 2012	83	162	87	157	16.4%	0.85 [0.54, 1.31]
Ghisdal L 2009	48	118	556	958	17.3%	0.50 [0.34, 0.73]
Jahromi M 2019	82	154	63	155	16.2%	1.66 [1.06, 2.61]
Van Lacke S 2009	38	75	77	179	14.6%	1.36 [0.79, 2.34]
Xie L 2016	13	37	169	360	11.9%	0.61 [0.30, 1.24]
Yu H 2016	26	85	104	333	15.1%	0.97 [0.58, 1.63]
Total (95% CI)		659		2268	100.0%	0.91 [0.63, 1.31]
Total events	296		1086			

Heterogeneity: Tau2 = 0.16; Chi2 = 19.69, df = 6 (P = 0.003); I2 = 70%
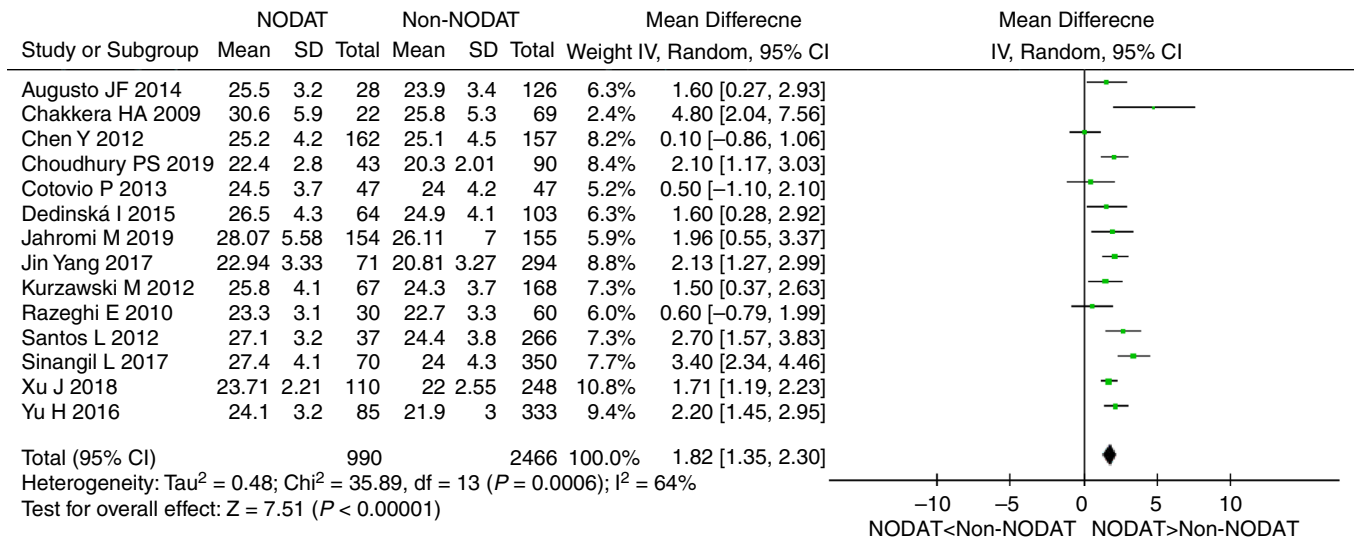Test for overall effect: Z = 0.52 (P = 0.61)

Figure 9 | Forest plots (random effects model) of meta-analysis on the association between cyclosporin A use and the risk of new-onset diabetes mellitus after renal transplantation.

Study or Subgroup	NODAT Events	Total	Non-NODAT Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Andrade-Sierra J 2006	52	53	461	469	3.9%	0.90 [0.11, 7.36]
Augusto JF 2014	28	28	118	126	1.7%	4.09 [0.23, 72.93]
Chen Y 2012	161	162	155	157	2.1%	2.08 [0.19, 23.14]
Cotovio P 2013	9	47	8	47	14.3%	1.15 [0.40, 3.31]
Dedinská I 2015	22	64	37	103	41.1%	0.93 [0.49, 1.80]
Jahromi M 2019	152	154	151	155	4.3%	2.01 [0.36, 11.16]
Xie L 2016	24	37	180	360	26.0%	1.85 [0.91, 3.74]
Yu H 2016	83	85	315	333	6.6%	2.37 [0.54, 10.43]
Total (95% CI)		630		1750	100.0%	1.42 [0.97, 2.08]
Total events	531		1425			

