Results of the prospective multicenter SoLKiD cohort study indicate bio-psycho-social outcome risks to kidney donors 12 months after donation

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The outcome after living kidney donation was assumed to be comparable to that of the general population. However, recent register studies reveal negative changes in kidney function, quality of life and fatigue. Avoiding methodological issues of previous studies, the Safety of the Living Kidney Donor (SoLKiD) cohort study analyzed the outcome of donors in a multicenter and interdisciplinary fashion. Donor data were collected pre-donation and two-, six- and 12-months post-donation in 20 German transplantation centers. Primary parameters were kidney function, quality of life, and fatigue. Secondary endpoints were blood pressure, hemoglobin, hemoglobin A1c, body mass index, depression and somatization. Parameters were analyzed with non-parametric statistical tests and a mixed model regression for changes in time, their clinical relevance and interaction encompassing 336 donors with mean age of 52 years. Most of the physical secondary parameters, depression, and quality of life showed little or no changes and regained their pre-donation level. Kidney function decreased significantly with a 37% loss of glomerular filtration rate and an increase of donors with chronic kidney disease stage 3 from 1.5% pre-donation to about 50%. Donors consistently showed increased fatigue and somatization. Mental fatigue increased from 10.6% to 28.1%. The main influencing factors for decreased kidney function and increased fatigue were their respective pre-donation levels, and donor age for kidney function and subject stress level in fatigue. Thus, our study showed that a significant number of donors developed clinically relevant changes in physical and mental health and emphasizes the urgent need to inform potential donors about these risks.

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Kidney transplantation is the only medical approach to regain renal function, improve quality of life (QoL), and enhance life expectancy in patients with end-stage renal disease (ESRD). Because of persistent organ shortage, living kidney donation (LKD) has attained considerable importance over the last few years in most health systems.[1,2] Besides the obvious benefits for the recipient, for example, preemptive transplantation, there is a major obligation to protect the physical and psychosocial health of donors. Until recently, the long-term health of donors was assumed to be comparable to or even better than that of the general population.[3,4] Because these results are mostly based on retrospective, monocentric, and monodisciplinary data, the informed consent procedure of the donor must be reviewed critically. To underline such skepticism, recent retrospective register studies found a higher incidence of ESRD[5,6] and decrease in QoL or increased fatigue in donors.[7] Furthermore, the correlation of physical and mental factors influencing the outcome after LKD is sparse and shows conflicting results. We hypothesized that the development of fatigue after LKD has been underestimated. Therefore, it is very important to investigate the outcome of donors in a prospective, multicenter, and interdisciplinary designed study. This cohort study will aim at the detection of clinically relevant changes in kidney function, QoL, or fatigue and underlying influencing factors after donation if such conditions are noticed and lasting. Therefore, the SoLKiD (Safety of the Living Kidney Donor) study examined the physical and psychosocial outcome of living donors in relation to their predonation health status.

METHODS

SoLKiD is a large prospective, multicenter, and multidisciplinary cohort study of the comprehensive outcome for living donors

conducted over a period of 12 months in Germany. The study protocol of SoLKiD has been described in detail.[8] Of 38 German transplantation centers (TCs) performing LKD, 20 participated in SoLKiD. Donors were recruited after verbal and written informed consent on a voluntary basis. The study was performed in accordance to the Declaration of Helsinki and in agreement with the ethics commissions of all TCs (Medical Faculty of the University of Münster and Westphalian Chamber of Physicians, 2013-587-f-S).

Inclusion criteria were scheduled LKD, age ≥ 18 years, and native language of German, Turkish, or Russian. Exclusion criteria included refusal to participate, donor not living in Germany, and inability to speak in 1 of the 3 languages listed above. Baseline recruitment was done between January 2014 and November 2017 with regular follow-ups in the first year. A total of 336 donors were included corresponding to about one-third of eligible donations in 20 German TCs during the 45-month recruitment period.

Donors were examined and data were collected predonation (T0), 2 (T1), 6 (T2), and 12 months (T3) postdonation at the regular aftercare visits. Because the answers of the donors could be influenced by concerns of the potential donor not to be considered suitable for donation, all data were collected after the definite donation decision. Data were documented in a case report form and centrally analyzed at the coordination center (Münster University). This included results from routine laboratory testing for serum creatinine (S-crea), hemoglobin, hemoglobin A1c, and plasma glucose. Renal function of donors was analyzed following the local practice of each TC. S-crea and estimated glomerular filtration rate (eGFR; calculated by the Chronic Kidney Disease Epidemiology Collaboration formula according to consensus guidelines) were documented.[9] Blood pressure, mean arterial pressure (MAP), body height, weight, body mass index, antihypertensive medication, smoking status, and self-perceived health status were documented.

All participants filled out paper-based questionnaires to assess psychosocial factors and QoL. For QoL, the short-form 36-Item Health Survey (SF-36) was used. The instruments' summary and 8 dimensions scores were calculated using the German standard. The Multidimensional Fatigue Inventory (MFI-20) is a standardized self-assessment tool, which measures perceived tiredness (fatigue) in extent, nature, and intensity. The 5 dimensions of the MFI-20—general fatigue, physical fatigue, mental fatigue, reduced activation, and reduced motivation—were interpreted separately. The Patient Health Questionnaire (PHQ) was developed to facilitate the detection of the most common mental disorders. Severity ratings for depression (PHQ-9) and somatization (PHQ-15) were used. Psychosocial negative consequences for a donor can be either a reduction in the mental health scores of SF-36 (reduction in QoL), an increase in the severity of depressive symptoms (PHQ-9) or somatization (PHQ-15), or an increase in fatigue (MFI-20). Donors were asked about their stress level during the last 2 weeks before the time points T0 to T3 by using the Perceived Stress Scale as a potential influential factor on the psychosocial variables. Detailed information on the questionnaires, subdimensions, and references can be found in Supplementary Table S1.

