# "Is the present allocation of kidney transplants optimal ? An analysis with data of the United States Renal Data System"

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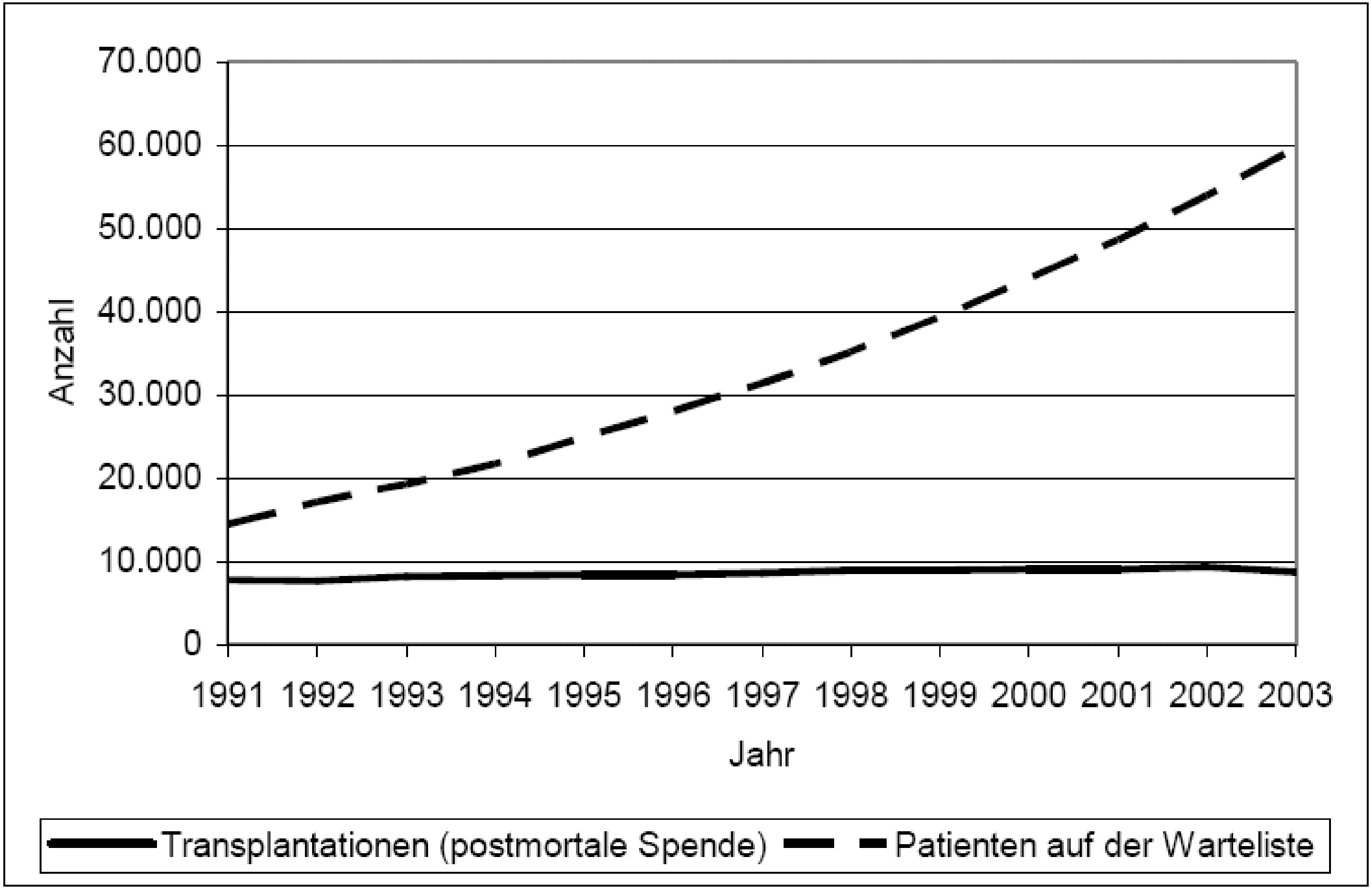
# a greater demand for donated kidneys than are available …

