Comparison of Long-term Outcomes of Living Kidney Donors With Longitudinal Healthy Control in the U.K.

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Abstract

Background: As live kidney donation rates increase, understanding the outcomes and risks for donors is increasingly important. Aim of this study was to investigate all-cause mortality plus long-term morbidity outcomes of live kidney donors compared with healthy cohort.

Methods: Datasets were obtained from UK Transplant Registry and a comparator non-donor cohort selected from The Health Improvement Network (THIN) database, a UK primary health care database. All live kidney donors(LD) from 1st January 2001 to 31st December, 2013 were included, with follow-up until 31st December 2016.

Results: There were 9750 LD and 27000 THIN participants. Median follow up (IQR) for LD 8.4 (6.0 to 11.3) years & THIN 5.3 (2.5 to 8.5) years. In up to 15 years follow-up no end stage renal disease (ESRD) was observed in LD versus 17 in THIN (P=0.01). Eight LD had eGFR<30 versus 91 in THIN (P<0.001), but no statistically significant difference in adjusted logistic regression analyses. Risk of diabetes, depression and cardiovascular disease was significantly higher for THIN cohort in adjusted analyses. The risk of hypertension was higher for LD at 5 years, but

was not significantly different in fully adjusted analyses at 10 & 15 years. There were 68 deaths in LD and 826 in THIN over the follow-up period, with significant difference in mortality favouring LD (P<0.001).

Conclusions: The long-term morbidity and mortality outcomes of LD in comparison with a healthy cohort suggest that live donation is safe, with no increased risk of mortality, ESRD or morbidity in up to 15 years follow-up.

Introduction

Living kidney donation has significantly improved recipient and graft survival worldwide(1). With a move to increase the number of living kidney donors further, it is important to have a better understanding of the short and long-term outcomes and risks of kidney donation.

Glomerular filtration rate both estimated and measured GFR (mGFR) have been shown to increase with time following donation for some years before deteriorating in the longer-term (2-4). Some studies have shown that survival and the risk of end stage renal disease (ESRD) is similar to those in the general population (5-9), while others have raised significant concerns (10-13).

A recent meta-analysis and two studies suggested that kidney donors have higher blood pressure (13-15). However, in other studies, blood pressure differences were not statistically significant, comparing donors and controls or hypertensive versus normotensive donors(16,17). A tool developed in North America, incorporating multiple health characteristics, to estimate the projected risk of ESRD in living kidney donors, produced risk projections higher in the presence of a lower eGFR, higher albuminuria, hypertension, current or former smoking, diabetes, and obesity (18).

This is the first long-term comparative study of live kidney donor outcomes in the UK. The aim of the study was to investigatethe long term outcomes of UK live kidney donors and to compare the outcomes with a cohort of healthy non-donors. In addition, to see if there was a difference in the outcomes from other studies as lifelong live donor follow up in the U.K is considered best practice by the British Transplantation Society (BTS) (19).

Methods

*Ethics:*National Health Service Blood and Transplant, Organ Donation and Transplant, (NHSBT) UK obtains informed consent from all patients undergoing a transplant and live donors in the UK for continuing data collection and subsequent analyses. The study protocol was approved by the UK Renal Registry projects advisory group before the live donor cohort dataset was released. For the comparative healthy cohort, ethics approval was already in place to accrue data from patients registered in UK general practices (NHS South-East Multicentre Research Ethics Committee, 2003). The study protocol was reviewed and approved by an independent scientific review committee (reference 16THIN033).

Cohorts for Study:

Live Donors (LD) *dataset:* The dataset obtained from the UK Transplant registry held by NHSBT, included all live kidney donors from 1st January 2001 to 31st December 2013, with a final follow-up end date of 31st December 2016 . Data collected for LD cohort comprised:

- Baseline characteristics
- Operative procedures and outcomes
- Follow up data for years 1, 2, 5,10 and 15
- All-cause mortality
- Longer term morbidity follow-up data including hypertension, eGFR, proteinuria, incident cardiovascular disease (CVD), depression and diabetes.

Comparative Non-donor Cohort dataset: The Health Improvement Network (THIN) database is a large UK general practice database which contains anonymized longitudinal patient records from over 500 practices, which is equivalent to about 6% of the UK population. The year of entry meant the presence of a valid record on the THIN database in the specific year, not necessarily a new entry on the database. Data from THIN were stratified by age, sex and year of cohort entry to reflect the LD cohort and included baseline characteristics, mortality and morbidity outcomes.THIN patients were selected to produce a healthy comparison cohort. Patients with the following baseline charateristics contraindicative to live kidney donation were excluded from

cohort selection:

- Less than 18 years of age
- Hypertension treated with 3 or more medications OR with Left Ventricular hypertrophy (LVH)
- Diabetes (DM) Type1 and 2
- Current or previous history of malignancy
- CVD including ischaemic heart disease (IHD), myocardial infarction (MI), unstable angina, coronary angioplasty or coronary artery bypass surgery (CABG)
- Peripheral vascular disease
- Chronic disease comprising chronic lung disease, chronic liver disease, chronic rheumatoid arthritis, lymphoma, myelofibrosis, proteinuria (ACR > 30 mg/mmol or PCR > 150 mg/mmol) and eGFR <30 ml/min/1.73m^2).

Statistical Methods:

Analyses of LD cohort included estimation and comparison of incident events, with 95% confidence intervals. Student's t-test was employed for comparison of continuous variables where appropriate, with use of non-parametric testing as needed and comparison of categorical variables used chi-squared tests. Kaplan Meier survival analysis, logistic regression modelling and Cox proportional hazards (PH) modelling were used for investigation of co-morbidities and all cause mortality.

Similar statistical methods were employed to compare baseline characteristics between the living donors and comparison cohort. Outcomes including mortality and co-morbidities were assessed using logistic regression, with Kaplan Meier survival analyses and Cox PH modelling as appropriate. For unadjusted survival analyses, all patients had a survival time, either to death or censoring; all were included in analyses. In adjusted analyses, where variables with missing values were used, analyses included only patients with valid data for all model variables; others were excluded. However, mortality and morbidity analyses were repeated using imputations for missing values in the strict LTF criteria for LD and restricted THIN cohort comparisons. Variables to be included in multivariable modelling comprised age and gender plus characteristics with

differences between the 2 cohorts and competing outcomes of interest, including morbidity, end stage renal disease or eGFR and year of entry into the cohort. Co-linearity was assessed for logistic models examining condition indices, with results >30 indicating unacceptable levels. In Cox PH models, proportionality of hazards assumption was assessed using the R routine 'Cox.Zph'; overall and individual variable estimates were examined.

Longer-term outcomes, including all-cause mortality, incidence of cardiovascular events, new onset hypertension, depression, diabetes mellitus, ESRD, proteinuria and changes in eGFR at follow-up years 1, 2, 5, 10 and 15 were analysed.