Statistical analyses

Primary outcome parameters were as follows: eGFR, SF-36 summary scores (physical component [Physical Component Scale] score and mental component [Mental Component Scale] score), and fatigue (MFI-20 subdimension). Secondary end points were systolic and diastolic blood pressure, MAP, hemoglobin, body mass index, hemoglobin A1c, SF-36 scores (its 8-dimension scores), depression (PHQ-9), and somatization (PHQ-15). Sample size and power calculations are given in Supplementary Methods SI1.

Stepwise analyses of the outcome variables were performed:

(i) Data of each parameter were reported at each time point. Because all outcome variables were not normally distributed, the results are presented as median and 25% to 75% percentile.

(ii) Differences in each parameter between the time points were tested using the Friedman test (χ^2) and controlled for type I errors with a Bonferroni-corrected P value ($P \leq 0.05/25 = 0.002$). If a significant change was detected, the effect size was calculated with Kendall's W.

(iii) For each parameter showing deviations in the time course, the difference between T0 and T3 was tested using the Wilcoxon test (Z) for paired samples and controlled for type I errors with a Bonferroni-corrected P value ($P \leq 0.05/25 = 0.002$). Effect sizes ($r = Z/\sqrt{N}$) were calculated if a change was significant.

(iv) For each variable showing a significant change during the time course after donation (analyses 2 and 3) and an at least moderate effect size of ≥0.30 according to Cohen,[10] the clinical relevance of changes was analyzed. To determine the number of LKDs that showed clinically relevant impairment, variable-specific cutoff scores were used. eGFR < 60 to 45 ml/min per 1.73 m^2 represents clinically relevant decreased renal function (chronic kidney disease [CKD] stage 3a or worse).[9] A PHQ-9 or PHQ-15 score of ≥10 is defined as a cut point for clinically relevant symptoms of depression or somatization.[11] For the other psychosocial variables for which no valid cutoff score exists, scores lower (SF-36) or higher (MFI) than 1SD of the mean of the German normal populations were defined as clinically relevant.[12,13] The McNemar test (χ^2) was used to compare frequencies of patients above and below the cutoff values between T0 and T3. Bonferroni-corrected P values were used ($P \leq 0.05/18 = 0.003$). Effect sizes ($r = \sqrt{(\chi^2/N)}$) were calculated if a significant change in a variable was detected.

(v) To assess the effect of multivariate factors on changes during the time course postdonation, a multivariate linear mixed model regression with repeated measures over time, an unstructured covariance matrix for the residual, and a random intercept for the center were constructed for each of the significant parameters (see step 4). For each target variable, the following parameters were considered as potentially influential: time course T1 to T3, age, sex, the interaction between age and sex, education, TC, surgical technique (open vs. minimal open), body mass index, smoking, hemoglobin, hemoglobin A1c, MAP, number of antihypertensives, stress level, donor's appraisal of recipients health status, and among psychosocial variables eGFR as well. Final models were established using backward variable elimination, keeping the variables time and the target variable predonation as fixed influential variables in the mixed model.

Statistical analyses were performed with SPSS version 25 (IBM) and SAS version 9.4 (SAS Institute).

RESULTS

Participants

A total of 336 living donors with a mean age of 52 years were included in the study. The majority of all participants had a vocational training, were full-time or part-time employed, and were female (Table 1).

Table 1 | Characteristics of the participating living kidney donors

Variable	Mean ± SD/*n*	Range/%
Age (yr) ($n = 336$)	52.30 ± 9.68	24–77
Male	51.10 ± 10.13	27–75
Female	53.03 ± 9.34	24–77
Sex ($n = 336$)		
Male	135	40.2
Female	201	59.8
Donor-recipient relation ($n = 318$)		
Related	147	46
Nonrelated	171	54
Donor-recipient living situation ($n = 330$)		
Same household	268	83.8
Separate household	52	16.2
Years school attended ($n = 315$)	11.04 ± 2.15	4–25
School education ($n = 317$)		
No degree	3	0.9
Elementary/secondary school	92	29.0
Middle school	119	37.5
High school	97	30.6
Other	6	1.9
Job education ($n = 307$)		
No degree	20	6.5
Professional training	185	60.3
Advanced professional training	21	6.8
College degree	3	1.0
School of applied sciences/university	54	17.6
Other	24	7.8
Employment status ($n = 314$)		
Full-time	166	52.9
Part-time (>15 h/wk)	54	17.2
Unregular (<15 h/wk)	12	3.8
Not employed	82	26.1

Physical and psychosocial situation predonation

MAP values were in the normal range before LKD. Seventy-five percent of donors had no antihypertensive medication, 16% took 1, 6% took 2, and 3% took >2 antihypertensives. Donors had a median hemoglobin A1c value of 5.50% and normal values of hemoglobin and kidney function (eGFR > 90 ml/min per 1.73 m^2), but in 5 donors predonation, eGFR was <60 ml/min (Figure 1).[9] Body mass index indicated slight overweight at T0 (Table 2). The SF-36 physical (median Physical Component Scale score 58.26) and mental (median Mental Component Scale score 55.36) component scores showed levels in the upper range of the standard normal population. The PHQ showed no major depressive (PHQ-9 score 1.00) or somatization (PHQ-15 score 3.00) symptoms (Table 3). Even in a situation where no clinical cut point in fatigue exists, our cohort showed no increased fatigue levels predonation compared with the healthy population (Figure 2).[14–16]

Physical and psychosocial situation postdonation

During follow-up, most of the physical variables, except eGFR, showed little or no change after LKD and regained their predonation level (Table 2). The number of donors on antihypertensive medication did not increase significantly (25.1%–26.3%, T0 vs. T3).