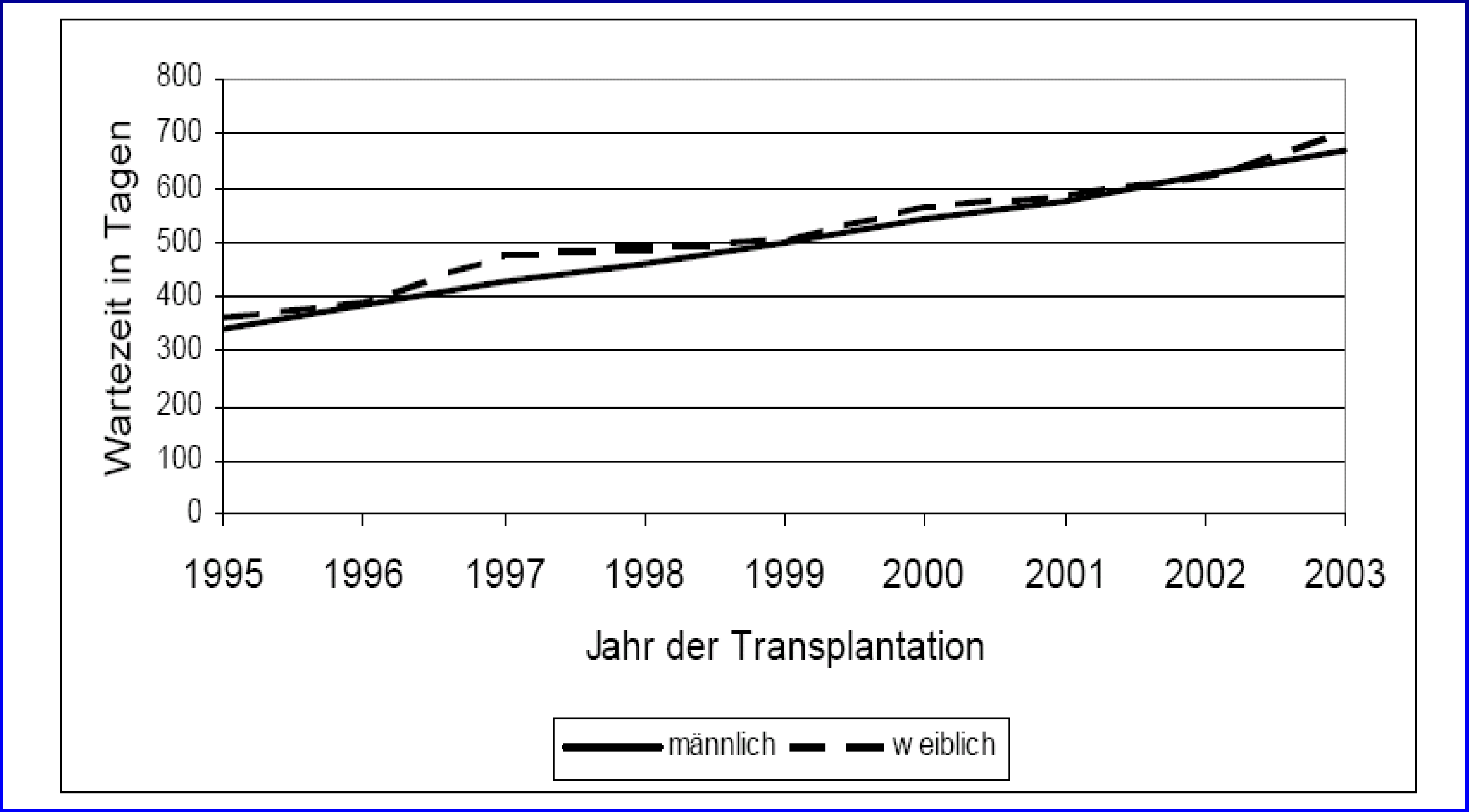
Despite all advances still it is not possible yet to provide all people who, because of a chronic kidney failure, need a kidney compensation therapy, a fully functional kidney either from a suitable animal donor ("Xeno-transplantation") or created from the patient's own body cells – some stem cells.

Thus, these patients still depend either on dialysis – quite a burdensome therapy with a greatly diminished lifespan - the supply of kidneys donated from other people. There is, however, a much greater demand for donated kidneys than are available. Consequently, not only is a considerable proportion of would-be recipients considered too ill to get a kidney at all, but also those who are found eligible, will have to wait for sometime before a suitable kidney becomes available, and, still, a substantial proportion of those found eligible, will die before a suitable organ is found for them.

# And the problem is getting worse – take the US as an example ...



# And the waiting time even for the lucky ones has doubled in just 8 years…



# Causal Morbidity

In the USA in 2003 of all new cases of End Stage Renal Disease (ESRD)

- 44% were caused by Diabetes (type 1 and 2);
- 28% were caused by high blood pressure
- 8% by Glomerulonephritis.

# The patient's immune system

the patient's immune system plays a crucial role for the short term and long term survival of the transplant in the recipient's body, and, therefore, is one of the crucial criteria for the allocation of an available kidney.

There is the HLA („human leukocyte antigens“) system. Various HLA classes are known, but important for kidney transplantation are HLA-A, HLA-B and HLA-DR classes. Donor and would-be recipient will be matched for HLA compatibility.