Heterogeneity: Chi^2 = 3.67, df = 7 (P = 0.82); I^2 = 0%
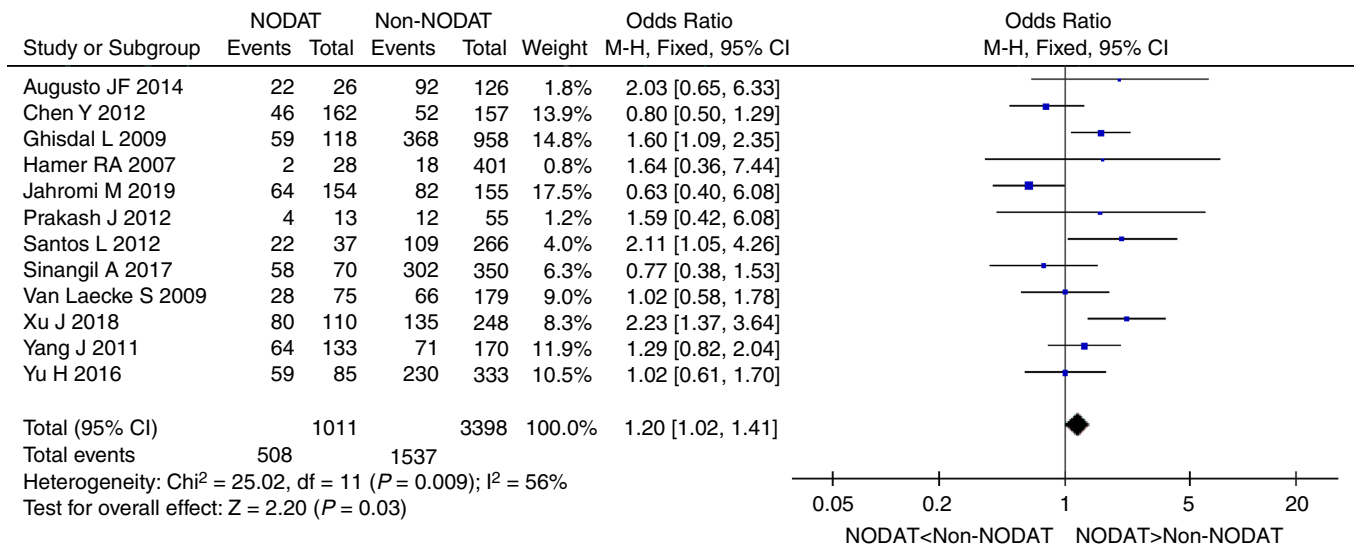Test for overall effect: Z = 1.80 (P = 0.07)

Figure 10 | Forest plots (fixed effects model) of meta-analysis on the association between steroid use and the risk of new-onset diabetes mellitus after renal transplantation.

after acute rejection, because high-dose glucocorticoid shock therapy could reduce the renal function of transplantation, and reduce the ability to clear insulin, which could lead to peripheral insulin resistance, and produce abnormal glucose metabolism[1,32,33]. In addition, acute rejection can increase the level of insulin antagonists, such as growth hormone,

Study or Subgroup	NODAT Events	Total	Non-NODAT Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Andrade-Sierra J 2006	27	53	124	469	10.1%	2.89 [1.62, 5.14]
Augusto JF 2014	4	28	17	126	4.3%	1.07 [0.33, 3.46]
Chen Y 2012	16	162	6	157	4.5%	2.76 [1.05, 7.24]
Ghisdal L 2009	37	118	172	958	21.2%	2.09 [1.37, 3.18]
Hamer RA 2007	12	28	186	401	11.4%	0.87 [0.40, 1.88]
Jin Yang 2017	18	71	29	294	6.9%	3.10 [1.61, 5.99]
Kurzawski M 2012	9	67	10	168	4.0%	2.45 [0.95, 6.34]
Namakura K 2005	3	10	20	60	3.3%	0.86 [0.20, 3.67]
Pinheiro Buarque MN 2014	11	61	16	246	4.3%	3.16 [1.38, 7.23]
Santos L 2012	9	37	64	266	9.7%	1.01 [0.45, 2.26]
Sinangil A 2017	2	70	20	350	5.3%	0.49 [0.11, 2.13]
Yang J 2011	30	133	14	170	7.8%	3.25 [1.64, 6.42]
Yu H 2016	9	85	24	333	7.2%	1.52 [0.68, 3.41]
Total (95% CI)		923		3998	100.0%	1.97 [1.61, 2.41]
Total events	187		702			

Heterogeneity: Chi² = 20.70, df = 12 (*P* = 0.05); I² = 42%
Test for overall effect: Z = 6.53 (*P* < 0.00001)

Figure 11 | Forest plots (fixed effects model) of meta-analysis on the association between acute rejection and the risk of new-onset diabetes mellitus after renal transplantation.