Kidney function decreased significantly after nephrectomy and remained decreased during follow-up (Table 2). S-crea significantly increased from a median value of 0.8 to 1.1 mg/dl (T3), and eGFR decreased from 96 ml/min (T0) to 60 ml/min (T1) and remained decreased at T3 (Figure 1). The total loss of eGFR was 32 ± 12 ml/min (38%) from T0 to T1 and 30 ± 10 ml/min (37%) from T0 to T3. Table 4 presents the distribution of eGFR according to the Kidney Disease: Improving Global Outcomes CKD classification.[9] From T1 to T3, more than half the donors showed a decreased CKD stage 3. There was no CKD stage 5 in the entire cohort.

Donors showed a significant decline in Physical Component Scale scores (T1), which did not fully recover during the subsequent follow-up visit. Mental Component Scale scores were nearly unaffected. With regard to SF-36 dimension scores, a decline was observed for bodily function, physical role, pain, general health, and vitality at T1, which also did not fully recover. Particularly, vitality was notably impaired after 12 months. At T3, donors had a slight but significant increase in depressive symptoms (PHQ-9; median score 1.00–2.00; $P < 0.001$; Cohen's $r = 0.26$) but a larger increase in somatization (PHQ-15; median 3.00–4.00; $P < 0.001$; Cohen's $r = 0.51$). An increase in fatigue was detectable 8 weeks postdonation and remained at an increased level in 4 of the 5 domains (general fatigue, physical fatigue, mental fatigue, and reduced activity) of the MFI (Table 3). Kidney function (S-crea and eGFR), SF-36 QoL (vitality), PHQ-15, and general and mental fatigue showed significant ($P \leq 0.002$; effect size > 0.3) changes during 12 months postdonation and were considered for the following analyses.

Clinical relevance of changes

The only change in somatic outcome was decreased kidney function. Because of the correlation between S-crea and eGFR, only eGFR was analyzed. The proportion of donors with decreased eGFR CKD stage 3 increased from 1.5% predonation to ~50%, but none showed ESRD (Tables 4 and 5). The proportion of donors with impaired vitality (vitality score <42.55) increased and remained increased at T3. The percentage of donors with clinically relevant somatization (PHQ-15 score >10) increased from 3.8% to 12.9%.

The percentage of donors with clinically relevant fatigue changed from 6.3% to 18.4% for general fatigue (general fatigue score >12.2) and from 10.6% to 28.1% for mental fatigue (mental fatigue score >10.9). From T0 to T3, 36 donors (12.7%) showed no change in mental fatigue, 215 (75.9%) showed an increase in mental fatigue (mean 3.5 ± 2.3; range 0.7–12), and 32 (11.3%) showed a decline in mental fatigue (mean −2.1 ± 2.5; range −1 to −12). In donors with increased fatigue, the extent of fatigue at T3 was about 2 times greater than that at T0 (mean 1.8 ± 0.5; range 1.1–4.0). Of these physical and psychosocial variables with significant changes of clinical relevance, only changes in eGFR and mental fatigue showed moderate (≥0.30) effect sizes (Table 5). Therefore, the multifactorial effects on the postdonation course were analyzed for these 2 variables only.

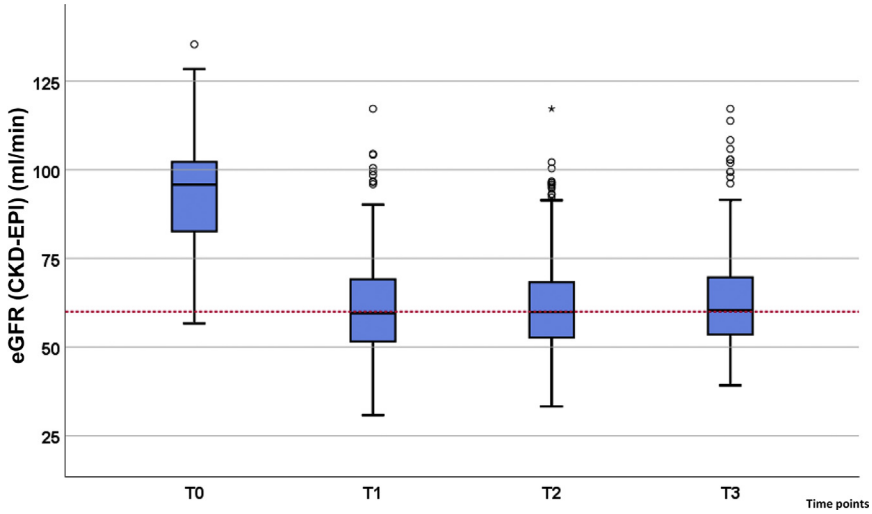

Figure 1 | Course of kidney function before and 12 months after kidney donation. The box plots show the development of estimated glomerular filtration rate (eGFR) in 336 donors before living kidney donation at time point predonation (T0) and after nephrectomy at time points 2 (T1), 6 (T2), and 12 (T3) months postdonation of follow-up in relation to grade 3 Kidney Disease: Improving Global Outcomes chronic kidney disease (KDIGO CKD). The red line represents CKD grade 3 with an eGFR of <60 ml/min.[9] The eGFR decrease from T0 to T3 was statistically significant (Wilcoxon test, $P < 0.001$). *Percentage of donors with eGFR < 60 ml/min at T0 vs. T3. CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration.