And there is the PRA („panel reactive antibodies“) system. Here, the would-be recipient's blood is searched for cytotoxic antibodies angainst a broad variety of frequent antigenes. A high level of immune sensibility can de derived from the proportion of offered antigenes which trigger a immune reaction – measured in percent panel reactivity. A high level of sensibility may be the result of past contact with foreign human tissue – e.g. blood transfusion, pregnancies, previous transplantations

# Scoring …

In the USA the allocation of a cadaveric kidney transplant follows a point scoring system. Eligibilty is determined by blood group match between donor and recipient.

All eligible candidates on the waiting list are scored by the following criteria (United Network for Organ Sharing UNOS, 2005):

(1) Time on the waiting list: The suitable candidate with the longest waiting time gets one point, the others get fractions of unity in relation to their individal time on the list

(2) Antigene Missmatch: No Mismatch HLA-B and HLA-DR: 7 points; one mismatch five points; two mismatches two points.

(3) Panel Reactive Antibody (PRA): patients on the list with PRA levels >=80%, i.e. highly sensibilized patients, get 4 points if the HLA test donor-recipient is negative. There are additional rules regarding PRA

(4) Age <18 years: candidates younger than 11 with no HLA mismatch get four points. Older than 11: three points.

(5) Donor-Status: candidates who have donated organs themselves (kidney, liver, lung, pankreas etc.) get four points.

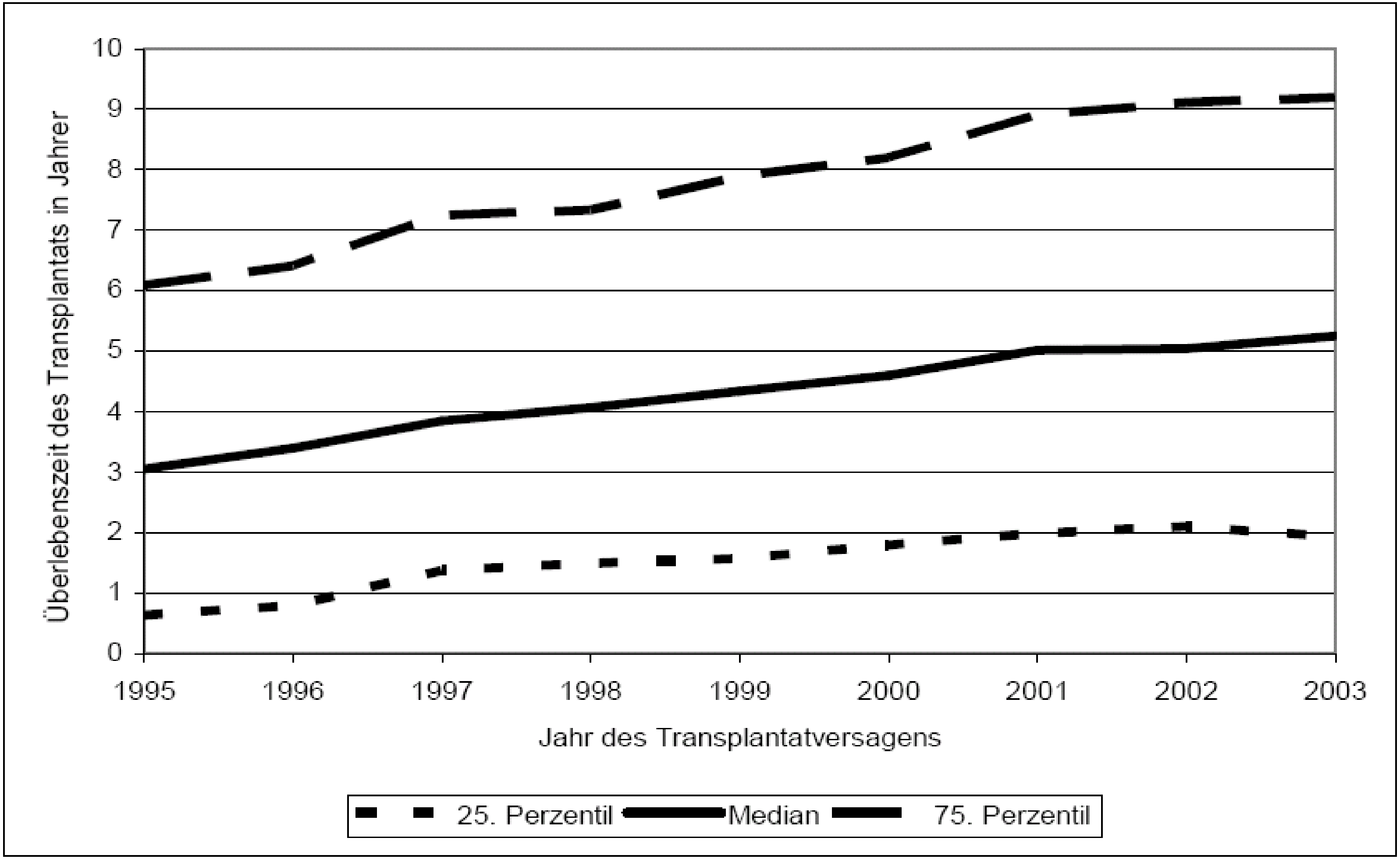
(6) Acute illness: already an acute episode of the common cold will throw you out of the race.