Study or Subgroup	NODAT Events	Total	Non-NODAT Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Jin Yang 2017	19	71	12	294	41.7%	8.59 [3.93, 18.75]
Kurzawski M 2012	2	67	3	168	22.6%	1.69 [0.28, 10.36]
Sinangil A 2017	5	70	13	350	35.7%	1.99 [0.69, 5.78]
Total (95% CI)		208		812	100.0%	3.53 [1.12, 11.13]
Total events	26		28			

Heterogeneity: Tau² = 0.67; Chi² = 6.00, df = 2 (*P* = 0.05); I² = 67%
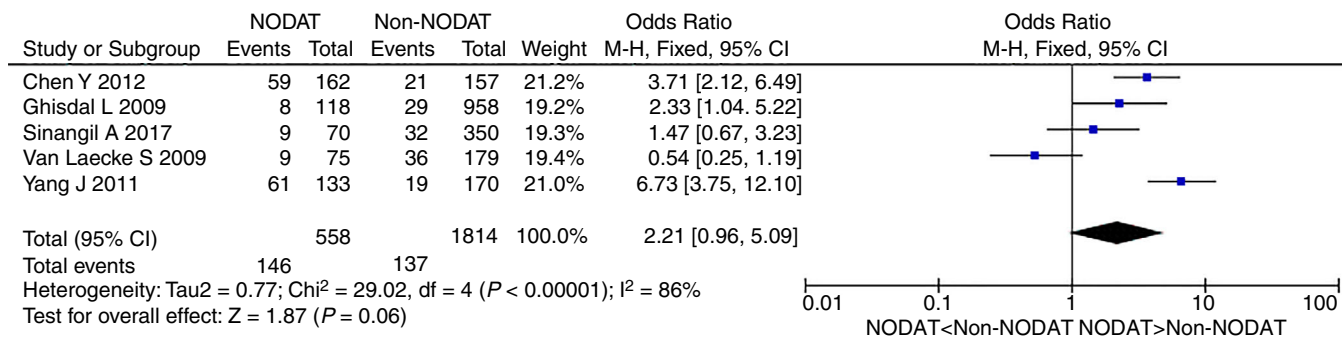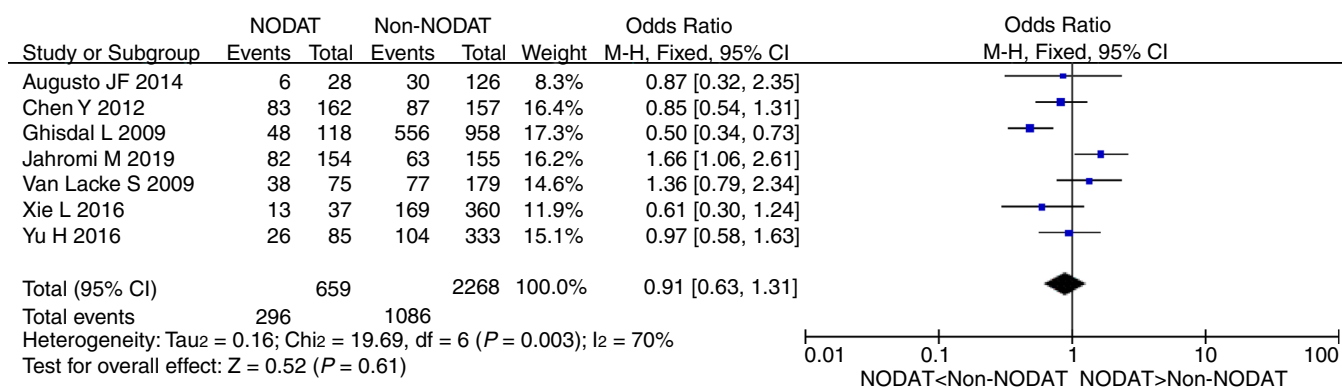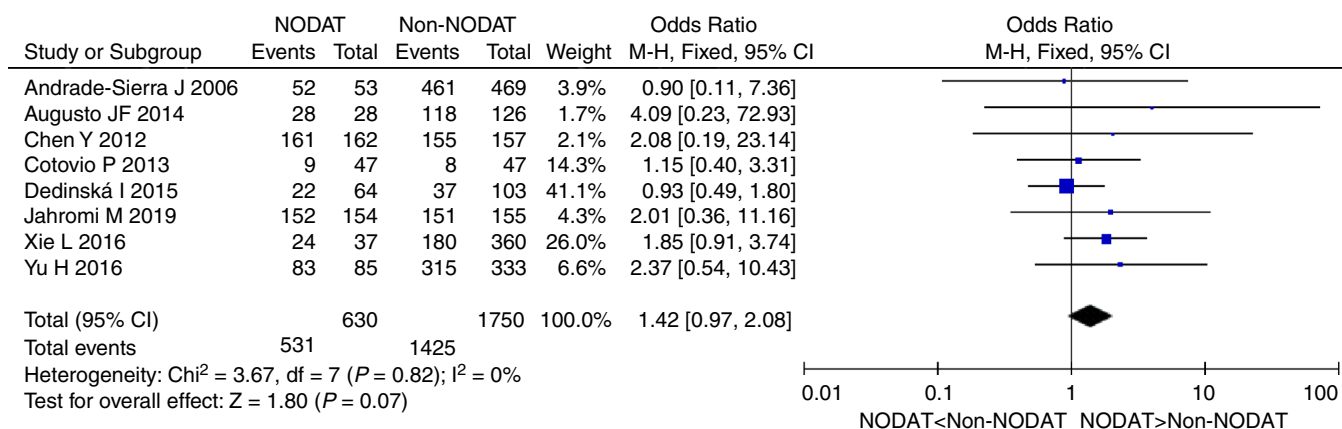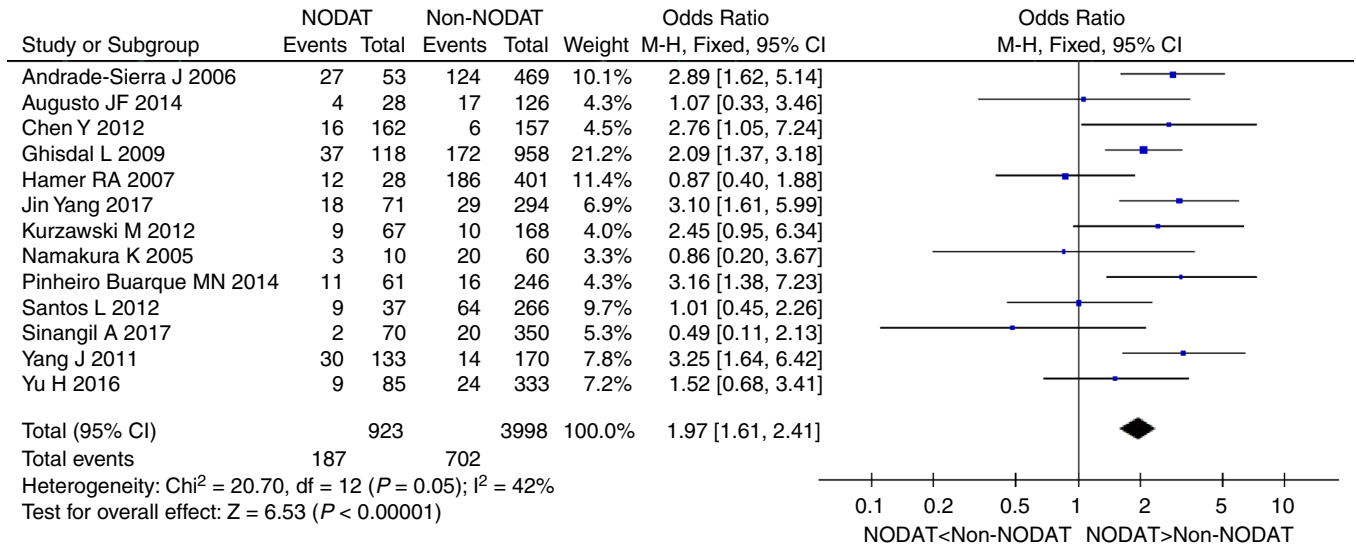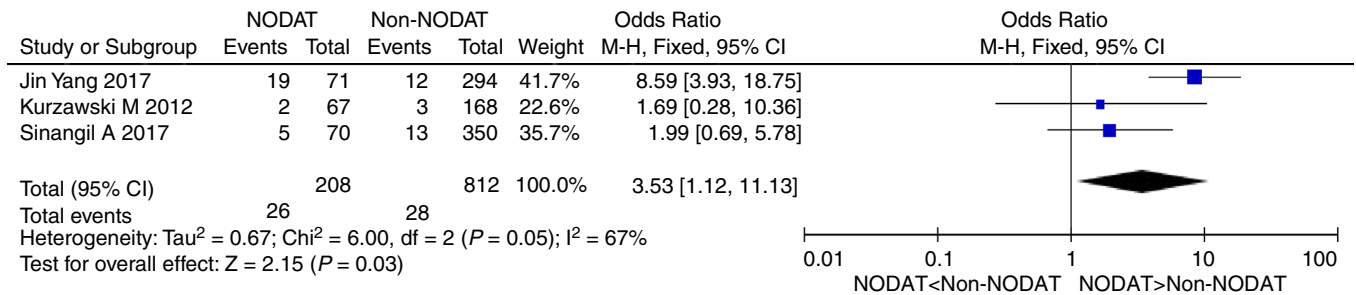Test for overall effect: Z = 2.15 (*P* = 0.03)