Factors influencing the health status after LKD

According to the results of the multivariate linear mixed model regression, kidney function (after decreasing between T0 and T1) continually increased from T1 to T3 ($P = 0.0167$) with higher eGFR at T2 (estimates 1.03 ml/min; 95% CI –0.25 to 2.31 ml/min; $P = 0.1138$) and at T3 (estimates 1.83 ml/min; 95% CI 0.57–3.08 ml/min; $P = 0.0044$) than at T1. Higher eGFR at T0 results in higher eGFR at follow-up (estimates 6.61 per 10 ml/min at T0; 95% CI 5.74–7.48 per 10 ml/min; $P < 0.0001$). Older age at baseline results in a lower eGFR during follow-up ($P < 0.0001$), with a decrease of 0.31 ml/min per year of life (95% CI –0.44 to –0.19 ml/min per year of life). Higher hemoglobin before nephrectomy was associated with a lower eGFR of –1.05 ml/min per unit of hemoglobin (95% CI –1.67 to –0.43 ml/min per unit of hemoglobin; $P = 0.0010$). Sex, smoking status, MAP, or number of antihypertensives (Table 6) did not influence the course of renal function. The classical patient on risk as a living kidney donor is a patient who is relatively old and has a low predonation eGFR (Supplementary Table S2).

According to the results of the multivariate linear mixed model regression, higher mental fatigue predonation results in higher mental fatigue postdonation (+0.21 per unit increase in baseline mental fatigue; 95% CI 0.14–0.27 per unit increase in baseline mental fatigue; $P < 0.0001$). After the significant increase in mental fatigue postdonation, mental fatigue did not change significantly at T1 versus T3 (Table 7). Higher stress (Perceived Stress Scale) results in higher mental fatigue (0.16 per unit increase in Perceived Stress Scale score;

Table 2 | Course of physical variables during 12 mo of follow-up

	Median (25%–75% percentile)				Friedman test		T0 vs. T3	
Variable	T0	T1	T2	T3	*P*	*W*	*P*	*r*
Kidney function								
Creatinine (mg/dl; $n = 244$[a])	0.79 (0.70–0.90)	1.17 (1.00–1.32)	1.15 (1.00–1.30)	1.13 (1.00–1.29)	<0.001	**0.61**	<0.001	**0.68**
eGFR (ml/min; $n = 244$)	95.83 (82.62–102.26)	59.50 (51.52–69.26)	59.88 (52.64–68.29)	60.33 (53.53–69.68)	<0.001	**0.61**	<0.001	**0.68**
Hemoglobin (g/dl; $n = 220$)	14.00 (13.03–14.88)	13.30 (12.60–14.10)	13.60 (13.06–14.50)	13.75 (13.00–14.68)	<0.001	0.17	NS	NA
HbA1c (%; $n = 118$)	5.50 (5.30–5.73)	5.40 (5.20–5.70)	5.50 (5.20–5.70)	5.45 (5.30–5.70)	NS	NA	NS	NA
Blood pressure								
Systolic (mm Hg; $n = 145$)	130.00 (122–140)	126 (119–135)	129 (120–138)	130 (120–138)	<0.001	0.04	NS	NA
Diastolic (mm Hg, $n = 144$)	80 (75–90)	80 (75–89)	80 (75–90)	80 (75–89)	NS	NA	NS	NA
MAP (mm Hg; $n = 144$)	96.67 (90.67–106.67)	96.67 (90.00–103.67)	96.67 (90.83–104.00)	96.67 (91.08–104.25)	NS	NA	NS	NA
BMI (kg/m^2; $n = 216$)	25.85 (23.74–29.01)	25.78 (23.25–28.33)	25.87 (23.67–28.49)	25.86 (23.30–28.96)	<0.001	0.03	NS	NA

BMI, body mass index; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; MAP, mean arterial pressure; NA, not applicable; NS, not significant ($P > 0.002$); *r*, effect size for the Wilcoxon test; T0, predonation; T1, 2 months postdonation; T2, 6 months postdonation; T3, 12 months postdonation; *W*, effect size for the Friedman test (Kendall's *W*).
[a]Number of subjects with complete data from T0 to T3.
Note: Effect sizes are shown in bold if ≥0.3.

Table 3 | Course of psychosocial variables during 12 mo of follow-up

Variable	Median (25%–75% percentile)				Friedman test		T0 vs. T3	
	T0	T1	T2	T3	*P*	*W*	*P*	*r*
Quality of life (SF-36)								
PCS ($n = 256$[a])	58.26 (56.22–59.81)	46.81 (39.08–53.19)	55.69 (50.73–58.67)	57.19 (52.23–59.15)	<0.001	**0.35**	<0.001	0.23
MCS ($n = 256$)	55.36 (51.33–58.13)	56.50 (51.23–59.56)	55.93 (50.83–58.17)	55.23 (50.08–57.65)	<0.001	0.03	NS	NA
PF ($n = 257$)	100.00 (95.00–100.00)	85.00 (70.00–94.22)	95.00 (85.00–100.00)	95.00 (85.00–100.00)	<0.001	**0.35**	<0.001	0.24
RP ($n = 255$)	100.00 (100.00–100.00)	50.00 (0.00–100.00)	100.00 (75.00–100.00)	100.00 (100.00–100.00)	<0.001	**0.42**	<0.001	0.24
BP ($n = 257$)	100.00 (100.00–100.00)	62.00 (42.00–84.00)	100.00 (74.00–100.00)	100.00 (74.00–100.00)	<0.001	**0.31**	<0.001	0.23
GH ($n = 259$)	82.00 (72.00–92.00)	77.00 (65.00–87.00)	82.00 (67.00–92.00)	82.00 (67.00–92.00)	<0.001	0.03	0.001	0.15
VT ($n = 258$)	75.00 (65.00–85.00)	65.00 (50.00–80.00)	70.00 (60.00–80.00)	70.00 (60.00–80.00)	<0.001	0.12	<0.001	**0.32**
SF ($n = 258$)	100.00 (87.50–100.00)	100.00 (75.00–100.00)	100.00 (87.50–100.00)	100.00 (87.50–100.00)	<0.001	0.06	NS	NA
RE ($n = 256$)	100.00 (100.00–100.00)	100.00 (100.00–100.00)	100.00 (100.00–100.00)	100.00 (100.00–100.00)	<0.001	0.03	0.002	0.14
MH ($n = 258$)	84.00 (76.00–90.50)	84.00 (72.00–92.00)	84.00 (76.00–92.00)	84.00 (72.00–88.00)	NS	NA	NS	NA
Mental health								
PHQ-9 ($n = 256$)	1.00 (0.00–3.00)	2.00 (0.00–4.00)	2.00 (0.00–4.00)	2.00 (0.00–4.00)	<0.001	0.04	<0.001	0.26
PHQ-15 ($n = 254$)	3.00 (1.07–5.00)	5.00 (2.11–7.50)	4.00 (2.00–6.43)	4.14 (2.00–7.00)	<0.001	0.10	<0.001	**0.38**
Fatigue (MFI-20)								
GenFat ($n = 255$)	7.00 (4.00–9.00)	9.00 (6.00–12.00)	8.00 (5.00–12.00)	8.00 (5.00–11.00)	<0.001	0.07	<0.001	**0.31**
PhysFat ($n = 252$)	6.00 (5.00–9.00)	9.00 (6.00–12.00)	7.00 (5.00–9.00)	7.00 (5.00–9.83)	<0.001	0.11	<0.001	0.16
MenFat ($n = 245$)	6.00 (4.00–8.00)	8.00 (8.00–11.00)	8.00 (8.00–11.00)	9.00 (8.00–11.00)	<0.001	**0.31**	<0.001	**0.51**
RedAct ($n = 231$)	6.00 (5.00–8.00)	8.00 (6.00–10.00)	7.00 (5.00–9.00)	7.00 (5.00–9.00)	<0.001	0.05	<0.001	0.17
RedMot ($n = 230$)	6.50 (5.00–8.00)	7.00 (5.00–9.00)	6.00 (5.00–8.00)	6.00 (5.00–8.00)	NS	NA	NS	NA