(7) Ethnicity, sex, SES, religion are no criteria

a kidney is a valuable thing: Remaining Life Expectancy by age and therapy status: US ESRD patients and Normal Population ...

| Age | Remaining Life Expectancy Normal US Population | Remaining Life Expectancy Under Dialysis | Remaining Life Expectancy After Transplantation | Net Gain by Transplantation |
|---|---|---|---|---|
| 0-14 | 70,9 | 18,3 | 50,0 | 31,7 |
| 15-19 | 61,1 | 16,0 | 39,7 | 23,7 |
| 20-24 | 56,3 | 13,9 | 36,2 | 22,3 |
| 25-29 | 51,6 | 12,0 | 32,3 | 20,3 |
| 30-34 | 46,8 | 10,5 | 28,5 | 18,0 |
| 35-39 | 42,1 | 9,0 | 25,2 | 16,2 |
| 40-44 | 37,5 | 7,8 | 21,9 | 14,1 |
| 45-49 | 33,0 | 6,8 | 19,0 | 12,2 |
| 50-54 | 28,6 | 5,9 | 16,3 | 10,4 |
| 55-59 | 24,4 | 5,0 | 13,8 | 8,8 |
| 60-64 | 20,4 | 4,3 | 11,5 | 7,2 |
| 65-69 | 16,8 | 3,7 | 9,6 | 5,9 |
| 70-74 | 13,4 | 3,1 | 7,9 | 4,8 |
| 75-79 | 10,4 | 2,6 | 6,7 | 4,1 |
| 80-84 | 7,8 | 2,2 | . | . |
| [illegible] | [illegible] | [illegible] | [illegible] | [illegible] |

# However, a donated kidney is not always for life



# Research Questions

1. Are there unequal chances by sex, ethnicity, and socio-economic status for getting a kidney ?

2. Is the present allocation in the USA of postmortal - donated kidneys optimal in the sense that it
   a) maximizes the total gain in general life expectancy, and
   b) minimizes the total loss in disability adjusted life years

   in the population of would-be recipients, i.e. the people on the waiting list ?

# Data

The data base is the United States Renal Data System (USRDS), containing all ESRD patients covered by MEDICARE.

Since 1972, every ESRD patient in the US is covered by MEDICARE, most of them from the first day of dialysis, the few who are not (because they have sufficient coverage from elsewhere), are covered after 36 months at most. But even of those, the „first ESRD service date (FSD)" is recorded and, once under the MEDICARE umbrella, the data situation for these cases is as good as for those who had been there from the first day of dialysis.

There were 1.270.001 patients (dead or alive) in the USRDS on 31st December 2002.

# Data

The „Dialysis Morbidity and Mortality Study (DMMS)" is a prospective follow-up of a random sample of USRDS patients, alive and receiving hemo dialysis on 31st December 1993.

There were four survey waves adminstered until 31st December 2002.

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# Data

our cases:

patients

- already on the waiting list;
- waiting only for a kidney (and no additional transplant);
- having received one transplant at most;
- no live-donor kidneys involved.

our sample: n= 1506,

554 no-transplant (154 alive + 400 dead)

952 transplant (595 alive + 357 dead)

variables = 109

# Answers to our questions ...

1. Are there unequal chances by sex, ethnicity, and socio-economic status for getting a kidney ?

We checked for effects of sex, age at „first ESRD service date (FSD)", ethnicity, education, income, employment status, family status on chances of receiving a kidney.

low age at FSD and high school graduation are strong predictors, having an Asian or European ancestry and being married are weak positive predictors for getting a kidney.

Being female is not a predictor, once the PRA („panel reactive antibodies") status is taken into account: women – mostly because of pregnancies – do have a higher PRA level.

## Answers to our questions …

2. Is the present allocation in the US of postmortal - donated kidneys optimal in the sense that it

   a) maximizes the total gain in general life expectancy
   b) minimizes the total loss in disability adjusted life years
   - in the population of would-be recipients, i.e. the people on the waiting list ?