The analyses were repeated with most extreme "lost to follow-up" (LTF) definition for live donors, where any donor with no valid new data at one of the defined time points was considered LTF and the previous time point was taken as the last known time. The following 'baseline' exclusion criteria for THIN were applied: GFR measurement <60 ml/min/1.73m^2 (Note: any subsequent measurement GFR>60 ml/min/1.73m^2 invalidated this exclusion and person was included); BMI >35.0 kg/m^2; current smoker; hypertension recorded as pre-existing condition; urine ACR >30 mg/mmol or baseline PCR >50 mg/mmol. This cohort is referred to as Restricted THIN.

Results

LD vs. THIN analyses:

Table 1 shows comparative baseline characteristics and comorbidities between the LD and restricted THIN dataset. The median follow up (IQR) for LD is 8.4 (6.0 to 11.3) years and for THIN is 5.3 (2.5 to 8.5) years. Comparative baseline characteristics of original THIN & LD are shown in Table S1.

1. *Changes in GFR:*

LD Patients had measured GFRs (mGFR)for 95% and eGFR for 5% at baseline and only eGFRs in the follow-up period. THIN had eGFRs throughout the study period. There is a difference of 20 to 25 mls between the corresponding mGFR and eGFR. Differences in absolute mean GFRs between cohorts were statistically significant at all time points and changes in eGFR were also significant except for Year 15 (Figure 1A, 1B). In the LD there was an average decline in GFR

of 35 mls/min/1.73m^2 (eGFR at 1 year – baseline mGFR) over the first year post donation, with eGFR increasing steadily thereafter up to 10 years post, followed by a slow decline. In the THIN cohort, there was a steady decrease in the eGFR of about 0.33 mls every year. The pattern of changing eGFR over time was consistent across age bands in both cohorts (Figures1C, 1D). Individual paired changes from the same patients in both the cohorts are shown in Figure 2.

2. All-cause Mortality:

There were a total of 894 deaths over the follow-up period, 68 (0.7%) in LD and 826 (3.06%) in THIN. For LD, strict LTF criteria were used. Some models included imputations for missing values. The data was analysed using original THIN cohort (Table S2) and then reanalysed using restricted THIN (Table 2 & Figure 3 A –D). The results were similar in all analyses. Cox PH modelling was used to assess mortality at 5, 10 and up to 15 years of follow-up; the hazard ratio (HR) was significantly higher (P<0.001) for the THIN group in all models with adjustment for potentially confounding factors. Crude mortality rates per 10000 person years for LD and THIN for each year of the study was plotted and UK mortality rates reference plot added (Figure 3E).

Cumulative numbers of deaths per year and average incidence per 100000 patient years is shown in Table S3. Analysis of cumulative number of deaths at the follow up periods according to age bands, showed that there was no difference between LD and THIN in 18-29 years age group, but there were very few deaths observed in this age group in both cohorts as shown in Table S4. There were significantly more deaths in the THIN cohort i) in age groups 30-44, at Year 10 (p= 0.020) and all years (p=0.012); ii) in age groups 45-59, at year 5 (P=0.001), year 10(P<0.001) and all years mortality(P<0.001). In the 60+ group, significant differences in mortality between cohorts were seen at all follow-up times and follow-up years (P<0.001). Cancer was the major cause of death in both the cohorts. However, as only 19% data was available for THIN, no formal comparative analyses were conducted.

3. Morbidity Outcomes:

Comparative 5, 10 and up to 15-year multiple regression morbidity outcomes between LD and THIN are shown in Table S5. LTF censored LD vs. restricted THIN, including analysis using imputations for missing values is shown in Table 3; year of cohort entry exhibited high co-

linearity with the intercept and was excluded from models. Risk of diabetes and depression was significantly higher for the THIN cohort in all analyses including adjusted models. CVD risk was higher for THIN, and was statistically significant in fully adjusted models at 5 and 15 years. The risk of hypertension was higher for LD at 5 years, but there was no statistically significant difference in fully adjusted analyses at 10 & 15 years. There was no LD with eGFR<30ml/min/1.73m^2 at 15 years follow-up. There was significantly more proteinuria in LD on unadjusted analyses. However, there were very few cases for THIN, adjusted analyses were not performed.

Discussion

This is the first registry-based study of live donors in the U.K to study the long term outcomes of kidney donation by comparing with healthy non-donors; in the UK lifelong live donor follow up is considered best practice by the British Transplantation Society (BTS) (12). The non-donor cohort was selected from a large UK general practice database, excluding those with contraindications for live kidney donation. The comparator group sampled to reflect the LD cohort was also matched for the year of entry.

We analysed long-term outcomes of living kidney donors and observed no increased risk of all-cause mortality in the LD compared to the healthy control cohort with up to 15 years of follow-up (median follow up of 8.6 years for LD and 5.4 for THIN). Some studies have previously reached similar conclusions, showing survival after living kidney donation including older donors, being the same as for similar matched individuals who did not donate (13, 20-23). However these studies did not have a longitudinal comparative cohort with matched year of entry. The statistically significant differences in all-cause mortality in our study were generally quite large, with the LD doing better. There were statistically significant differences in ‘all years’ mortality in all age groups, with greater mortality in THIN when compared to LD, except 18-29, where there was no difference with very small numbers in both cohorts. The older the age group, the less years of follow-up needed for emergence of significant differences in mortality. This is similar to a published review of evidence which claimed that the risk of the primary outcome of

death was lower in donors than in non-donors and that the older age group were associated with a higher risk of death in both donors and non-donors (24).

Similarly, our study did not any show increase in comorbidities including ESRD in LD when compared to THIN. This was true for analyses of eGFR<30 and eGFR<15. To adjust for potential confounding factors, comorbidities were used as covariates in multivariable Cox PH and logistic regression analyses. Similar results were seen in all analyses, comparing LTF censored LD versus restricted THIN and in the full cohorts.

Other groups have reported findings contradictory to ours (10-13). They have shown that donor nephrectomy appears to increase the risk of end-stage renal disease (ESRD), when compared with healthy controls, although the absolute risk remains low. A study showed that donors of African origin are substantially at a higher risk than Caucasians (10). Our study had predominantly (>85%) Caucasian donors. Also, another study showed that 0.47% donors developed ESRD with a median time of 18.7 years (11). Thus it is possible that as our cohort had a median follow up of 8.4 years, there was insufficient time to observe any ESRD. Nevertheless, BTS guidelines recommends lifelong follow up of live donors in the U.K. Thus, it is possible that early diagnosis and intervention is contributing to the difference in the outcome.

DM and depression were significantly higher in our healthy cohort in all analyses including fully adjusted models at all follow-up periods ($p<0.001$), which is consistent with a recent review (25). CVD was higher in THIN at all follow-up periods but differences were not always statistically significant in fully adjusted analyses. Another study has reported lower incidence of CVD in donors in comparison to healthy cohort (24). Risk of hypertension was generally significantly higher in LD, but not in fully adjusted model for 15 years follow-up, This is possibly due to earlier detection and management of hypertension, which could have mitigated the long-term risk. A recent study of predominantly white donors found that hypertension was common after donation, though well controlled in most donors and also showed that use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers was associated with a lower risk for developing eGFR<45 and ESRD (26).