BP, bodily pain; GenFat, general fatigue; GH, general health; MCS, Mental Component Scale, MenFat, mental fatigue; MFI-20, Multidimensional Fatigue Inventory; MH, mental health; NA, not applicable; NS, not significant ($P > 0.002$); PCS, Physical Component Scale; PF, physical functioning; PHQ, Patient Health Questionnaire; PhysFat, physical fatigue; *r*, effect size for the Wilcoxon test; RE, role emotional; RedAct, reduced activity; RedMot, reduced motivation; RP, role physical; SF, social functioning; SF-36, short-form 36-Item Health Survey; T0, predonation; T1, 2 months postdonation; T2, 6 months postdonation; T3, 12 months postdonation; VT, vitality; *W*, effect size for the Friedman test (Kendall's *W*).

[a]Number of subjects with complete data from T0 to T3.

Note: Effect sizes are shown in bold if ≥0.3.

95% CI 0.14–0.19 per unit increase in Perceived Stress Scale score; $P < 0.0001$).

The classical patient on risk as a living kidney donor is a patient who has a relatively high predonation mental fatigue and stress level (Perceived Stress Scale; Supplementary Table S3). Of the 257 donors who had a mental fatigue score below the threshold of clinical significance at predonation, 22% showed clinically relevant fatigue at T3. Of the 26 donors who showed relevant fatigue at T0, 53.8% remained at a relevant fatigue level at T3 (Figure 3).

DISCUSSION

The aim of the largest prospective study by far on the safety of LKD was to comprehensively investigate, for the first time, the combined physical and psychosocial outcome of LKD in a multidisciplinary approach. The results over a period of

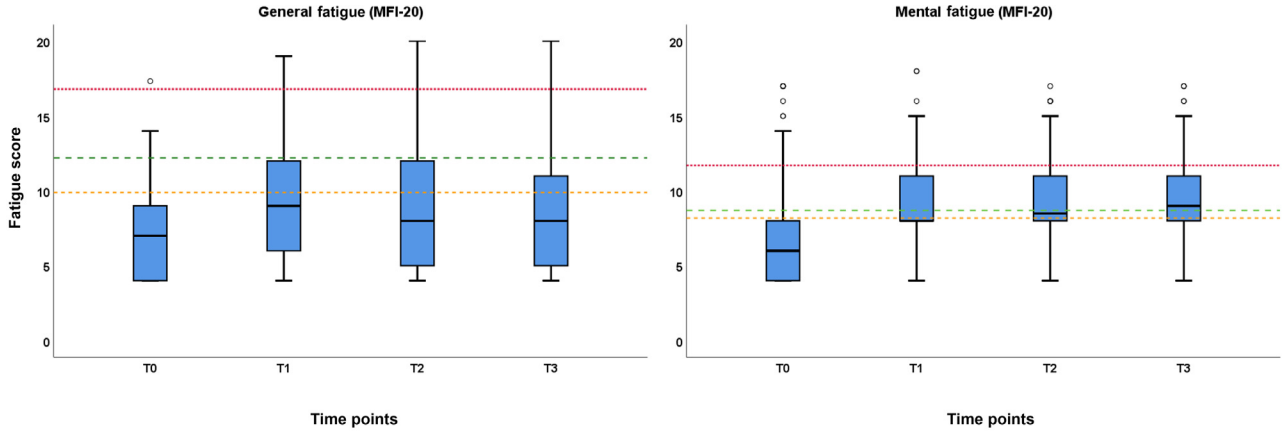

Figure 2 | Development of the mental fatigue score before and after living donor nephrectomy. The box plots show the development of general and mental fatigue in donors before and after living kidney donation, with representation of mean scores of general fatigue and mental fatigue in chronic oncological or nononcological patients. The orange dotted line represents the mean score of cancer survivors[14]; the green line represents the mean score of patients with chronic critical illness 3 months after the transfer from the intensive care unit[15]; and the red line represents the mean score of patients in palliative cancer care.[16] MFI-20, Multidimensional Fatigue Inventory; T0, predonation; T1, 2 months postdonation; T2, 6 months postdonation; T3, 12 months postdonation.