Figure 12 | Forest plots (random effect model) of meta-analysis on the association between hepatitis B virus and the risk of new-onset diabetes mellitus after renal transplantation.

catecholamine, glucagon and glucocorticoid, and then increase the level of blood glucose[34,35]. The combined analysis of 12 case–control studies in the present study showed that acute rejection increases the risk of NODAT after renal transplantation by 1.95-fold.

Immunosuppressants are one of the risk factors for NODAT. The previously reported immunosuppressants that can cause NODAT include corticosteroids, calcineurin inhibitors and rapamycin target protein inhibitors[6,10,27]. In the present study, the combined results showed that tacrolimus use is a risk factor for NODAT after renal transplantation. The possible mechanism of NODAT caused by tacrolimus is as follows: (i) tacrolimus has a direct damage effect on β-cells of islets, which are morphologically manifested as the expansion, vacuolation and reduction of dense-core secretory granules of β-cells of islets; and (ii) the synthesis of insulin is inhibited. Tacrolimus is an inhibitor of neurocalcin, which can not only inhibit calcineurin to exert its

immunosuppressive effect, but also specifically and reversibly inhibit the transcription of the insulin gene, so as to reduce insulin synthesis[35,36]. However, the use of sirolimus or cyclosporin A is not a risk factor for NODAT after renal transplantation in the present study, which might be related to the short observation time of NODAT and the low dose of cyclosporine A in some studies[12,13]. In addition, our combined results showed that steroid use is not a risk factor for NODAT after renal transplantation, which might be related to the short use time or low dose of steroids in some studies[3,12,17].

The infectious factors that affect NODAT include HBV, HCV and CMV infection. Its pathogenesis might be related to the direct damage to islet β-cells caused by infection, the increase of insulin resistance caused by insulin receptor deficiency, and the decrease of liver glucose uptake and glycogen production[31]. The present study showed that HBV and HCV infections are risk factors for NODAT after renal transplantation, but CMV infection is not.

Study or Subgroup	NODAT Events	Total	Non-NODAT Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Andrade-Sierra J 2006	3	53	18	469	9.2%	1.50 [0.43, 5.28]
Chakkera HA 2009	3	22	3	69	3.3%	3.47 [0.65, 18.63]
Cotovio P 2013	2	47	5	47	12.8%	0.37 [0.07, 2.03]
Dedinská I 2015	3	64	1	103	1.9%	5.02 [0.51, 49.30]
Jahromi M 2019	12	154	1	155	2.4%	13.01 [1.67, 101.37]
Kurzawski M 2012	2	67	4	168	5.9%	1.26 [0.23, 7.06]
Pinheiro Buarque MN 2014	4	61	13	246	12.9%	1.26 [0.40, 4.00]
Prakash J 2012	1	13	3	55	2.8%	1.44 [0.14, 15.12]
Santos L 2012	3	37	13	266	7.8%	1.72 [0.47, 6.34]
Sinangil A 2017	0	70	13	350	12.0%	0.18 [0.01, 3.02]
Xu J 2018	6	110	10	248	15.5%	1.37 [0.49, 3.88]
Yang J 2011	5	133	6	170	13.5%	1.07 [0.32, 3.58]
Total (95% CI)		831		2346	100.0%	1.51 [1.01, 2.24]
Total events	44		90			