Our study showed that from one-year post-donation eGFR level improves slowly for 10 years in LD. Thereafter eGFR decreases slowly, similar to the THIN cohort at 15 years. Though, some studies (2,3,27) have observed this, this is the largest up to 15-year follow up study to show this trend.

Overall, LD group seemed to do better than THIN. This may be partly explained by healthy life-style, regular follow-up, and early detection and intervention of the LDs as opposed to the THIN cohort. As depression was significantly lower in LD, it could be speculated that the LD group was more positive and motivated, again possibly contributing to the better long-term health outcomes. In the UK, NHS health care is free at point of access; most live kidney donors are followed up regularly because of the BTS guidelines and such regular consultations facilitate donors access to early intervention if required.

Strengths and Limitations

Major strength of our study is the sizable donor data combined with a large comparative healthy cohort. However as it was a registry-based study, though we had considerable numbers, data were not available at all time points for all cohort members. To compensate for this, we reanalysed the data, using a stringent LTF definition, where LD with new valid data available at each time point were included and others were considered censored at the last new observation. We also repeated some analyses using imputation of missing data and the results were consistent. However, it should be noted that new data for donors may not have been recorded due to the prevailing normal health of the individuals. Thus, excluding this group could also potentially introduce a bias.

Though the comparative THIN cohort were sampled to reflect the LD cohort, there were some differences at baseline due to large numbers emphasising small differences. We acknowledge that this could have introduced a selection bias. We repeated analyses using the full THIN cohort and using further strict exclusion criteria at baseline (restricted THIN). In addition, we compared the yearly mortality rates for both LD and restricted THIN with the general population of U.K.

The mortality rates were much less for the THIN and LD than the general population of U.K. This confirms that the study cohorts were well matched, and that the THIN group were also healthier than the average general population.

The consistent message in all the analyses was that the LD group were not disadvantaged in comparison to the THIN cohort and that live kidney donation seemed safe. A study looking at adherence to healthy lifestyle or interaction with formal health services would perhaps enable us to understand the difference in outcomes between the donors and matched non-donor cohort. The gold standard evidence to promote or denounce living donation would be from a large randomized live donor study. However, ethical and practical considerations make such a study unlikely. Cohort analyses provide robust evidence of comparability of outcomes. Sustaining and improving registry data reporting is an essential pre-requisite for future high quality assessments.

Conclusions

The long-term morbidity and mortality outcomes of live donors in comparison with a healthy cohort suggest that live donation is safe, with no increased risk of mortality, ESRD or morbidity in up to 15 years follow-up. This could be due to healthy lifestyle, regular long-term follow up, early detection and medical intervention in donors, suggesting that promotion of live kidney donation is appropriate provided that long term regular monitoring, alongside high quality medical care can be guaranteed for donors.

Disclosure

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Table 1: Baseline characteristics and comorbidities between the Live Donor and Restricted THIN Cohort

Characteristic	**Living Donors(%) N=9750**	**THINcohort(%) N=19071**	**Total(%) N=28821**
Gender Female Male	 5214 *(53)* 4536 *(47)*	 9479 *(50)* 9592 *(50)*	 14693 *(51)* 14128 *(49)*
Broad age bands:			

18-29	917 *(9)*	1964 *(10)*	2881 *(10)*
30-44	3235 *(33)*	5680 *(30)*	8915 *(31)*
45-59	4136 *(42)*	7594 *(40)*	11730 *(41)*
60+	1462 *(15)*	3833 *(20)*	5295 *(18)*
Ethnicity			
White	8397 *(87)*	6472 *(91)*	14869 *(88)*
Asian	682 *(7)*	375 *(5)*	1057 *(6)*
Black	371 *(4)*	154 *(2)*	525 *(3)*
Other	232 *(2)*	135 *(2)*	367 *(2)*
Ethnicity (3 groups)			
White	8397 *(87)*	6472 *(91)*	14869 *(88)*
Asian	682 *(7)*	375 *(5)*	1057 *(6)*
All Other	603 *(6)*	289 *(4)*	525 *(3)*
Entry Year:			
2001	359 *(4)*	1461 *(8)*	1820 *(6)*
2002	372 *(4)*	1453 *(8)*	1825 *(6)*
2003	451 *(5)*	1461 *(8)*	1912 *(7)*
2004	463 *(5)*	1423 *(7)*	1886 *(7)*
2005	544 *(6)*	1493 *(8)*	2037 *(7)*
2006	671 *(7)*	1462 *(8)*	2133 *(7)*
2007	804 *(8)*	1400 *(7)*	2204 *(8)*
2008	924 *(9)*	1375 *(7)*	2299 *(8)*
2009	978 *(10)*	1417 *(7)*	2395 *(8)*
2010	1027 *(11)*	1550 *(8)*	2577 *(9)*
2011	1024 *(11)*	1525 *(8)*	2549 *(9)*
2012	1030 *(11)*	1530 *(8)*	2560 *(9)*
2013	1103 *(11)*	1521 *(8)*	2624 *(9)*
Smoking status:			
Never	6005 *(67)*	12692 *(77)*	18697 *(73)*
Ex-smoker	1358 *(15)*	3815 *(23)*	5173 *(20)*
Current	1641 *(18)*	0 *(0)*	1641 *(6)*
Co-morbidity:			
Hypertension (Baseline condition or BP > 140/90)			
No	8134 *(83)*	16118 *(85)*	24252 *(84)*
Yes	1616 *(17)*	2953 *(15)*	4569 *(16)*
BMI (standard bands)			
<18.5 (underweight)	75 *(1)*	289 *(2)*	364 *(2)*
18.5 - < 25 (standard)	2786 *(30)*	5594 *(39)*	8380 *(36)*
25 - < 30 (overweight)	4341 *(47)*	5956 *(42)*	10297 *(44)*
30+ (obese)	1993 *(22)*	2482 *(17)*	4475 *(19)*
BMI (extended bands)			
<18.5	75 *(1)*	289 *(2)*	364 *(2)*
18.5 - < 25	2786 *(30)*	5594 *(39)*	8380 *(36)*
25 - < 30	4341 *(47)*	5956 *(41)*	10297 *(44)*
30 - <35	1768 *(19)*	2359 *(16)*	4127 *(18)*
35 - <40	194 *(2)*	123 *(2)*	317 *(1)*
40+	31 *(-)*	0 *(0)*	31 *(-)*
	Mean (SD)	Mean (SD)	Mean (SD)
Age at cohort entry	46.5 (11.8)	47.7 (14.4)	47.3 (13.6)
Height	1.7 (0.1)	1.7 (0.1)	1.7 (0.1)
Weight	76.1 (14.3)	73.4 (14.5)	74.5 (14.5)
BMI	26.6 (4.0)	25.7 (3.9)	26.0 (3.9)
Systolic BP	126.7 (14.3)	127.6 (16.1)	127.3 (15.5)
Diastolic BP	75.4 (9.3)	77.7 (9.6)	76.9 (9.7)
Creatinine (mL /min)	78.8 (16.4)	80.5 (15.7)	79.6 (16.1)
GFR (mL /min)	98.1 (18.4)	76.4 (13.0)	91.3 (19.7)