Table 4 | Distribution of eGFR in donors according to 2012 KDIGO CKD classification

	n[a] (%)			
CKD stage (eGFR)	T0	T1	T2	T3
G1–2 (>60 ml/min)	331 (98.5)	147 (47.7)	127 (48.8)	149 (49.7)
G3a (45–59.99 ml/min)	4 (1.2)	133 (43.2)	111 (42.7)	132 (44.0)
G3b (30–44.99 ml/min)	1 (0.3)	27 (8.8)	22 (8.5)	19 (6.3)
G4 (<30.00 ml/min)	0 (0)	1 (0.3)	0 (0)	0 (0)

CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; KDIGO, Kidney Disease: Improving Global Outcomes; T0, predonation; T1, 2 months postdonation; T2, 6 months postdonation; T3, 12 months postdonation.
[a]Number of subjects with complete data.

12 months show that most of the documented physical and psychosocial factors exhibit an initial impairment within the first weeks of donation, followed by a regain of the initial level. However, kidney function remained moderately impaired. It is noteworthy that health-related QoL was impaired. Fatigue and somatization were increased, whereas depression did not change. The most prominent result was the impairment in mental fatigue, which did not resolve after 12 months and was independent of decreased renal function or physical changes. Even the amount of fatigue mostly remained in the range of the normal population, but in a significant number of subjects, the increase in fatigue was clinically relevant. It is important to note that some donors already at inclusion showed clinically relevant decreased kidney function and signs of depression, somatization, or fatigue. The course after donation was mainly influenced by variable levels at baseline, donor's age in case of kidney function, and subject's stress level in fatigue. These novel findings will be discussed in detail according to the specific variable.

Alteration in kidney function after LKD

Previous studies on the physical consequences of LKD showed divergent results regarding the age-dependent decrease in the eGFR of 30% within 10 years of donation. In contrast, older studies did not find an increased risk in impaired kidney function compared to the nonselected normal population.[2,17–19] However, these studies were based on younger and healthier donors. More recent studies[20] conclude a 25% to 30% loss of GFR in 6 months and 9 years of follow-up. They also found an increase in eGFR of 1.5 ml/min/yr in donors but a decline of 0.4 ml/min/yr in a control group of a healthy normal population. The United States and Norway register studies compared donors with a cohort of healthy potential donors and found higher rates of ESRD in donors, and even reduced life expectancy.[5,6] These studies, however, have some limitations because of their methodological approach.

A recent and more detailed analysis reveals that the mostly biologically related donors with presumably similar immunological diseases as the recipients have a higher risk of ESRD. Among others, genetic and racial factors are responsible for a worse renal outcome.[21,22] Donors in the present Caucasian study cohort were mostly unrelated to their recipients, of older age, and slightly overweight, indicating the trend of accepting increasingly older donors.[23,24] We found a greater decline in eGFR than expected after 12 months (37%). A minority of the TCs accepted donors with eGFR < 60 ml/min (1.5% of cases). Fenton *et al.* show that a significant proportion of healthy persons older than 60 years have eGFR < 60 ml/min. They therefore suggest implementing an age-related threshold for the acceptance of donors.[25] In the present study, 1 year after LKD, 50% of donors had persistent CKD stage 3. Higher donor age had a significant impact on

Table 5 | Distribution of donors with clinically relevant impairment in physical or psychosocial functioning at different time points

	Number of cases/no cases (%)				T0 vs. T3	
Variable (cutoff)	T0	T1	T2	T3	*P*	*r*
Kidney function						
eGFR (<60 ml/min)	5/331 (1.5)	161/147 (51.9)	133/127 (51.2)	151/149 (50.3)	<0.001	**0.70**
Quality of life (SF-36)						
VT (<42.55)	9/314 (2.8)	47/270 (14.8)	32/260 (11.0)	37/258 (12.5)	<0.001	0.24
Mental health (PHQ)						
PHQ-15 (≥10)	12/307 (3.8)	43/270 (13.7)	31/261 (10.6)	38/257 (12.9)	<0.001	0.26
Fatigue (MFI-20)						
GenFat (>12.2)	20/300 (6.3)	57/259 (17.2)	50/240 (17.2)	54/240 (18.4)	<0.001	0.28
MenFat (>10.9)	34/286 (10.6)	95/217 (30.4)	78/207 (27.4)	81/207 (28.1)	<0.001	**0.34**

eGFR, estimated glomerular filtration rate; GenFat, general fatigue; MenFat, mental fatigue; MFI-20, Multidimensional Fatigue Inventory; PHQ, Patient Health Questionnaire; *r*, effect size for the McNemar test; SF-36, short-form 36-Item Health Survey; T0, predonation; T1, 2 months postdonation; T2, 6 months postdonation; T3, 12 months postdonation; VT, vitality.
Note: Effect sizes are shown in bold if ≥0.3.

