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Author Contributions

AS, BL and BK were contributors in the design, analysis and writing of this study. CF, AI, PJ, WO, WG, MN, EVL and SA contributed to data collection and literature review. AS, BL, BK, KO, GT, GK, SA, AI, PJ, WO, JT and MN and EVL contributed samples and phenotypes. AS, BL, BK, MN and EVL contributed to, advised on and supervised statistical analysis. AS, BL, KO, SA and BK composed and revised the manuscript drafts. All coauthors read and approved the final manuscript for submission.

Competing Interests statement

All coauthors declare no competing financial interests.

ABSTRACT

Post-transplant diabetes mellitus (PTDM) is a complication which reduces allograft and recipient life-span. Polygenic risk scores (PRS) robustly show association with greater type 2 diabetes (T2D) development risk. We examined T2D-PRS in transplant recipients and donors using genome-wide genotyping in 1581 liver recipients, and 1555 donors and 2062 kidney recipients and 533 donors from four centers. Liver and kidney recipient T2D-PRS was associated with pre-transplant T2D and PTDM development. Liver donor, but not kidney donor, T2D-PRS was an independent risk factor for PTDM development. Inclusion of a combined liver recipient and donor T2D-PRS significantly improved PTDM prediction vs clinical characteristics-only models: AUC (95%CI): 67.6% (64.1% - 71.1%) vs. 62.3% (58.8% - 65.8%), $p=0.0001$. Liver recipients in the highest quintile of recipient-donor combined T2D-PRS had the greatest PTDM risk: OR (95%CI) = 3.22 (2.07 - 5.00), $p=1.92E-07$, compared to the lowest quintile. T2D-PRS allows identification of transplant candidates with high PTDM risk, for whom early preemptive diabetes management is warranted. Pre-transplant knowledge of donor T2D-PRS in the setting of living liver donation should optimized selection of donors to reduce PTDM.

MAIN

Post-transplantation diabetes mellitus (PTDM), previously referred to as New Onset of Diabetes after transplant (NODAT), is a common complication following solid organ transplantation, occurring in approximately 16-44% of kidney and liver transplant recipients^{1,2}. The diagnosis is established by either hemoglobin A1C (A1c) and/or fasting glucose levels, starting 45 days post-transplantation, and is observed within the first 6 months after transplantation^{3,4}. PTDM shares many metabolic syndrome characteristics with T2D, including insulin resistance and decompensated insulin release, hypertriglyceridemia, obesity, hypertension, and low-grade inflammation^{5,6}. The development of PTDM, and the related metabolic syndrome phenotype(s), are associated with an increase in cardiovascular disease complications, which is now one of the leading causes of recipient death after transplantation^{7,8}. The modifiers causing rapid onset of PTDM include the acute exposure to diabetogenic immunosuppression therapy (IST), specifically, the exposure to high doses of steroids, maintenance calcineurin (CNI) and/or mTOR inhibitors, leading to either early transient non-symptomatic or the persistent manifestation of PTDM⁹⁻¹². Considering the well-established role of individuals' genetic background in the development of T2D in general populations^{13,14}, we questioned whether the stress introduced by the acute exposure to diabetogenic IST post-transplant may lead to the early induction and persistent of PTDM in subsets of transplant recipients with high T2D genetic risk exposure. Another fundamental question is whether the risk of PTDM is impacted by the transfer of the organ donor T2D genetic risk, and whether this is specific to the type of solid organ transplant. In the setting of liver transplantation this hypothesis is very relevant, as this organ plays a central role in metabolic homeostasis and is a major site for synthesis, metabolism, storage and redistribution of carbohydrate and lipids^{15,16}.

Genome-wide association studies (GWAS) have uncovered contributions of inherited variants across a spectrum of common complex disease and phenotypes¹⁷⁻¹⁹. Polygenic risk scores (PRS) aggregate and weight the effects of many genetic variants across the human genome into a single score and have been shown to have predictive value for multiple common diseases²⁰. Recent aggregated genotyping data from T2D GWAS including 74,124 T2D cases, and 824,006 controls in European-descent cohorts revealed a combined set of 403 common and rare independent T2D-risk genetic signals, with the derived T2D polygenic risk scores (T2D-PRS) having robust association with the development of T2D in the general population²¹. The generation of T2D-PRS that capture aspects of the etiological and clinical heterogeneity that contributes to variable clinical outcomes, provides a potential mechanism for identifying transplant candidates who are at risk of developing PTDM.