Missing data: Ethnic group LD 68 (1%) vs. THIN 11935 (63%); Smoking status LD 746 (8%) vs. THIN 2564 (13%); Height LD 488 (5%) vs. THIN 4757 (25%); Weight LD 212 (2%) vs. THIN 4465 (23%); GFR LD 519 (5%) vs. THIN 14830 (78%); BMI LD 555 (6%) vs. THIN 4750 (25%) ; Systolic BP LD 265 (3%) vs. THIN 2765 (14%); Diastolic BP LD 265 (3%) vs. THIN 2765 (14%); Creatinine 33, (0.3%) LD vs. THIN 11391 (60%).

Table 2 : All-cause Mortality at 5 , 10 and up to 15 years follow-up Live Donor and Restricted

	5 years		10 year		Up to 15 years	
Cox PH Modelling - All years mortality	**HR (95% ci)**	**P-value**	**HR (95% ci)**	**P-value**	**HR (95% ci)**	**P-value**
Model 1 THIN cohort vs. Live Donors (No adjustment)	3.89 (2.82, 5.36)	<0.001	5.29 (4.07, 6.88)	<0.001	5.82 (4.51, 7.52)	<0.001
Model 2 THIN cohort vs. Live Donors Adjusted for: Gender (Male vs. Female) & Age	2.15 (1.55, 3.00)	<0.001	3.18 (2.43, 4.15)	<0.001	3.64 (2.814.72)	<0.001
Model 3 THIN cohort vs. Live Donors As model 2 + BMI, incident proteinuria, depression, CVD, diabetes or hypertension during follow-up, mean eGFR	1.83 (1.21, 2.77)	0.004	2.98 (2.17, 4.09)	<0.001	3.44 (2.50, 4.73)	<0.001
Model 4 THIN cohort vs. Live Donors	2.00 (1.26, 3.17)	0.003	3.45 (2.40, 4.96)	<0.001	3.87 (2.71, 5.55)	<0.001
Age*	1.14 (1.12, 1.16)	<0.001	1.13 (1.12, 1.15)	<0.001	1.14 (1.12, 1.15)	<0.001
Sex (M vs. F)	1.80 (1.28, 2.54)	<0.001	1.43 (1.13, 1.82)	0.003	1.38 (1.10, 1.74)	0.006
BMI**	0.97 (0.92, 1.01)	0.150	0.99 (0.95, 1.02)	0.412	1.00 (0.97, 1.03)	0.922
Incident proteinuria	0.63 (0.15, 2.62)	0.526	0.81 (0.29, 2.23)	0.682	1.02 (0.44, 2.37)	0.961
Depression	1.71 (0.95, 3.08)	0.071	1.32 (0.90, 1.95)	0.151	1.35 (0.94, 1.95)	0.105
CVD	1.61 (0.92, 2.84)	0.097	1.03 (0.69, 1.55)	0.874	1.10 (0.76, 1.59)	0.628
Diabetes	1.25 (0.51, 3.10)	0.627	1.20 (0.73, 1.96)	0.467	1.30 (0.82, 2.06)	0.264
Hypertension (ever)	0.65 (0.45, 0.93)	0.017	0.64 (0.50, 0.82)	<0.001	0.50 (0.39, 0.65)	<0.001
Mean eGFR§	1.02 (1.01, 1.03)	<0.001	1.01 (1.01, 1.02)	<0.001	1.01 (1.00, 1.02)	0.003
eGFR<30§§	3.12 (0.41, 23.41)	0.269	3.21 (1.43, 7.25)	<0.001	3.51 (1.73, 7.12)	<0.001
Year donation/ cohort entry	1.03 (0.97, 1.08)	0.370	1.04 (0.99, 1.08)	0.119	1.03 (0.99, 1.08)	0.150
Ex-smoker	1.26 (0.88, 1.81)	0.207	1.21 (0.93, 1.57)	0.150	1.27 (1.00, 1.63)	0.055
Current smoker	2.89 (1.38, 6.07)	0.005	2.62 (1.42, 4.82)	0.002	2.34 (1.27, 4.29)	0.006
Model 5 #*# THIN cohort vs. Live Donors	2.02 (1.37, 2.99)	<0.001	3.33 (2.42, 4.59)	<0.001	3.96 (2.90, 5.41)	<0.001
Age*	1.14 (1.12, 1.15)	<0.001	1.13 (1.12, 1.14)	<0.001	1.14 (1.13, 1.15)	<0.001
Sex (M vs. F)	1.36 (1.08, 1.72)	0.009	1.23 (1.03, 1.48)	0.021	1.21 (1.02, 1.44)	0.031
BMI**	0.99 (0.95, 1.02)	0.479	1.00 (0.97, 1.03)	0.982	1.01 (0.99, 1.04)	0.354
Incident proteinuria	0.91 (0.28, 2.95)	0.880	0.97 (0.39, 2.41)	0.939	1.09 (0.50, 2.38)	0.831
Depression	1.39 (0.92, 2.10)	0.115	1.40 (1.05, 1.86)	0.022	1.31 (1.00, 1.72)	0.053
CVD	2.05 (1.39, 3.02)	<0.001	1.28 (0.95, 1.73)	0.098	1.26 (0.96, 1.67)	0.101
Diabetes	1.29 (0.70, 2.38)	0.414	1.19 (0.81, 1.76)	0.365	1.32 (0.93, 1.89)	0.120
Hypertension (ever)	0.54 (0.41, 0.71)	<0.001	0.60 (0.49, 0.72)	<0.001	0.49 (0.40, 0.59)	<0.001
Mean eGFR§	1.02 (1.01, 1.03)	<0.001	1.01 (1.01, 1.02)	<0.001	1.01 (1.00, 1.02)	<0.001
eGFR<30§§	4.45 (1.05, 18.85)	0.043	3.62 (1.93, 6.80)	<0.001	3.45 (1.99, 5.99)	<0.001
Year donation/ cohort entry	0.96 (0.93, 0.99)	0.020	0.96 (0.94, 0.99)	0.021	0.96 (0.93, 0.99)	0.004
Ex-smoker	1.18 (0.91, 1.54)	0.217	1.15 (0.93, 1.41)	0.197	1.20 (0.98, 1.46)	0.075

Current smoker	2.51 (1.23, 5.14)	0.012	2.30 (1.26, 4.19)	0.006	2.12 (1.19, 3.79)	0.011

*Per year, which equates to about HR of 3.7 for 10 years; **Per unit BMI, equates to HR approximately 0.85 for 5 point increase in BMI; §Mean eGFR over time (5, 10 or all years as appropriate); §§eGFR<30 (i.e. CKD stage 4/5, Yes vs. No, up to the end of the appropriate time period.