Table 6 | Multivariate regression analysis of renal function (eGFR)

Variable	Estimate (ml/min)	95% CI (ml/min)	P
Intercept	30.89	13.64 to 48.14	0.0015
eGFR at T0			
+10 ml/min	6.61	5.74 to 7.48	<0.0001
Time point of measurement			
T1 vs. T2 vs. T3			0.0167
T2 vs. T1	1.03	−0.25 to 2.31	0.1138
T3 vs. T1	1.83	0.57 to 3.08	0.0044
Age at baseline			
+1 yr	−0.31	−0.44 to −0.19	<0.0001
Hemoglobin at baseline			
+1 g/dl	−1.05	−1.67 to −0.43	0.0010
HbA1c at baseline			
+1%	−0.18	−0.42 to 0.05	0.1235

CI, confidence interval; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; T0, predonation; T1, 2 months postdonation; T2, 6 months postdonation; T3, 12 months postdonation.

decreasing kidney function. However, a patient who is young at the time of donation might have a larger lifetime risk than does an elderly donor. A limitation of our study is that it does not address a living kidney donor's lifetime risk of an adverse outcome >12 months postdonation. For now, it is not possible to conclude whether the loss of kidney function is permanent or will improve over time. Furthermore, it is questionable whether this, in the absence of renal pathology, should be regarded as a risk factor for CKD progression and increased lifetime risk of adverse health outcome.[9] Limited data are available on the course of kidney function in older healthy donors like in our cohort. As the rate of decline is widely variable across individuals of the general population, the characterization of age-dependent eGFR loss requires a larger cohort.[26,27]

Table 7 | Multivariate regression analysis of the psychosocial outcome (MFI-20, mental fatigue)

Variable	Estimate	95% CI	P
Intercept	7.49	5.11 to 9.88	<0.0001
Mental fatigue at baseline			
+1 unit	0.21	0.14 to 0.27	<0.0001
Time point of measurement			
T2 vs. T1	−0.16	−0.46 to 0.14	0.2899
T3 vs. T1	−0.27	−0.58 to 0.05	0.0954
Age at baseline			
+1 yr	0.01	−0.01 to 0.03	0.2784
School education			
High school vs. other	−1.62	−3.45 to 0.22	0.0838
Middle school vs. other	−1.17	−2.98 to 0.64	0.2037
Elementary/secondary school vs. other	−1.30	−3.10 to 0.50	0.1563
No degree vs. other	−0.56	−2.77 to 1.65	0.6186
Duration of education (school)			
+1 yr	−0.02	−0.04 to 0.01	0.1463
Smoker			
No vs. yes	−0.38	−0.79 to 0.04	0.0733
PSS-10 at baseline			
+1 unit	0.16	0.14 to 0.19	<0.0001

CI, confidence interval; MFI-20, Multidimensional Fatigue Inventory; PSS-10, Perceived Stress Scale; T0, predonation; T1, 2 months postdonation; T2, 6 months postdonation; T3, 12 months postdonation.

Increased fatigue after LKD

The SoLKiD study shows a significant increase in all fatigue dimensions except reduced motivation. The number of donors showing an extent of fatigue higher than 1SD of that in the general German population increased from 6% to 18% for general fatigue and from 11% to 28% for mental fatigue. Because no cutoff exists, the clinical relevance of changes in the individual level is difficult to evaluate. It is problematic to determine the level of fatigue causing a clinically relevant burden for a donor. The mean level of mental fatigue before donation was lower than that in the German general population.[13] This is in line with several studies showing that living donors normally represent a very healthy population. Twelve months after donation, the mean score of mental fatigue increased (mean score 9.34) and was within the range for cancer survivors (mean score 8.19),[14] patients after intensive care unit discharge (mean score 8.9),[15] outpatients awaiting surgery[16] (mean score 8.7), and patients receiving radiotherapy[16] (mean score 10.2; Figure 4). These "control" groups were ∼10 years older, and a sound comparison with fatigue scores of SoLKiD donors is not possible. The increase in mental fatigue after LKD must be stated as clinically relevant. Our data show that even upon a small change in mental fatigue (3.45 score points), our very healthy donor cohort changed into a group of chronically ill patients with regard to mental fatigue. Because a relatively healthy donor cohort was selected, the reported findings are rather an underestimation of mental health outcomes. Consequently, our results may be generalized only to individuals with similar backgrounds as those included in our study.

Data on fatigue as a complication of LKD are rare. A retrospective study ("Giessen Subjective Complaints List") reports 7% of fatigue up to 226 months after donation in an extent worse than that in the average population.[28] Kok *et al.*[29] show increased fatigue (MFI-20) in several domains, which did not recover completely within 5 years of donation.[30] Even after 10 years, most fatigue dimensions remained high. The mean increase fell in the range of 0.1 (mental fatigue) to 2.2 (general fatigue) but was rated clinically irrelevant because the predefined MFI limit of 10 points was not reached.[31] From our perspective, this conclusion is questionable. The maximum MFI score range is 16 points, showing that it is almost impossible to reach a clinically relevant change if a change of 10 points is requested. For example, if a donor experiences an increase in mental fatigue level from 5 predonation to 14, he or she would show a fatigue level as high as in oncological patients receiving radiotherapy or palliative care but in the authors' view[31] does not reflect a clinically relevant change. Irrespective of this controversy, whether an increase in fatigue is clinically relevant or not, our analysis shows that donors with signs of fatigue before LKD have a higher risk of increased fatigue 12 months postdonation. Because of the negative impact of fatigue on the