# Answers to our questions ...

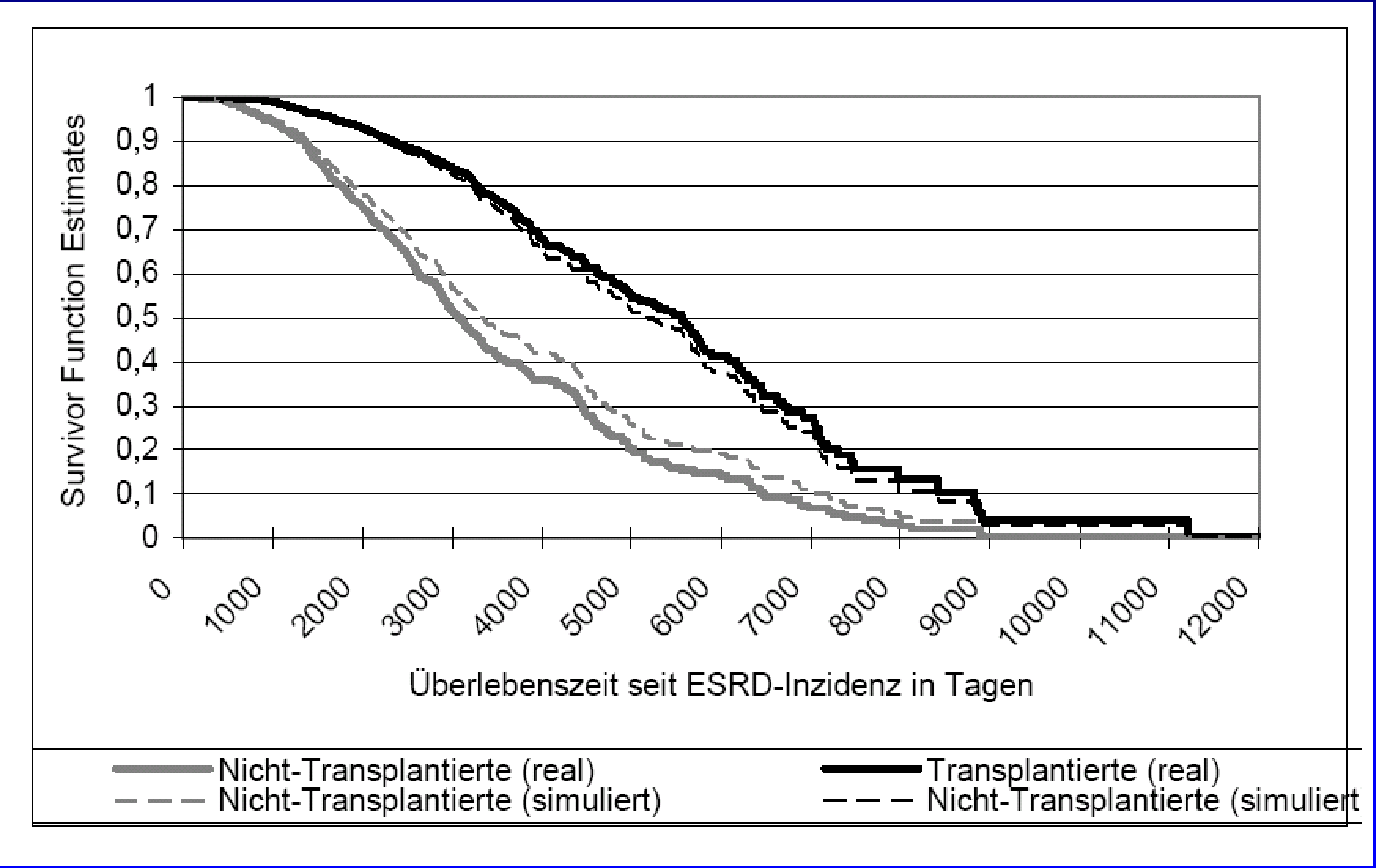
Procedure:

- Produce the (real) survival curves for non-recipients and for recipients as well.
- Identify all variables predicting the survival chances of non-recipients and of recipients as well, and, among the group of recipients, also the timing of the transplantation.
  These were sex, FSD, ethnicity, family status, employment status, education, diastolic blood pressure, serum albumin, Body Mass Index > 30, creatinine, peripheral vasculare disease, smoking status:
- Knowing the βs of the according regression models, simulate survival curves for non-recipients, asuming that all had received a transplant at the predicted time.
- Knowing the βs of the according regression models, also simulate survival curves for recipients, asuming that none had received a transplant.

# Answers to our questions ...

5. Calculate for every recipient the individual loss in life expectancy / DALYs by subtracing the simulated survival in the no-transplant condition from the real survival curve.
6. Calculate for every non-recipient the individual gain in life expectancy / DALYs by subtracing the real survival from the simulated survival curve in the transplant condition.
7. If the allocation of kidneys is optimal, even the recipient with the smallest gain in life expectancy / DALYs will have experienced a larger gain than the non recipient with the largest gain.
8. Also, the simulated survival curve for the non-recipients will always lie below the real survival curve for the recipients.