We applied this T2D-PRS in the setting of liver and kidney transplantation, with the aim of determining the association of recipient and/or donor genetics, both independently and in concert, with the

development of PTDM. Quantifying T2D-PRS in transplant candidates may be used to personalize immunosuppression, such as steroid avoidance protocols, and to risk-stratify those who may benefit from aggressive treatment such as dieting, glucose monitoring, and insulin therapy^{22,23}. In the liver transplant setting it may also be possible to reduce the risk of transmission of T2D-PRS with the donated organ via better donor-recipient matching, such as when organs are offered from multiple living donors.

RESULTS

Patient Populations: The study characteristics of four cohorts, two liver transplant cohorts and two kidney transplant cohorts, are shown in Table 1. Both liver cohorts include donor-recipient (D-R) pairs. Study participants include liver transplant recipients at the University of Pennsylvania (Penn = 579 recipients, 509 donors), and Baylor University Medical Center (Baylor n= 815 D-R pairs), where complete clinical data and genome wide genotyping (GWG) data was available. The two kidney transplant cohorts included D-R pairs from the Deterioration of Kidney Allograft Function (DeKAF) Genomics Consortium (863 recipients, n=533 D-R pairs)²⁴⁻²⁶, and recipient-only datasets obtained from Katholieke University, Leuven (Leuven, n=1199. Principal component (PC) analysis of the GWG data from the Baylor and Penn liver transplant recipient cohorts revealed 70.5% and 75.5% of recipients are of European descent respectively. Whereas, the great majority of patients enrolled in Leuven (98%), and those in the DeKAF included in this study (100%), were of European descents.

Association between T2D-PRS and pre-transplant diabetes in both liver and kidney transplant recipients: The rate of pre-transplant T2D varied between 17% to 31% amongst cohorts. T2D-PRS was strongly associated with clinical diagnosis of pre-transplant T2D diagnosis in both liver and kidney transplant recipients (Table 2). Other known clinical risk exposure variables, including BMI and age, were verified for pre-transplant diabetes status. These results confirm the validity of genetic association of T2D-PRS and T2D clinical phenotypes in the study cohorts. The results shown in Table 2 reflect the summary statistics for combined liver cohorts, and combined kidney cohorts. The association results for each individual cohort are shown in the Supplementary Table 1.

Relationship between T2D-PRS and PTDM in liver transplant recipients: After removing recipients with pre-transplant T2D, both recipient and donor T2D-PRS were found to be independently associated with PTDM risk in liver transplant recipients (Table 3). The combined statistics demonstrated that recipient T2D-PRS (OR= 1.48 (1.28 - 1.71), p=1.3E-07), and donor T2D-PRS (OR = 1.17 (1.02 - 1.35), p=0.03) independently contributed to PTDM risk. T2D-PRS were adjusted for both recipients' and donors' age, sex, BMI, and genetic ancestry (using the top 10 PCs derived from the respective GWG data), and donors' T2D status.

For liver transplant, the performance of the T2D-PRS model, plus clinical covariates to predict PTDM development in these population, is similar to that reported for T2D genetic predictors in the general population²¹. For the combined Penn and Baylor liver transplant cohorts, the observed AUC (95%CI) for the full PTDM multivariate model including both recipients and donors' T2D-PRS, and clinical variables including recipient age, BMI, sex, and transplant center was 67.6% (95%CI: 64.1% - 71.1%). Inclusion of recipient and donor T2D-PRS significantly improve the prediction of PTDM when

compared to the clinical-characteristics-only model (AUC (95%CI): 62.3% (58.8% - 65.8%)), $p=0.0001$.

Relationship between T2D-PRS and PTDM in kidney transplant recipients: In the kidney cohort, recipient T2D-PRS was significantly associated with PTDM development (Table 4). Recipient clinical variables including age and BMI, also had substantial influence on PTDM development. Analyses of the kidney cohort was limited to recipients of European ancestry since > 98% patients enrolled in Leuven are of European ancestry, and the results should thus be interpreted in this setting only. The limited donor data available from the DeKAF cohort indicates that kidney donor genomics, and/or clinical variables does not have impact PTDM development (Table 4).