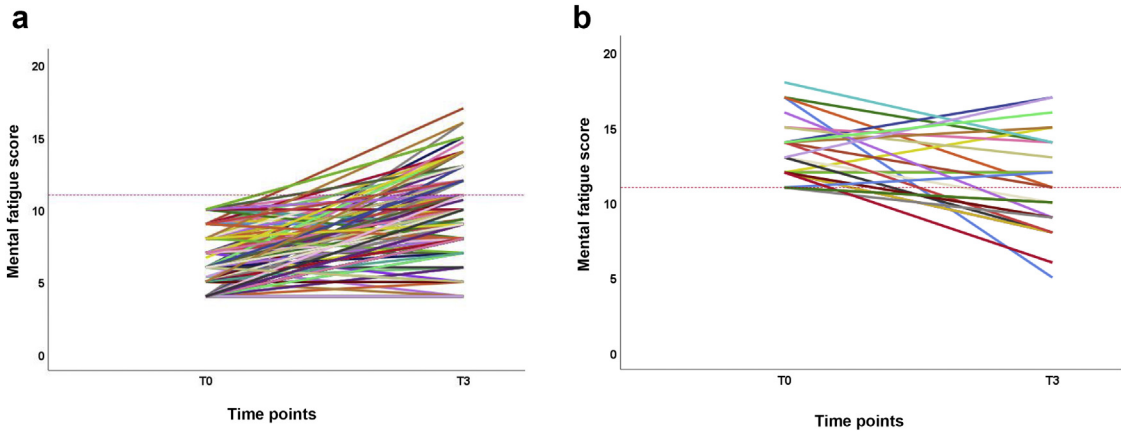

Figure 3| Course of mental fatigue (Multidimensional Fatigue Inventory [MFI-20]) from predonation (T0) to 12 months postdonation (T3) in donors under (left) and above (right) a clinically relevant score level at baseline. (**a**) The spaghetti plot shows the course of MFI-20 during follow-up from T0 to T3 of donors who had a fatigue score under a clinically relevant level before living kidney donation (LKD). (**b**) The spaghetti plot shows the course of MFI-20 from T0 to T3 of donors who had a significantly higher fatigue score above a clinically relevant level already before LKD.

QoL of donors, future studies should focus on the psychophysical etiology of fatigue after LKD and on preventive strategies.

Conclusion

This large prospective study on physical and psychosocial outcomes of donors shows that although LKD seems to be a safe procedure, impairment in kidney function and increased fatigue occurs in a significant number of donors. Our study underlines the need to inform future donors about these potential medical and psychosocial risks of LKD. Noteworthy, half of the donors developed renal impairment, but this was not correlated to changes in QoL. At this time, it is not possible to conclude whether impaired kidney function will improve or might influence the morbidity and mortality of donors. Special attention should be given to the evaluation of elderly donors because renal outcome is mainly influenced by donor age and baseline GFR. Our data show an increased risk of fatigue in subjects with signs of fatigue and stress predonation. Because it is not known *a priori* which donor will experience relevant fatigue, we should feel obliged to inform donors about the postdonation risk of fatigue, which might influence their QoL. If we could characterize the risk of negative consequences for each donor, we might be able to provide individually tailored risk information and prevention strategies for donors on risk. More work on the individual risk of a negative physical and psychosocial health outcome in living donors should be the focus of future studies.

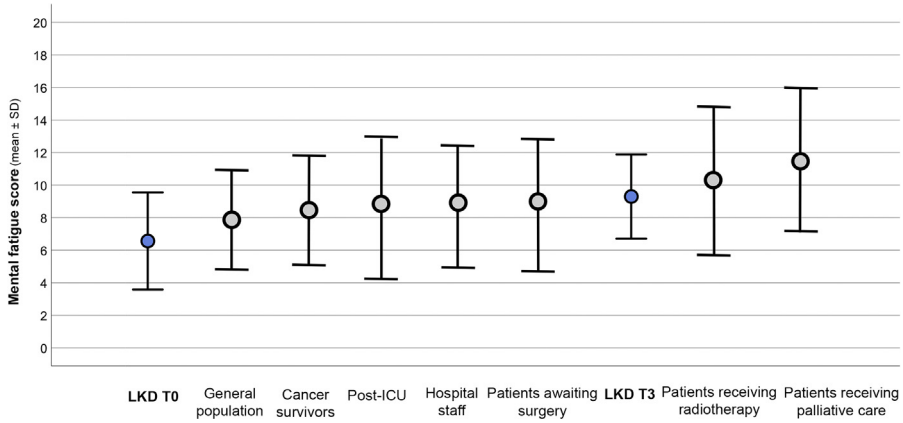

Figure 4| Mental fatigue (Multidimensional Fatigue Inventory [MFI-20]) scores in different patient populations and in the study living donor cohort. The figure depicts the level of mental fatigue in the general population,[13] hospital staff,[16] and different patient populations as patients 1 week after intensive care unit (ICU) discharge,[15] cancer survivors,[14] outpatients awaiting general surgery, oncological patients receiving radiotherapy, and oncological patients in palliative care.[16] Living donors showed a mental fatigue score lower than the score of the general population before donation. But 12 months postdonation, donors had an MFI-20 score as high as that of patients after ICU discharge or those awaiting surgery and almost in the range of oncological patients. This figure gives a clinical impression about the relevance of the increase in mental fatigue in our cohort. The group-specific scores were represented as mean (dot) and 1SD. LKD, living kidney donation; T0, predonation; T3, 12 months postdonation.

APPENDIX

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DISCLOSURE

All the authors declared no competing interests.

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AUTHOR CONTRIBUTIONS

BS, HW, KBe, and MB designed the Safety of the Living Kidney Donor (SoLKiD) study. JWOG, EB, BS, and MB performed statistical analyses and interpretation. BS, MB, and VW comprised the data analysis and writing team and received input from Klemens Budde (Member of the Charite Berlin, SoLKiD Study Group), MK, and the SoLKiD study group. BS and MB were recruiters. MK, SK, RW, LR, CS, MZ, Klemens Budde (Member of the Charite Berlin, SoLKiD Study Group), FH, KI, AH, PR, AP, AM, UF, and RW were the members of the SoLKiD study group. The manuscript was drafted by BS, MB, and JWOG and reviewed by all authors. All authors provided significant intellectual contributions to the manuscript and approved the final and revised version.

SUPPLEMENTARY MATERIAL

Supplementary File (Word)

Supplementary Methods.

Table S1. Detailed information about questionnaires and outcome variables.

Table S2. Exemplary patients with predicted estimated glomerular filtration rate (eGFR) 12 months post-donation (T3).

Table S3. Exemplary patients with predicted psychosocial outcome (Multidimensional Fatigue Inventory, mental fatigue) 12 months post-donation (T3).

Supplementary Information SI1. Sample size and power calculations.

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