# First – just the survival ...



# First – just the survival ...

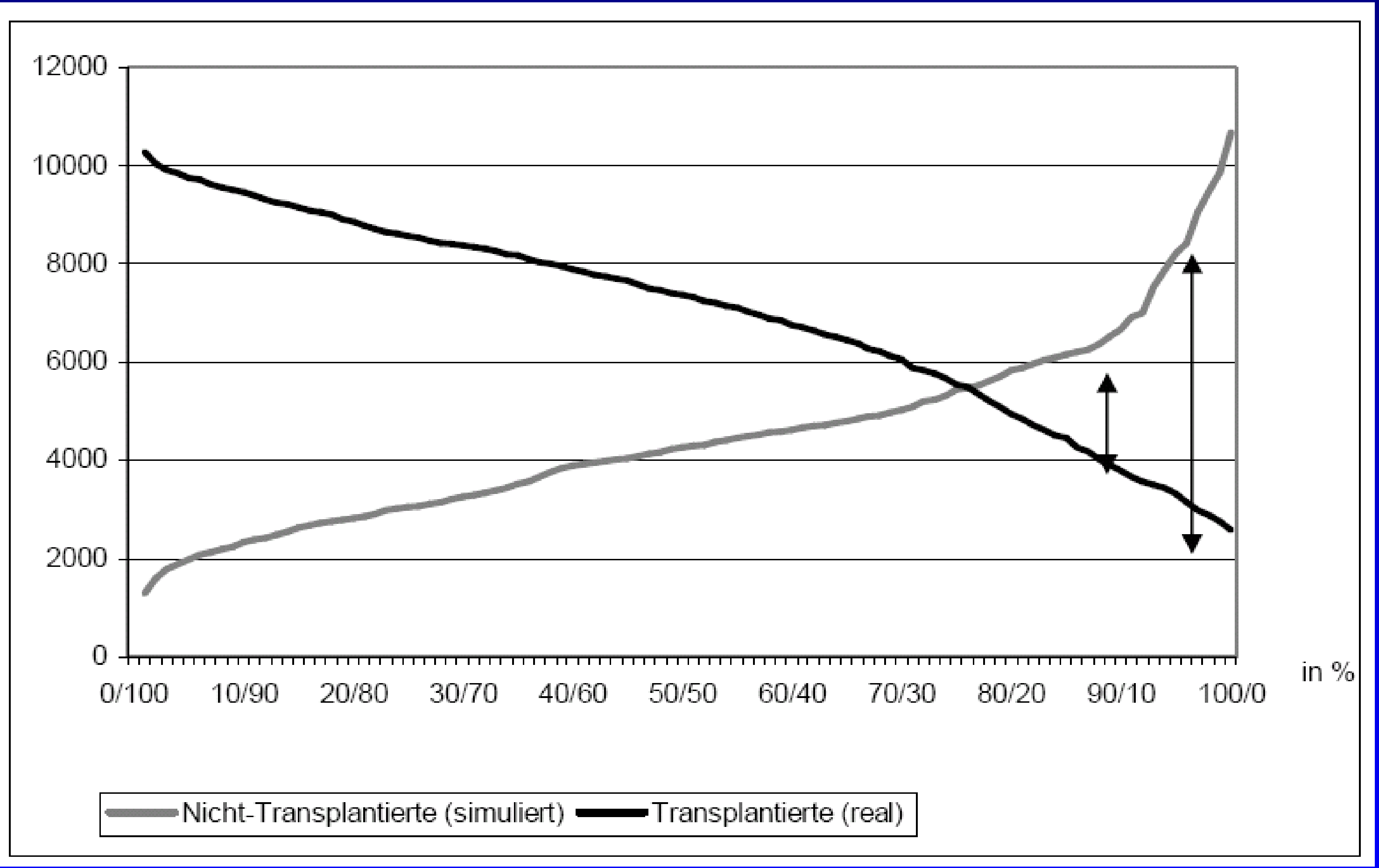
Clearly, almost every recipient would have been worse of without a transplant, and almost every non-recipient would have been better off with a transplant.

# First – just the survival ...

Next, we determine the Lorenz curves for the gain in life expectancy – real for the recipients and simulated for the non-recipients, and let the one run from left to right and the other from right to left.

Thus, a suboptimal allocation could be detected once, say, the survival gain of the 90th percentile of the non recipients would be greater than the 10th percentile of the recipients, since, in this case, those 10% of non recipients between the 90th and the 100th percentile on the Lorenz curve for the non recipients would have benefitted more from a transplant than those those 10% of non recipients between the 1th and the 10th percentile on the Lorenz curve for the recipients.