Heterogeneity: Chi^2 = 11.57, df = 11 (P = 0.40); I^2 = 5%
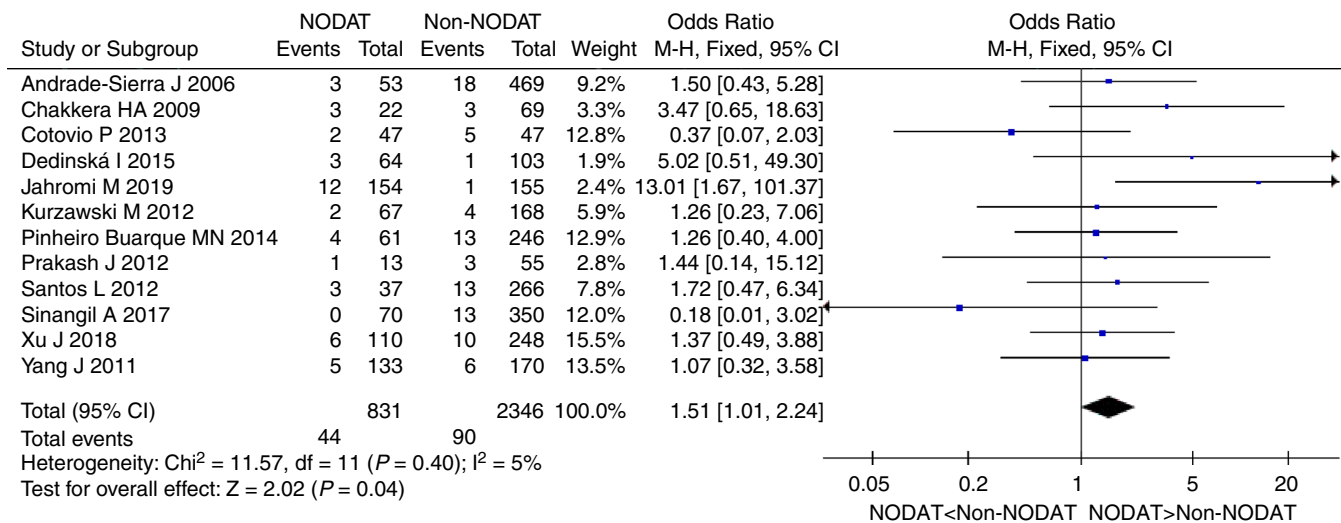Test for overall effect: Z = 2.02 (P = 0.04)

Figure 13 | Forest plots (fixed effects model) of meta-analysis on the association between hepatitis C virus and the risk of new-onset diabetes mellitus after renal transplantation.
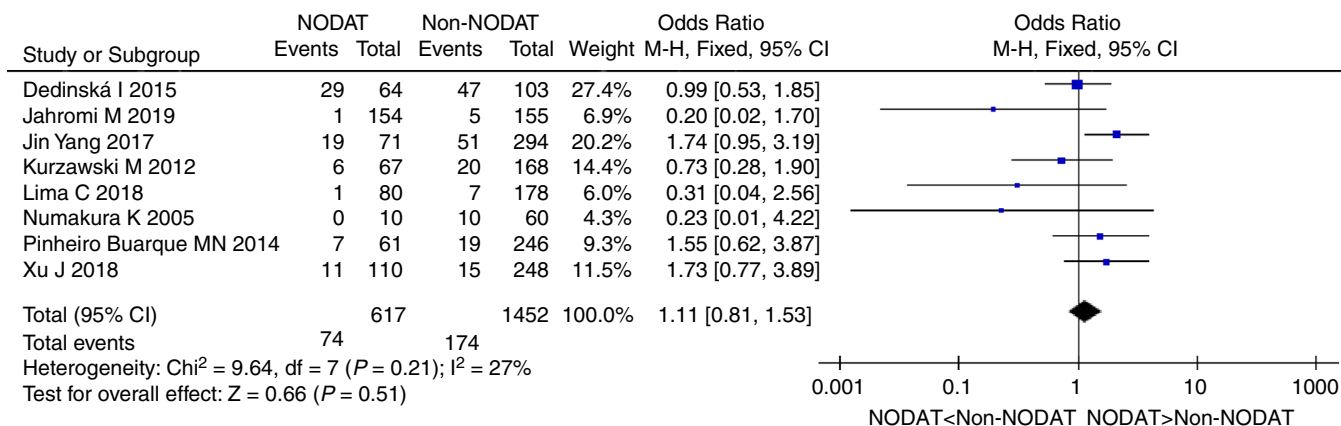