#*# Model 5 includes imputation for BMI - all missing BMI replaced with grand mean BMI 26.01; Mean GFR -all missing mean GFR replaced with GFR=90; Smoking - all missing replaced with never smoker.

Numbers included in models and missing data:

5 years survival:
Model 1 N=28821, 303 deaths (no missing values)
Model 2 N=28821, 303 deaths (no missing values)
Model 3 N=16472, 152 deaths (10515 GFR missing, 5305 BMI Missing)
Model 4 N=15734, 147 deaths (10515 GFR missing, 5305 BMI Missing, 3310 smoking status missing)
Model 5 N=28821, 303 deaths (missing values replaced by imputed)

10 years survival:
Model 1 N=28821, 507 deaths (no missing values)
Model 2 N=28821, 507 deaths (no missing values)
Model 3 N=17959, 299 deaths (8463 GFR missing, 5305 BMI Missing)
Model 4 N=17177, 290 deaths (8463 GFR missing, 5305 BMI Missing, 3310 smoking status missing)
Model 5 N=28821, 507 deaths (missing values replaced by imputed)

Up to 15 years:
Model 1 N=28821, 553 deaths (no missing values)
Model 2 N=28821, 553 deaths (no missing values)
Model 3 N=18159, 320 deaths (8175 GFR missing, 5305 BMI Missing)
Model 4 N=17368, 311 deaths (8175 GFR missing, 5305 BMI Missing, 3310 smoking status missing)
Model 5 N=28821, 553 deaths (missing values replaced by imputed)

Table 3: Five, 10 & 15 Year Morbidity Outcomes: Live Donor and Restricted THIN Cohort - Logistic Regression Analyses

		5 years follow-up		10 years follow-up		15 years follow-up	
Outcome:	**Model - variables**	**OR (95% ci)**	**P-value**	**OR (95% ci)**	**P-value**	**OR (95% ci)**	**P-value**
CKD stage 4/5	1 THIN vs. LD	0.49 (0.17, 1.42)	0.188	3.44 (0.45, 26.33)	0.234	#	#
	2 THIN vs. LD	0.22 (0.07, 0.70)	0.010	2.11 (0.27, 16.58)	0.477		