# First – just the survival ...




Arrows indicate suboptimal allocation

# First – just the survival ...

In fact, the two Lorenz curves intersect at the 76th percentile of the recipients' and at the 24th percentile of the non-recipients' curve.

That means that in one quarter of all cases of a transplantation, the kidney should better have gone to someone else on the list, who, during the whole observation time, in fact did not receive one.

# Second – the DALYs ...

There are no accepted weights for ESRD with dialysis and with transplant. In the Global Burden of Disease 2001 Study of the WHO, published just these days, there is only the cryptic estimation: *„End-stage renal disease: 0.098 (0.087–0.107), varies with age and treatment"* (Colin D. Mathers, Alan D. Lopez, and Christopher J. L. Murray (2006): Global Burden of Disease and Risk Factors. WHO 2006, p. 122.

There is just one publication on the subject: Kaminota (2001) had these weight estimated by 43 physicians with specific experiences. The raters had been given the table with the 7 disability classes and the 22 indicator conditions of the GBD 1990 project, that you all know.

The median weights given by Kaminota's physicians were 0.231 for patients under dialysis and 0.1 für patients with a transplant. We shall use these weights here.

## Gauging the severity of disability: classes and weights set by the Global Burden of Disease 1990 protocol for 22 indicator conditions

| Disability class | Severity weights | Indicator conditions |
|---|---|---|
| 1 | 0.00-0.02 | Vitiligo on face, weight-for-height less than 2 standard deviations |
| 2 | 0.02-0.12 | Watery diarrhoea, severe sore throat, severe anemia |
| 3 | 0.12-0.24 | Radius fracture in a stiff cast, infertility, erectile disfunction, rheumatoid arthritis, angina |
| 4 | 0.24-0.36 | Below-the-knee-amputation, deafness |
| 5 | 0.36-0.50 | Rectovaginale fistula, mild mental retardation, Down syndrome |
| 6 | 0.50-0.70 | Unipolare depression, blindness, paraplegia |
| 7 | 0.70-1.00 | Psychosis, dementia, severe migraine, quadriplegia |

Note: These weights were established using the person trade-off (PTO) method with an international group of health workers who met at WHO in Geneva in August 1995. Each condition is actually a detailed case. For example, angina in this exercise is defined as *"reproducible chest pain, when walking 50 meters or more, that the individual would rate as a 5 on a subjective pain scale from 0 to 10."*

# Second – the DALYs …

We do the same as for the general life expectancy: we calculate the real loss in DALYs for the recipients and the non-recipients – and simulate the loss for recipients under the no-transplant condition and for the non-recipients under the transplant condition.