Combining donor and recipient T2D-PRS to predict PTDM risk in liver transplant recipients: In the clinical setting of liver transplantation, the products of the recipient and donor genomes act in synergy. Consequently, it is appropriate to test the model in clinical scenarios, in which the donor and recipients T2D-PRS are combined (D+R T2D-PRS). Recipients were divided into quintiles based on the combined recipient's and their respective-donor's T2D PRS. Using recipients in the lowest D+R T2D-PRS quintile (Q1) as a reference, the risk of PTDM (OR (95%CI)) for the recipients in the second (Q2), third (Q3), fourth (Q4), and highest (Q5) quintiles were 1.50 (0.94 - 2.40), 2.37 (1.51 - 3.71), 2.60 (1.66 - 4.06) and 3.22 (2.07 - 5.00) respectively (Table 5 and Figure 1a). The predictive trend was significantly impacted by D+R T2D-PRS (P-Value for trend = $6.4E-09$), (Figure 1b).

We tested two clinical scenarios, in which modification of induction and maintenance immunosuppression results in 30% or 60% reduction of PTDM in the recipients among the highest risk categories (quintile 4 and 5) based on the combined donor-recipient T2D-PRS. These interventions targeting those patients at highest genetic risk would be expected to lower the overall incidence of PTDM in the entire recipient population, from the observed 28.1%, to the expected 23.8% and 19.5% respectively (Supplementary Table 2).

DISCUSSION

PTDM is recognized as a common complication of solid organ transplantation which requires intensive patient management. The clinical risk factors are well characterized, and overlap with some of the well-known variables associated with T2D in the general population such as age, gender, and BMI^{27,28}. Unique to the transplant population is the rapid development of diabetes post-transplant, which is attributed to the use of multiple diabetogenic drugs, specifically steroids and calcineurin inhibitors⁹⁻¹². Previous work identified PTDM as independent predictor of mortality, and there is a significant association with the development of cardiovascular events^{7,8}. It is likely that novel risk stratification tools, incorporating predictive clinical and genetic variables, are needed to predict the risk of PTMD development, and to assist in the design of strategies to reduce the clinical expression.

Recent advances in the identification and characterization of DNA polymorphisms associated with individual clinical predisposition to T2D, provide integrated PRS that have the potential to influence clinical management. Aggregated genotyping data from European-descent GWAS of 74,124 T2D cases, and 824,000 controls, imputed using high density reference panels, revealed a combined set of 403 highly significant T2D-risk genetic variant signals²¹. Other large population studies identify similar signals, confirming the potential of T2D-PRS in predicting the development of disease^{21,29} and their association with cardiovascular, renal, and neuropathy complications^{21,29}. Our study applied these T2D-PRS approaches in the transplant setting, hypothesizing that the PTDM clinical phenotype is rapidly induced by predisposing recipient clinical variables and immunosuppression drugs, in genetically susceptible recipients. Consequently, identifying individuals at risk could lead to the development of preemptive therapeutic strategies, and/or donor-selection, to prevent diabetes complications.

As a proof of principle, our study tested whether the T2D-PRS can identify solid-organ transplant candidates who develop T2D prior to their transplantation. Analyses of subjects with pre-transplant T2D vs non pre-transplant T2D demonstrated strong association with T2D status, consistent with the original GWAS meta-analyses results from which the T2D-PRS was derived²¹.

To examine the potential for practical application of the T2D-PRS based predictive model in the transplant setting, we tested whether the recipient genomics contribute to PTDM development regardless of the specific organ transplanted. Our results demonstrated that irrespective of the type of the solid-organ transplanted, recipient T2D-PRS is a predictor of PTDM. Multivariate analyses confirmed that recipient T2D-PRS, with adjustment of known prognostic clinical variables, was an independent contributor to PTDM risk in both liver and kidney transplant settings. The findings were independently confirmed in the different liver and kidney centers cohorts, regardless of the different

selection criteria of the transplant candidates, donor-specific clinical variables, or center-specific post-transplant immunosuppression protocols.