Study or Subgroup	NODAT Events	Total	Non-NODAT Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Dedinská I 2015	29	64	47	103	27.4%	0.99 [0.53, 1.85]
Jahromi M 2019	1	154	5	155	6.9%	0.20 [0.02, 1.70]
Jin Yang 2017	19	71	51	294	20.2%	1.74 [0.95, 3.19]
Kurzawski M 2012	6	67	20	168	14.4%	0.73 [0.28, 1.90]
Lima C 2018	1	80	7	178	6.0%	0.31 [0.04, 2.56]
Numakura K 2005	0	10	10	60	4.3%	0.23 [0.01, 4.22]
Pinheiro Buarque MN 2014	7	61	19	246	9.3%	1.55 [0.62, 3.87]
Xu J 2018	11	110	15	248	11.5%	1.73 [0.77, 3.89]
Total (95% CI)		617		1452	100.0%	1.11 [0.81, 1.53]
Total events	74		174			

Heterogeneity: Chi^2 = 9.64, df = 7 (P = 0.21); I^2 = 27%
Test for overall effect: Z = 0.66 (P = 0.51)

Figure 14 | Forest plots (fixed effects model) of meta-analysis on the association between cytomegalovirus and the risk of new-onset diabetes mellitus after renal transplantation.

At present, there is no single study showing that hypertension is a risk factor for NODAT after renal transplantation. We have included eleven articles and found that hypertension is also a risk factor for NODAT after renal transplantation. This might be related to the increased secretion of inflammatory factors caused by the increase of homocysteine in patients with hypertension, which could lead to the abnormal function of adipose tissue, and increased production and secretion of resistin, leading to the occurrence of inflammatory reaction and insulin resistance[37–39].

The present study had some limitations. The research quality of the included studies was roughly the same. Only Chinese and English studies were included. As one of the 24 included articles was written in Chinese and 23 of them were written in English, they could not fully reflect the differences in ethnicity,

regions and other influencing factors. In the present study, the number of articles on some influencing factors was small. Therefore, it was difficult to determine the relationship between those factors and the occurrence of NODAT after kidney transplantation. Furthermore, the sample size of some of the included studies was small. Therefore, multicenter and large-sample epidemiological studies are required to further clarify the risk factors for NODAT after kidney transplantation.