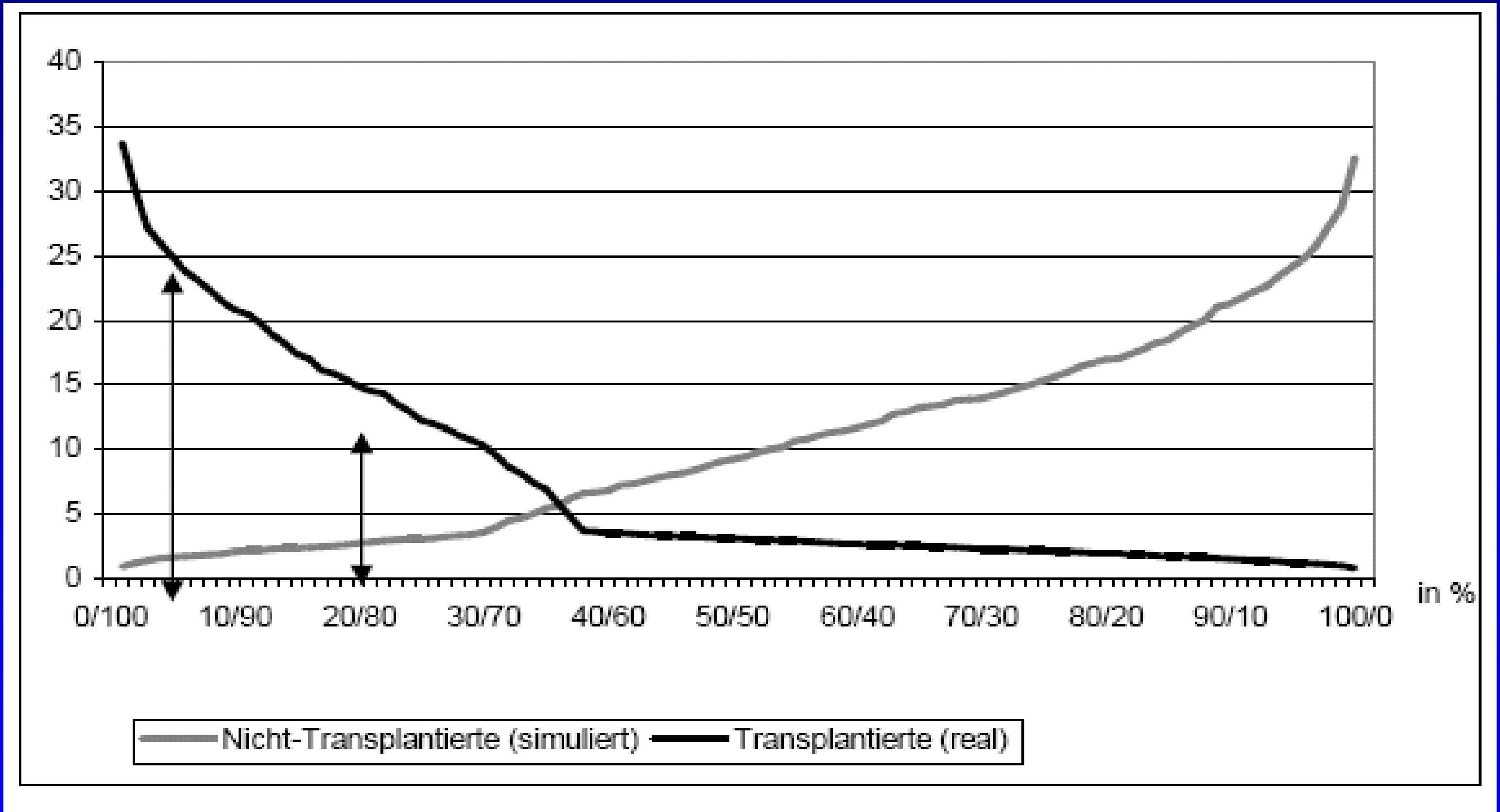
With little surprise, we find that almost all recipients would have experienced a greater loss in DALYs, had they not received a kidney, and that almost all non recipients would have experienced a smaller loss in DALYs, had they received a kidney.

# Second – the DALYs …

Next, we determine the Lorenz curves for the loss in DALYs – real for the recipients and simulated for the non-recipients, and let the one run from left to right and the other from right to left.

When interpreting the next figure, keep in mind that DALYs measure a loss, which should be minimized. That means, that top percentiles of recipients – those who despite transplantation have experienced the largest losses in DALYs – have to be compared with those non-recipients, who had experienced the smallest loss in DALYs, had they received a kidney.

# Second – the DALYs ...




Arrows indicate suboptimal allocation

# Second – the DALYs ...

In fact, the two Lorenz curves for the DALYs intersect at the 65th percentile of the recipients' and at the 35th percentile of the non-recipients' curve.

That means that, when we consider not only mortality, but also disability, in one third of all cases of a transplantation, the kidney should better have gone to someone else on the list, who, during the whole observation time, in fact did not receive one.

# Discussion

That the relative amount of misallocation is larger when we consider DALYs instead of general life expectancy may reflect that the DALY concept as defined by the WHO Global Burden of Disease project, discriminates against men and against the elderly.

It discriminates against men, because the GBD project takes it as God's will that men even in best of all environments have to live lifes which are at least 2.5 years shorter than women – and since women on the waiting list are less likely to receive a transplant because of their less favourable PRA status, the higher proportion of women among non recipients increases the loss in DALYs as compared with the gain in life expectancy.

# Discussion

It discriminates against the elderly, because in the GBD 1990 version, there is an age weighting function, reflecting that the economic value of a young adult is larger than of a child or of an elderly. So denying a kidney to a younger person and giving it to an older, but otherwise equal individual has a greater impact on DALYs than on the life expectancy. (The GBD 2001 version has disabandoned the age weighting function).

Remember that all comorbidity and the less favourable immune situation which typically comes with advancing age, is already taken into account in the allocation rules – so age beyond the 18th year should not appear as a predictor of the chance for a new kidney.

# Discussion

Since the Global Burden of Disease 2001 study has been published just a few weeks ago, we have not yet calculated the DALYs without an age weighting function – but will do.

The next obvious step would be to look into those subgroups affected by the misallocation: those recipients who gained less by a transplant than those non-recipients would have gained by getting one. It could be asked for the sociodemographic characteristics which discriminate these two groups. So far, no consistent patterns have be detected.

Remember – blacks & American natives; singles; high school drop-outs; not full-time employed persons (except housekeepers) typically ARE in poorer health – and, therefore, will have shorter lifespans in both groups: those with and without a transplant.