We next determined whether the donor T2D-PRS and/or clinical phenotype should be considered as risk exposures for PTDM development. Donor T2D-PRS was found to be associated with PTDM in liver transplant, but not kidney transplant, demonstrating unique contribution of the donor liver for PTDM development. This is not surprising, considering the central role of the liver in the regulation of glucogenesis, glucose metabolism and in insulin clearance, as well as regulation of lipogenesis^{15,16}. There was no evidence that the liver or the kidney donor clinical phenotype is associated with the development of PTDM in this study. This observation leads us to conclude that unique to the liver transplant setting, the donor T2D-PRS is as an independent risk variable, and that the risk score should include combined impact of the recipient and donor genomics. The limited data from the kidney cohort suggested that the donor genomics does not impact PTDM outcomes, and that the predictive score may be determined by the recipient genomics alone.

Previous studies suggest that induction and maintenance immunosuppressive drugs, including the use of high dose steroids and CNIs early after transplantation, account for 74% of the risk for PTDM^{30,31}. Consequently, it is reasonable to hypothesize that these medications are most likely promoting and accelerating the manifestation of PTDM in the genetically susceptible recipients. The relatively rapid appearance of the clinical PTDM phenotype provides an opportunity to test whether T2D-PRS can be utilized in the preemptive design of intervention strategies to reduce the development of the clinical complication. The approach should include modification of immunosuppression, such as steroid-free immunosuppression induction protocols, substituting CNIs with costimulatory blockade, and aggressive monitoring and early treatment of PTDM, that can significantly reduce the observed incidence in the entire transplant population³⁴⁻³⁶. Adjustment of immunosuppression must balance the risk of rejection versus the benefit of reduction in PTDM incidence³⁷⁻³⁹. Consequently, the clinical application should be first tested in selected recipients who have increased risk of PTDM development, and who are at low rejection risk.

To demonstrate the potential impact, we proposed scenarios in which only recipients with highest combined donor/recipient T2D-PRS quintiles undergo modification in post-transplant management, and calculated the outcomes if a portion of these selected recipients would respond well by avoiding the development of PTDM. Targeting high T2D-PRS upper quintile recipients, and reduction of the incidence of PTDM in this subset of recipients, will significantly reduce the incidence of PTDM in overall liver transplant populations.

Unique to the liver transplantation is the question whether living donor T2D-PRS should be tested prior to donation, and whether D-R genomic matching should be a consideration. This is far more relevant in the pediatric liver transplant setting, where polygenic risk variants transferred with the transplanted allograft, may impact the long term survival of the allograft and the child. We would advocate for non-immune related genetic matching, aiming to avoid identifiable risk exposure to the development of this complication, specifically when large pools of living liver donors are available.

There are several limitations of this study. First, the PRS used in this study derived from studying T2D in general population, not in transplant specific setting where additional exogenous factors such as stress from surgery and medication which may interact with additional genetic variants for the development of PTDM. GWAS of large transplant cohorts may reveal additional genetic variations contributing specifically to PTDM and incorporation of additional PTDM-specific genetic variants into T2D-PRS would likely enhanced its ability to predict the risk of PTDM. Secondly, we have limited power to detect the effect from kidney donors due to the low PTDM incidence rate in the DeKAF cohort. Our null observation of kidney donor genetic contribution to PTDM would require to be confirmed in other kidney cohorts with larger sample sizes, or with higher PTDM incidence.

Our study demonstrates the importance, and the potential application, of PRS in solid-organ transplantation. Using T2D-PRS as a clinical predictive assay could lead to personalized treatment strategies, aiming to reduce the occurrence of PTDM. While the study focuses on the risk exposure for the development of PTDM, the same approach could be used to explore the impact of recipient and donor genetics on the development of other significant morbid complications, that influence long term recipient survival e.g. chronic kidney disease.