(eGFR<30ml/ min/1.73m^2)	M vs. F	0.89 (0.31, 2.59)	0.836	1.43 (0.49, 4.15)	0.515		
	Age (year)	1.18 (1.11, 1.26)	<0.001	1.18 (1.10, 1.26)	<0.001		
	3 THIN vs. LD	0.61 (0.36, 1.04)	0.067	2.06 (0.73, 5.81)	0.172		
	M vs. F	0.65 (0.41, 1.05)		1.35 (0.70, 2.59)	0.372		
	Age (year)	1.17 (1.14, 1.20)	0.076	1.15 (1.11, 1.19)	<0.001		
	BMI (baseline)	1.24 (1.18, 1.31)		0.97 (0.88, 1.07)	0.545		
	Hypertension	0.26 (0.16, 0.43)	<0.001	1.14 (0.46, 2.83)			
	CVD	0.09 (0.00, 1.81)	<0.001	0.05 (0.00, 1.13)	0.782		
	DM	0.11 (0.00, 3.12)	<0.001	1.93 (0.71, 5.21)			
	Depression	0.49 (0.14, 1.64)	0.116	1.05 (0.37, 3.04)	0.060		
	Smoking (Y)	1.73 (1.08, 2.77)	0.196	2.66 (1.39, 5.07)	0.197		
			0.245		0.923		
			0.022		0.003		
Hypertension (clinically assigned OR BP>140/90)	1 THIN vs. LD	0.64 (0.59, 0.69)	<0.001	0.82 (0.72, 0.94)	0.004	0.82 (0.67, 0.99)	0.040
	2 THIN vs. LD	0.60 (0.56, 0.65)	<0.001	0.81 (0.71, 0.93)	0.003	0.83 (0.68, 1.01)	0.067
	M vs. F	1.06 (0.99, 1.14)	0.010	1.03 (0.92, 1.16)	0.575	0.93 (0.77, 1.11)	0.412
	Age (year)	1.04 (1.04, 1.04)	<0.001	1.03 (1.03, 1.04)	<0.001	1.03 (1.02, 1.03)	<0.001
	3 THIN vs. LD	0.66 (0.61, 0.73)	<0.001	0.86 (0.73, 1.00)	0.048	0.89 (0.71, 1.13)	0.333
	M vs. F	1.06 (0.98, 1.15)	0.156	1.03 (0.90, 1.18)	0.698	0.91 (0.72, 1.13)	0.387
	Age (year)	1.03 (1.03, 1.04)	<0.001	1.03 (1.02, 1.03)	<0.001	1.02 (1.01, 1.03)	0.002
	BMI (baseline)	1.07 (1.06, 1.08)	<0.001	1.06 (1.04, 1.08)	<0.001	1.05 (1.02, 1.09)	0.001
	CVD	1.52 (1.15, 2.01)	0.003	0.98 (0.70, 1.38)	0.929	1.19 (0.71, 1.99)	0.509
	DM	1.43 (1.04, 1.96)	0.029	1.15 (0.80, 1.67)	0.447	1.60 (0.87, 2.94)	0.129
	Depression	1.17 (0.99, 1.39)	0.061	1.03 (0.83, 1.28)	0.771	0.98 (0.69, 1.38)	0.894
	eGFR<30	0.62 (0.19, 1.97)	0.414	0.97 (0.29, 3.26)	0.966	#	#
	Smoking (Y)	1.03 (0.94, 1.13)	0.521	1.14 (0.97, 1.34)	0.101	1.02 (0.79, 1.32)	0.854
Diabetes	1 THIN vs. LD	3.43 (2.18, 5.39)	<0.001	2.36 (1.46, 3.81)	<0.001	2.94 (1.58, 5.44)	0.001
	2 THIN vs. LD	3.04 (1.93, 4.78)	<0.001	2.16 (1.33, 3.50)	0.002	2.86 (1.54, 5.32)	0.001
	M vs. F	2.10 (1.58, 2.80)	<0.001	1.65 (1.22, 2.23)	0.001	1.33 (0.86, 2.06)	0.198
	Age (year)	1.05 (1.04, 1.06)	<0.001	1.05 (1.04, 1.06)	<0.001	1.05 (1.03, 1.07)	<0.001
	3 THIN vs. LD	4.20 (2.52, 6.98)	<0.001	3.31 (1.81, 6.06)	<0.001	4.09 (1.77, 9.48)	0.001
	M vs. F	2.08 (1.49, 2.90)	<0.001	1.51 (1.03, 2.22)	0.033	1.15 (0.63, 2.08)	0.656
	Age (year)	1.03 (1.01, 1.04)	<0.001	1.02 (1.00, 1.04)	0.013	1.03 (1.00, 1.06)	0.046
	BMI (baseline)	1.17 (1.13, 1.21)	<0.001	1.21 (1.15, 1.27)	<0.001	1.23 (1.13, 1.34)	<0.001
	Hypertension	3.84 (2.43, 6.08)	<0.001	6.93 (2.95, 16.29)	<0.001	5.90 (1.38, 25.19)	0.017
	CVD	1.15 (0.55, 2.43)	0.712	1.29 (0.65, 2.55)	0.461	1.15 (0.44, 3.02)	0.777
	Depression	1.91 (1.17, 3.13)	0.010	1.18 (0.68, 2.05)	0.566	1.20 (0.52, 2.77)	0.678
	eGFR<30	-	-	1.31 (0.15, 11.14)	0.803	#	#
	Smoking (Y)	1.27 (0.91, 1.76)	0.161	1.56 (1.05, 2.30)	0.026	1.56 (0.83, 2.92)	0.163
CVD	1 THIN vs. LD	2.09 (1.50, 2.92)	<0.001	1.70 (1.13, 2.55)	0.010	2.43 (1.39, 4.26)	0.002
	2 THIN vs. LD	1.64 (1.17, 2.31)	0.004	1.40 (0.93, 2.12)	0.108	2.20 (1.24, 3.90)	0.007
	M vs. F	1.82 (1.41, 2.34)	<0.001	2.18 (1.61, 2.94)	<0.001	2.46 (1.56, 3.86)	<0.001
	Age (year)	1.09 (1.07, 1.10)	<0.001	1.09 (1.07, 1.10)	<0.001	1.09 (1.07, 1.12)	<0.001
	3.THIN vs. LD	1.63 (1.13, 2.35)	0.008	1.19 (0.75, 1.89)	0.451	2.00 (1.02, 3.94)	0.045
	M vs. F	1.74 (1.31, 2.31)	<0.001	2.08 (1.46, 2.96)	<0.001	2.21 (1.30, 3.76)	0.004
	Age (year)	1.07 (1.06, 1.08)	<0.001	1.08 (1.06, 1.09)	<0.001	1.09 (1.06, 1.12)	<0.001
	BMI (baseline)	0.99 (0.95, 1.03)	0.675	0.99 (0.94, 1.04)	0.617	1.03 (0.96, 1.11)	0.437
	Hypertension	2.95 (2.01, 4.33)	<0.001	2.21 (1.31, 3.70)	0.003	2.89 (1.11, 7.51)	0.030
	Diabetes	1.13 (0.53, 2.39)	0.753	1.17 (0.59, 2.31)	0.658	1.13 (0.43, 2.97)	0.800
	Depression	2.31 (1.51, 3.54)	<0.001	2.86 (1.84, 4.45)	<0.001	3.27 (1.70, 6.28)	<0.001
	eGFR<30	-	-	-	-	#	#
	Smoking (Y)	1.54 (1.16, 2.05)	0.003	1.58 (1.11, 2.26)	0.012	1.44 (0.83, 2.50)	0.192
Depression	1 THIN vs. LD	9.55 (6.97, 13.08)	<0.001	9.65 (6.01, 15.50)	<0.001	11.93 (6.28, 22.66)	<0.001
	2 THIN vs. LD	10.03 (7.32, 13.75)	<0.001	10.19 (6.34, 16.39)	<0.001	12.46 (6.55, 23.70)	<0.001
	M vs. F	0.50 (0.44, 0.58)	<0.001	0.57 (0.48, 0.68)	<0.001	0.60 (0.45, 0.80)	<0.001
	Age (year)	0.99 (0.98, 0.99)	<0.001	0.98 (0.97, 0.99)	<0.001	0.98 (0.97, 0.99)	0.002
	3 THIN vs. LD	11.30 (8.02, 15.93)	<0.001	12.40 (7.21, 21.31)	<0.001	16.96 (7.83, 36.73)	<0.001
	M vs. F	0.50 (0.43, 0.59)	<0.001	0.56 (0.45, 0.71)	<0.001	0.54 (0.37, 0.79)	0.001
	Age (year)	0.98 (0.97, 0.99)	<0.001	0.97 (0.96, 0.98)	<0.001	0.97 (0.95, 0.98)	<0.001
	BMI (baseline)	1.01 (0.99, 1.03)	0.262	1.01 (0.98, 1.04)	0.419	1.03 (0.98, 1.08)	0.223
	Hypertension	1.08 (0.91, 1.28)	0.362	1.00 (0.79, 1.28)	0.981	0.85 (0.56, 1.27)	0.422
	CVD	2.41 (1.58, 3.68)	<0.001	2.99 (1.93, 4.63)	<0.001	3.33 (1.75, 6.32)	<0.001

	Diabetes	1.87 (1.15, 3.05)	0.012	1.17 (0.67, 2.02)	0.581	1.08 (0.47, 2.46)	0.856
	eGFR<30	-	-	1.13 (0.14, 9.02)	0.911	#	#
	Smoking (Y)	1.35 (1.14, 1.60)	0.001	1.48 (1.16, 1.89)	0.001	1.23 (0.82, 1.85)	0.319

No Live Donors with eGFR<30ml/min/1.73m^2 at 15 years follow-up.

Numbers in analysis and missings:

5 years analyses
Maximum LD (4165) and THIN (15866): THIN reduced by stringent cohort selection, LD have had LTF applied.
All cases LD 4165, THIN 11304 = maximum 15469 observations.
All outcomes have same missings as BMI and smoking status based on baseline measurement only.
Model 1 - 15469 observations, 14 outcomes, no missing data.
Model 2 - 15469 observations, 14 outcomes, no missing data.
Model 3 - 11824 observations, 12 outcomes. Missing 3645: 3267 BMI, 2021 Smoking status.

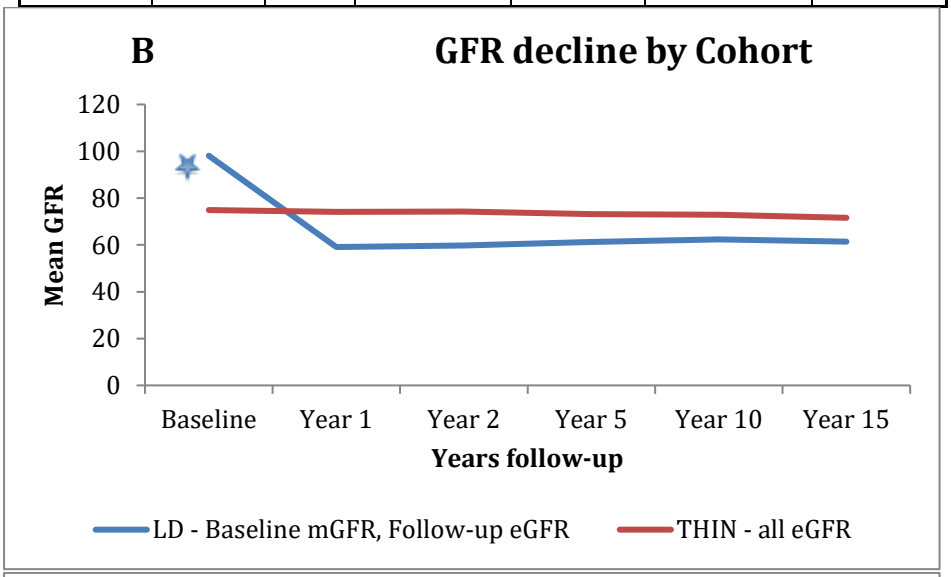
10 years analyses:
Maximum LD (1095) and THIN (5702): THIN reduced by stringent cohort selection, LD have had LTF applied.
All cases LD 1095, THIN 4147 = maximum 5242 observations.
All outcomes have same missings as BMI and smoking status based on baseline measurement only.
Model 1 - 5242 observations, 14 outcomes, no missing data.
Model 2 - 5242 observations, 14 outcomes, no missing data.
Model 3 - 3727 observations, 11 outcomes. Missing 1515: 1367 BMI, 967 Smoking status.