To summarize, age, BMI, family history of diabetes, history of hypertension, polycystic kidney disease, acute rejection, HBV infection, HCV infection and tacrolimus use are risk factors for NODAT in kidney transplant recipients. Therefore, the clinical implications of these factors warrant attention. More studies with high demonstration intensity are required in the future.
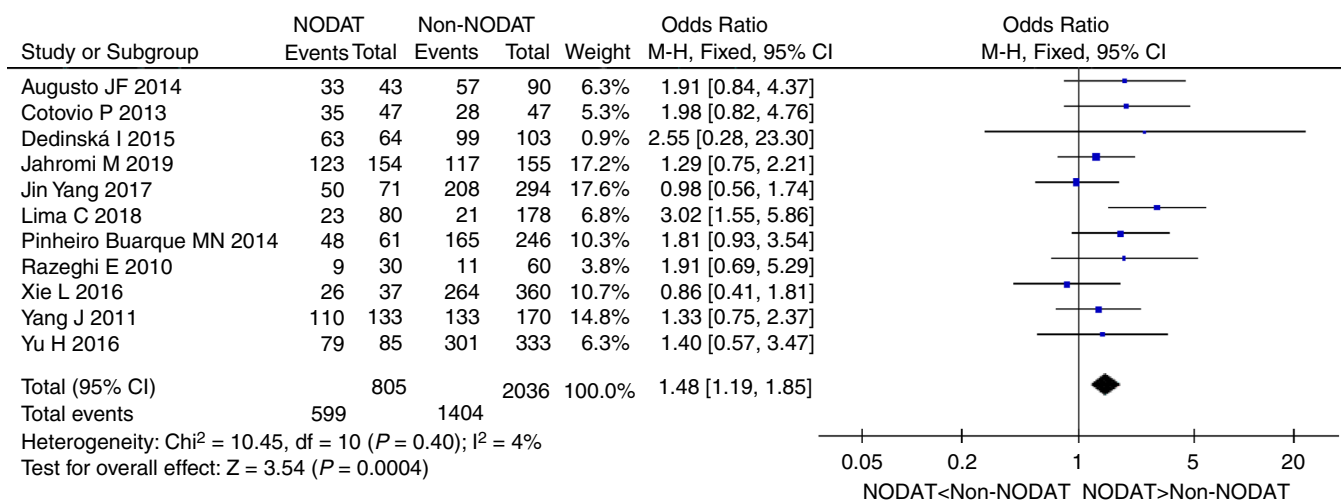
Study or Subgroup	NODAT Events	Total	Non-NODAT Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Augusto JF 2014	33	43	57	90	6.3%	1.91 [0.84, 4.37]
Cotovio P 2013	35	47	28	47	5.3%	1.98 [0.82, 4.76]
Dedinská I 2015	63	64	99	103	0.9%	2.55 [0.28, 23.30]
Jahromi M 2019	123	154	117	155	17.2%	1.29 [0.75, 2.21]
Jin Yang 2017	50	71	208	294	17.6%	0.98 [0.56, 1.74]
Lima C 2018	23	80	21	178	6.8%	3.02 [1.55, 5.86]
Pinheiro Buarque MN 2014	48	61	165	246	10.3%	1.81 [0.93, 3.54]
Razeghi E 2010	9	30	11	60	3.8%	1.91 [0.69, 5.29]
Xie L 2016	26	37	264	360	10.7%	0.86 [0.41, 1.81]
Yang J 2011	110	133	133	170	14.8%	1.33 [0.75, 2.37]
Yu H 2016	79	85	301	333	6.3%	1.40 [0.57, 3.47]
Total (95% CI)		805		2036	100.0%	1.48 [1.19, 1.85]
Total events	599		1404			

Heterogeneity: Chi^2 = 10.45, df = 10 (*P* = 0.40); I^2 = 4%
Test for overall effect: Z = 3.54 (*P* = 0.0004)

Figure 15 | Forest plots (fixed effects model) of meta-analysis on the association between hypertension and the risk of new-onset diabetes mellitus after renal transplantation.
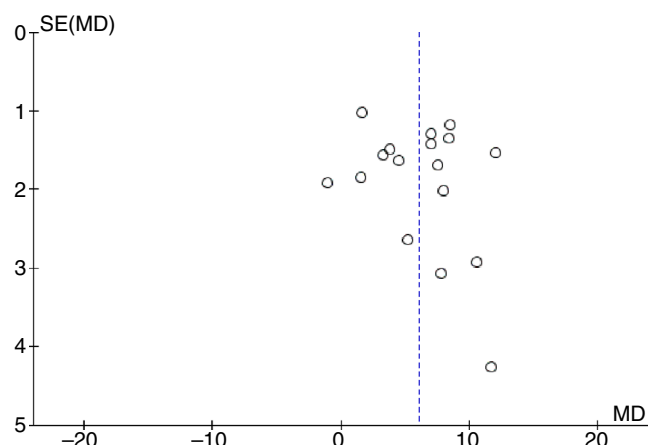
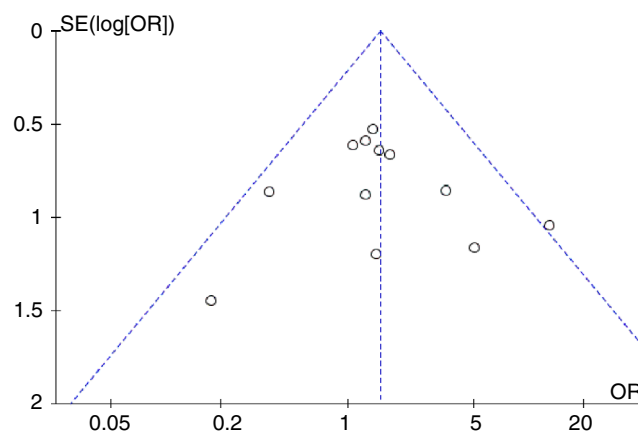**Figure 16** | Funnel chart results of age as a risk factor. MD, mean difference; SD, standard deviation.

Figure 17 | Funnel chart results of HCV infection as a risk factor. OR, odds ratio; SE, standard error.

DISCLOSURE

The authors declare no conflict of interest.

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