METHODS

The study included two liver and two kidney transplant cohorts, transplanted at nine North American and one European centers. The first liver cohort, included recipients and their respective donors, transplanted at the University of Pennsylvania between 2012-2017, and enrolled in BioTIP study (Biorepository of the Transplant Institute at Penn). A second liver cohort included recipient and their respective donors, transplanted at the Baylor University Medical Center between 1998-2010, and enrolled in the Annette C. and Harold C. Simmons Transplant Institute biorepository and liver transplant research database⁴⁰. The first kidney cohort included recipients only, transplanted at Leuven University between March 2004 and September 2017. All patients gave written informed consent for collection and analysis of the samples in the Kidney Transplant Biobank, approved by the local ethical committee (S61239). A second kidney transplant cohort included recipient and their

respective donors, transplanted at seven DeKAF (Deterioration of Kidney Allograft Function) participating centers between 2005-2011, enrolled in DeKAF Genomics study (NCT00270712) and provided written, informed consent. At all centers, participants were enrolled in prospective biorepository and clinical database, collecting biological samples and clinical data at the time of transplantation, and at predetermined intervals after transplantation.

T2D was diagnosed according to the American Diabetes Association definition: hemoglobin A1c >6.5%, fasting plasma glucose ≥ 126 mg/dL, a 2-hour plasma glucose level of ≥ 200 mg/dL or higher during a 75-gram oral glucose tolerance test, a random plasma glucose of 200 mg/dL or higher on two occasions, or requiring medication for the management of hyperglycemia). PTDM was defined as transplant patients who had no pre-transplant T2D but developed sustained PTDM (duration > 6 months) within the 1st year post-transplant.

Immunosuppression management was directed as per center practice-specific guideline. For the liver transplant recipients, standard induction immunosuppression protocols included high dose steroids, tacrolimus, with the addition of azathioprine or mycophenolic mofetil for a background of kidney dysfunction. At Penn, 3 months after transplantation recipients' maintenance immunosuppression included calcineurin inhibitors (tacrolimus 97.9% or cyclosporine 1.3%), antimetabolites (MMF 6.8% or azathioprine 19.3%), and prednisone 75.3%. At Baylor, recipients' maintenance immunosuppression at 3 months post-transplant consisted of calcineurin inhibitors (tacrolimus 65% and cyclosporine 30%), antimetabolites (mycophenolate 51%), and prednisone 54%⁴⁰.

For the kidney transplant recipients, the standard immunosuppression protocols included antibody induction therapy in the first week, high dose steroids, tacrolimus, with the addition of azathioprine or mycophenolic mofetil. At Leuven 3 months after transplantation recipients' maintenance immunosuppression included calcineurin inhibitors (tacrolimus 92.4% or cyclosporine 4.7%), antimetabolites (MMF 89.8% (MPA 92.9%)), and prednisone 97.8%. At DeKAF 3 months after transplantation recipients' maintenance immunosuppression included calcineurin inhibitors (tacrolimus 62.1% -or cyclosporine 30.8%), antimetabolites (MMF 88.2% or azathioprine 1.9%), and prednisone 58.4%.

The studies were approved by the Institutional Review Boards at each of the respective institutions. The participants signed informed consents prior to transplantation, and at the time of organ donation.

Genotyping: Genotyping was conducted as previously described using a custom genome-wide genotyping tool, the Affymetrix Axiom Transplant Array, which was tailored with content for transplantation outcomes⁴¹. Quality control and assurance of these datasets was performed in accordance with the iGeneTRiN GWAS pipelines⁴². Details of genotyping, genotyping data quality

control, imputation, and the determination of racial clusters using principle components (PCs) can be found in the supplemental document.

Statistical Analysis: We used the published summary statistics of a set of 403 T2D-associated, independent risk signals from a recent T2D GWAS including 74,124 T2D cases, 824,006 controls to calculate PRS²¹. Genotyping data quality control and imputation procedure were detailed in the supplementary information. SNPs with imputation info score > 0.8, minor allele frequency >0.001, and Hardy-Weinberg Equilibrium (HWE) P value >1E-6 were qualified to be included to calculate T2D-PRS. In total, 361, 361, 326 and 355 either direct genotyped or imputed SNPs in Baylor, BioTIP, DeKAF and Leuven cohorts, respectively, overlapped with the top 403 T2D-associated independent signals and were included in the calculation of T2D-PRS using PRSice2⁴³. The combined donor and recipient T2D-PRS was calculated as the linear combination of donor's and paired recipient's PRS, with the coefficients of donor- and recipient- PRS derived from multivariate logistic regression including other significant covariates, such as recipient sex and recipient BMI at transplant.