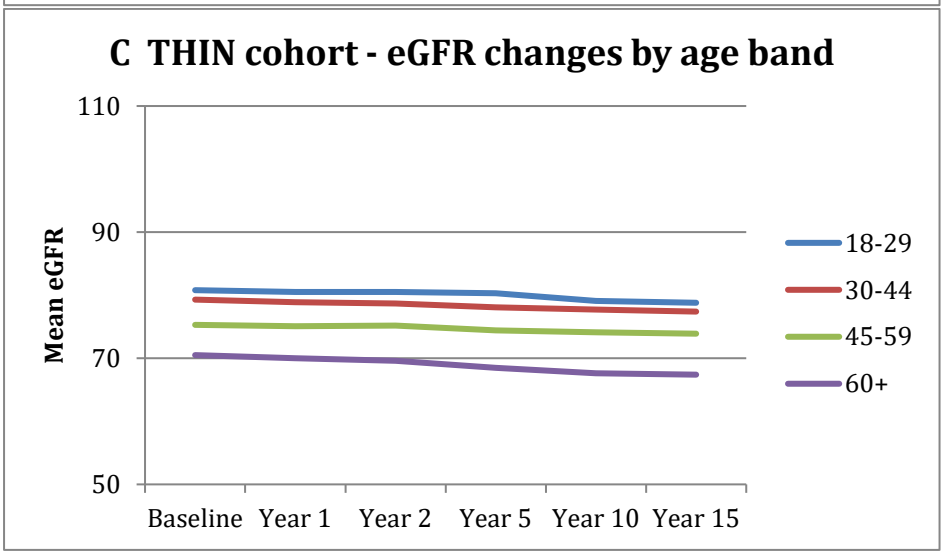
Up to 15 years analyses:
Maximum LD (595) and THIN (1334): THIN reduced by stringent cohort selection, LD have had LTF applied.
All cases LD 595, THIN 1334 = maximum 1929 observations.
CKD (GFR<30) - too few observations, no analyses.
All outcomes have same missings as BMI and smoking status based on baseline measurement only.
Model 1 - 1929 observations, 1279 outcomes, no missing data.
Model 2 - 1929 observations, 1279 outcomes, no missing data.
Model 3 - 1370 observations, 951 outcomes. Missing 559: 496 BMI, 377 Smoking status

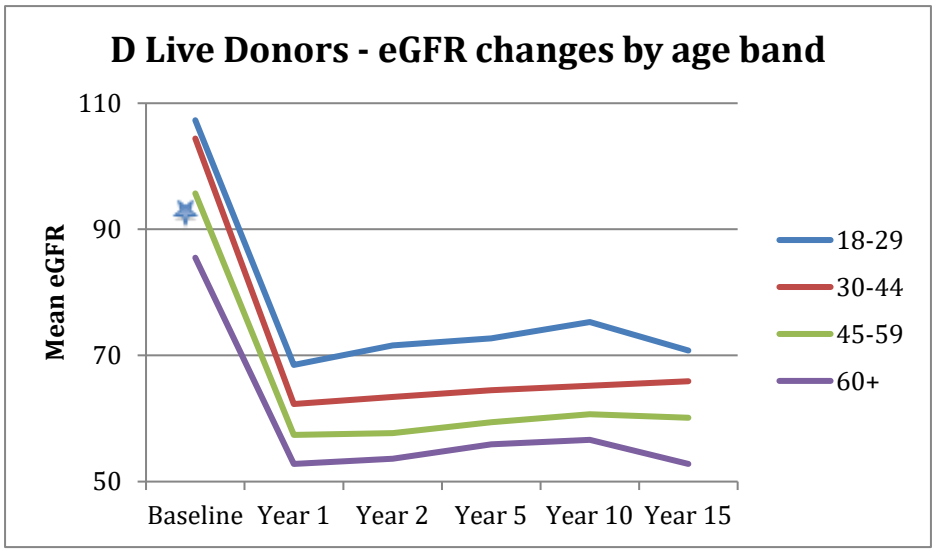
Figure 1: Changes in GFR: A) Over 15 year period in Live Donor and THIN Cohorts, both mean and paired differences form the same patients; B) Overall GFR changes over time by cohort; C) Ageband GFR changes over time for Live Donor; and D) Ageband GFR changes over time for THIN Cohort

A	Cohort	N	Cohort Median (IQR) *	Paired differences N	Paired differences Median (IQR)	Mann-Whitney U-test

Baseline	LD THIN	9231 6563	95 (86, 108) 75 (60, 88)	-	-	-
Year 1	LD THIN	4172 3070	58 (51, 65) 75 (60, 86)	4039 1603	-34 (-43, -26) -1 (-7, 6)	P<0.001
Year 2	LD THIN	3561 3189	59 (52, 66) 75 (62, 87)	2635 981	2 (-4, 6) 1 (-6, 6)	P<0.001
Year 5	LD THIN	2611 5206	60 (53, 68) 74 (60, 86)	1530 1082	0.7 (-1.0, 2.3) -0.3 (-2.7, 2.0)	P<0.001
Year 10	LD THIN	793 3081	60 (53, 69) 74 (60, 87)	450 1075	0.4 (-0.6, 1.6) -0.2 (-1.8, 1.4)	P<0.001
Year 15	LD THIN	66 812	59.5 (52, 69.5) 73 (60, 84)	55 532	-0.6 (-1.6, 0.4) -0.6 (-1.8, 0.8)	P=0.905







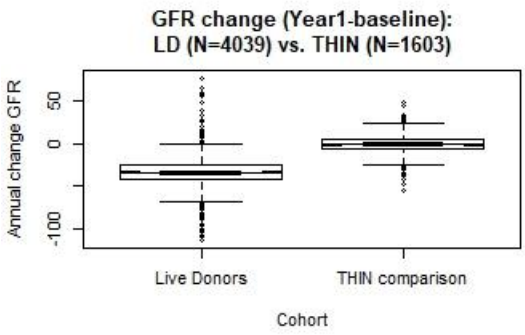
Panel A:

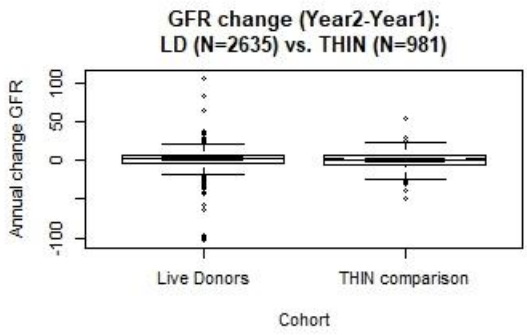
- Cohort median comparisons statistically significant, Mann-Whitney U-test P<0.001.