The relationships between recipient T2D-PRS and pre-transplant DM were assessed using logistic regression, adjusting for recipient age, recipient sex, recipient BMI at transplant, 10 principal components calculated using PLINK, and enrollment centers when applicable. The relationships between PTDM and both the recipients' and paired donors' T2D-PRS were assessed using logistic regression, adjusting for recipient age, recipient sex, recipient BMI at transplant, donor age, donor sex, principal components of both recipients and donors, and enrollment centers when applicable. All statistical tests reported in this manuscript are two sided unless otherwise noted.

Data Availability: Upon request, the authors will provide the de-identified genetic and clinical datasets that were used for analysis, including clinical covariates, outcomes of interest, and T2D-PRS calculated from top 403 T2D-associated independent signals.

FIGURES AND TABLES

Figure 1a - The distribution of the standardized combined donor and recipient D+R T2D-PRS in liver transplantation cohorts is shown, with mean set to 0 and a standard deviation of 1. Color shaded areas show the quintiles of the population. The corresponding point estimates of OR and 95% CI for PTDM development among patients in the quintiles were shown as points and whiskers with OR scale indicated on right y-axis (Q1, the lowest D+R T2D-PRS quintile, used as reference).

Figure 1b - Relationship between percentile of donor and recipient Type 2 Diabetes Polygenic risk score (D+R T2D-PRS) in liver transplantation cohorts and incidence of post-transplant diabetes, shown with linear regression line and 95%CI bands.

Table 1: Patient Clinical and Demographic Characteristics

Organ	Study population	Pre-transplant T2D N(%)	PTDM N (%)	BMI at Transplant Median [IQR]	Age at Transplant Median [IQR]	Male N(%)
Liver (Penn)	Recipient (n=579)	178 (30.7%)	118 (34%)	27.0 [23.4, 30.9]	59 [52, 64]	411 (71%)
	Donor (n=509)	NA	NA	27.1 [23.5, 32.8]	43 [27.5, 55]	284 (56%)
Liver (Baylor)	Recipient (n=1002)	168 (17%)	229 (25%)	27.8 [24.2, 31.9]	52 [46, 57]	631 (63%)
	Donor (n=1046)	NA	NA	25.7 [22.4, 29.5]	41 [24, 55]	615 (59%)
Kidney (DeKAF)	Recipient (n=863)	269 (31%)	32 (6%)	27.7 [24.0, 31.9]	52 [41, 61]	563 (65%)
	Donor (n=533)	NA	NA	NA	44 [36, 52]	224 (42%)
Kidney (Leuven)	Recipient (n=1199)	207 (17%)	246 (24.9%)	24.9 [22.4, 28.2]	56 [45.6, 64]	757 (63%)

Table 2: PRS-T2D- Association with pre-transplant DM (multivariate analyses)

	Liver recipients (344 cases/1228 controls), all recipients		Kidney recipients 461 cases/1540 controls), European descent recipients only	
Variable	OR (95%CI)	p-value	OR (95%CI)	p-value
Recipient Age	1.05 (1.04 - 1.07)	4.20E-12	1.04 (1.03 - 1.05)	1.03E-14
Recipient BMI	1.05 (1.03 - 1.07)	1.01E-05	1.08 (1.03 - 1.14)	7.05E-11
Recipient Sex (M vs F)	1.03 (0.89 - 1.18)	0.71	1.02 (0.64 - 1.61)	0.15
Recipient T2D-PRS	1.43 (1.23 - 1.76)	5.04E-06	1.31 (1.04 - 1.65)	7.69E-06

*Recipients dropped out of this analysis due to missing covariates such as missing recipient BMI (n=28 in kidney recipients), missing donor BMI (n=2 in liver recipients, n=35 in kidney recipients), missing recipient sex (n=3 in kidney recipients), missing donor sex (n=7 in kidney recipients), missing recipient age (n=3 in kidney recipients), and missing donor age (n=10 in kidney recipients).

Table 3. Multivariate analyses of T2D-PRS association with PTDM in liver transplant, all recipients (after removing pre-transplant diabetes). Clinical variables were considered at the time of transplantation.

Transplant cohort	Penn		Baylor		Combined	
	(116 cases vs. 224 controls)		(205 cases/601 controls)		(321 cases/825 controls)	
Variable	OR (95%CI)	p-value	OR (95%CI)	p-value	OR (95%CI)	p-value
Recipient T2D-PRS	1.53 (1.15 - 2.02)	0.003	1.48 (1.22 - 1.79)	8.04E-05	1.48 (1.28 - 1.71)	1.33E-07
Donor T2D-PRS	1.20 (0.92 - 1.55)	0.17	1.21 (1.01 - 1.47)	0.04	1.17 (1.02 - 1.35)	0.03
Recipient Age	1.02 (0.99 - 1.04)	0.13	1.00 (0.98 - 1.02)	0.99	1.01 (0.99 - 1.02)	0.34
Recipient BMI	1.04 (1.00 - 1.09)	0.08	1.04 (1.01 - 1.06)	0.01	1.03 (1.01 - 1.06)	0.004
Recipient Sex (=M)	1.37 (0.76 - 2.46)	0.30	1.51 (1.04 - 2.21)	0.03	1.54 (1.14 - 2.1)	0.005
Donor Age at	1.01 (0.99 - 1.02)	0.41	1.00 (0.99 - 1.01)	0.64	1.0 (1.00 - 1.01)	0.37
Donor BMI	1.01 (0.97 - 1.05)	0.64	1.00 (0.97 - 1.03)	1.00	1.00 (0.98 - 1.03)	0.70
Donor Sex (M vs F)	1.05 (0.64 - 1.72)	0.85	0.95 (0.66 - 1.37)	0.78	0.96 (0.72 - 1.28)	0.79
Donor DM	1.14 (0.50 - 2.61)	0.76	1.23 (0.71 - 2.15)	0.46	1.21 (0.78 - 1.89)	0.40

* Only Recipients without pre-transplant DM were included in the analysis. Donor-recipient pairs dropped out of this analysis due to missing recipient BMI (n=5), donor BMI (n=9), and donor DM status (n=7).

Table 4. Multivariate analyses of T2D-PRS association with PTDM in kidney transplant (after removing pre-transplant diabetes), recipients of European descents only

Transplant cohort	Leuven		DeKAF	
	(224 cases/686 controls)		(32 cases/501 controls)	
Variable	OR (95%CI)	P-Value	OR (95%CI)	P-Value
Recipient T2D_PRS	1.32 (1.12 - 1.55)	0.0011	1.9 (1.21 - 2.99)	0.0057
Donor T2D_PRS	-	-	0.78 (0.51 - 1.18)	0.24
Recipient age	1.04 (1.02 - 1.05)	5.15E-07	1.07 (1.03 - 1.11)	0.00011
Recipient BMI	1.12 (1.08 - 1.16)	5.51E-09	1.09 (1.01 - 1.17)	2.00E-02
Recipient sex (M vs F)	0.75 (0.54 - 1.03)	0.08	1.21 (0.54 - 2.73)	0.65
Donor Age	0.99 (0.98 - 1.00)	0.11	1.00 (0.97 - 1.04)	0.96
Donor BMI	1.01 (0.97 - 1.05)	0.65	-	-
Donor sex (M vs F)	1.57 (1.13 - 2.19)	0.007	1.21 (0.54 - 2.73)	0.65

* Only Recipients without pre-transplant DM were included in the analysis. Donor-recipient pairs dropped out of this analysis due to missing recipient BMI (n=23), donor BMI (n=28), recipient sex (n=3), donor sex (n=6), recipient age (n=3), and donor age (n=8).

Table 5. PTDM incidence rates and ORs in the Quintiles of D/R-combined (weighted) T2D-PRS, all races liver recipient & donors (n=1153).

D+R PRS* Quintile	N (%) PTDM cases	OR (95%CI)	P Value
Q1 (reference)	37 (11.5%)	1	--
Q2	52 (15.8%)	1.50 (0.94 - 2.40)	0.09
Q3	71 (22.0%)	2.37 (1.51 - 3.71)	0.0002
Q4	78 (23.5%)	2.60 (1.66 - 4.06)	2.67E-05
Q5	89 (27.2%)	3.22 (2.07 - 5.00)	1.92E-07

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