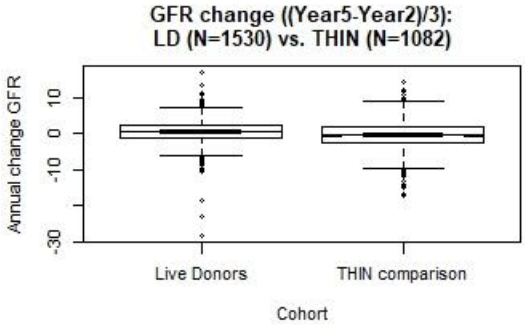
Panel B & D

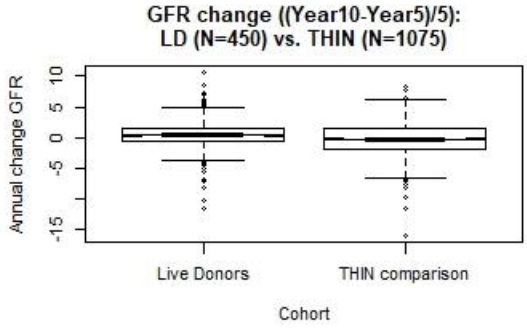
- LD Patients had measured GFRs at baseline (mGFR) and eGFRs in the follow-up period. There is a difference of 20 to 25 mls between the corresponding mGFR and eGFR. THIN had eGFRs throughout the study period.

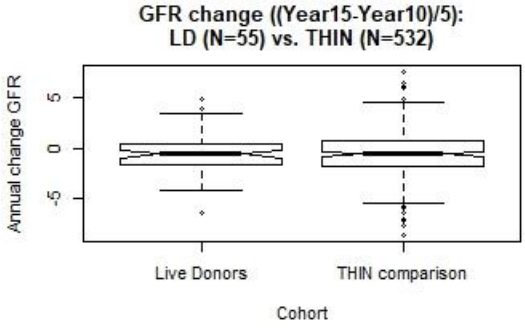
Figure 2: Individual and combined annual changes in GFR comparing LD vs. THIN.







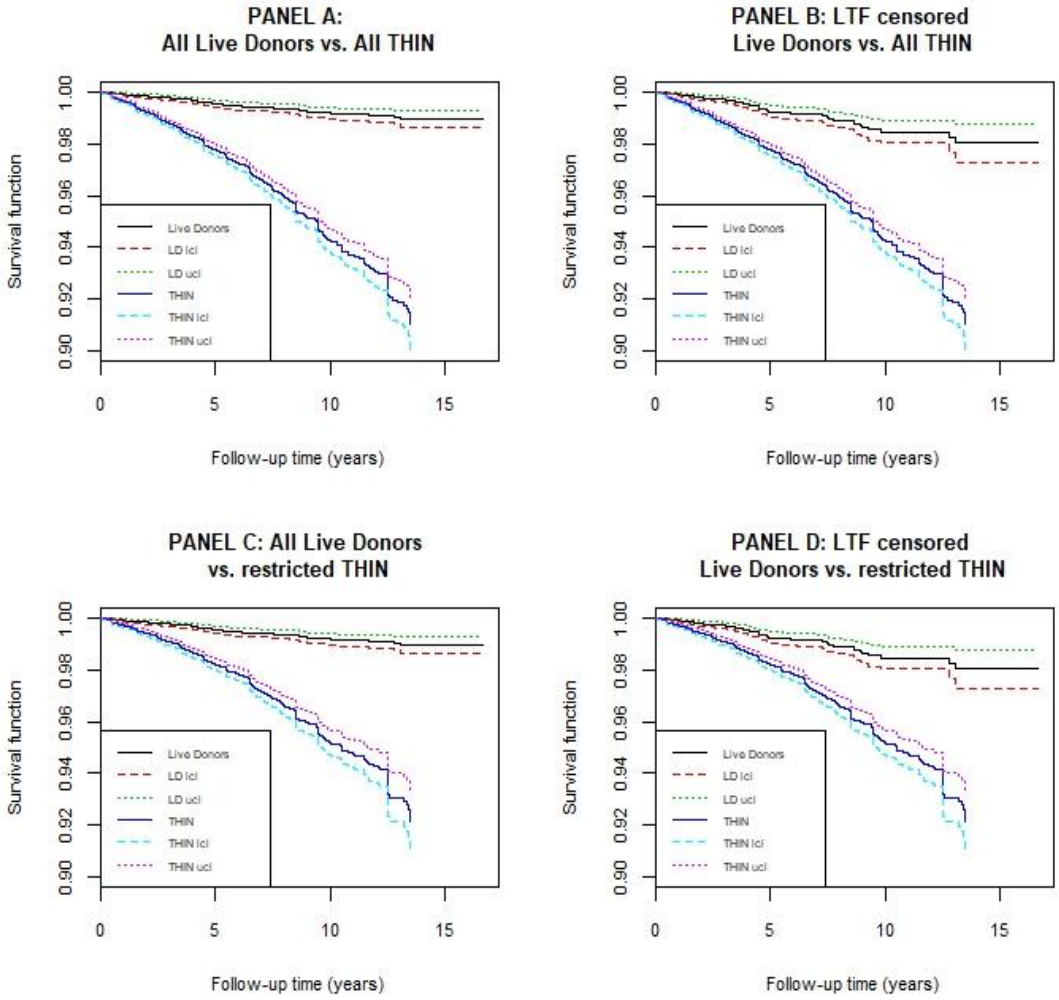




Changes are estimated as time period measure - previous time period measure divided by number of years for individual cohort member. All included in any plot have both measures needed to generate the difference, so these are paired (within individual differences) not just comparing mean for LD cohort vs. THIN.

Figure 3: Mortality plots

A) All Live Donors vs. THIN B) LTF censored Live Donors vs. THIN C) All Live Donors vs. Restricted THIN D) LTF censored Live Donors vs. Restricted THIN. (Figures A-D Log Rank test P<0.001).
E) Yearly Mortality Rates of All Live Donors & Restricted THIN in comparison with Yearly Mortality Rates of UK adults over 18.



PANEL E