Nutrition and growth in European children with end-stage renal disease

Bonthuis, M.

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ADULT HEIGHT IN PATIENTS WITH ADVANCED CHRONIC KIDNEY DISEASE REQUIRING RENAL REPLACEMENT THERAPY DURING CHILDHOOD

Jérôme Harambat, **Marjolein Bonthuis**, Karlijn J van Stralen, Gema Ariceta Nina Battelino Anna Bjerre, Timo Jahnukainen, Valérie Leroy, György Reusz, Ana R Sandes, Manish D Sinha, Jaap W Groothoff, Christian Combe, Kitty J Jager, Enrico Verrina, Franz Schaefer

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Background and objectives: Growth and final height are of major concern in children with ESRD. Our aim was to describe the distribution of adult height of patients who started renal replacement therapy (RRT) during childhood, and to identify determinants of final height in a large cohort of RRT children.

Design, setting, participants, and measurements: A total of 1612 patients from 20 European countries who started RRT before 19 years of age and reached final height between 1990 and 2011 were included. Linear regression analyses were performed to calculate adjusted mean final height standard deviation score (SDS) and to investigate its potential determinants.

Results: The median final height SDS was –1.65 (median of 168 cm in boys and 155 cm in girls). Fifty-five percent of patients attained an adult height within the normal range. Adjusted for age at start of RRT and primary renal diseases, final height increased significantly over time from –2.06 SDS in children who reached adulthood in 1990-1995 to –1.33 SDS among those reaching adulthood in 2006-2011. Older age at start of RRT, more recent period of start of RRT, cumulative percent time on a functioning graft, and greater height SDS at initiation of RRT were independently associated with a higher final height SDS. Patients with congenital anomalies of the kidney and urinary tract (CAKUT) and metabolic disorders had a lower final height compared with other primary renal diseases.

Conclusions: Although final height remains suboptimal in children with ESRD, it has consistently improved over time.

ABSTRACT

INTRODUCTION

Growth failure remains one of the major long-term challenges in the management of childhood-onset end-stage renal disease (ESRD). Poor growth in ESRD children is multifactorial and influenced by nutritional, metabolic and hormonal alterations [1–3] and has been associated with an increased risk of hospitalization and death [4]. Short stature has major consequences for quality of life and self-esteem; more than one-third of young adults with childhood-onset ESRD report to be dissatisfied with their body height [5]. Short adult height is associated with major shortcomings in social and work life such as a lower level of education, a lower level of employment and a lower chance of being married [6]. Achieving a normal final height is therefore a crucial issue for children on renal replacement therapy (RRT). Improvements in the management of chronic kidney disease (CKD)-related growth failure have led to better height attainment at the time of renal transplantation (Tx) but following Tx, growth is generally not sufficient to compensate for the deficit that has been acquired pre Tx [7,8].

In children, height is reported in standard deviations scores (SDS) from the general population. In recent years, several single centre reports have specifically addressed final height after Tx in childhood [9–13]. The proportion of patients who achieved a final height within the normal range ranged from 47 to 75%, which appears considerably improved over early reports in which normal adult height was only achieved in 23 to 38% [14,15]. Growth is a marker of quality of care in childhood CKD and ESRD. Through improvement in the management of children with kidney diseases over decades, growth failure and therefore adult short stature seems to decrease in this population. In this study, we used the population-based dataset of the European Society for Paediatric Nephrology/European Renal Association and European Dialysis and Transplant Association (ESPN/ERA-EDTA) registry to describe the final height distribution of patients who started RRT while in paediatric care in Europe, to analyse trends over time and to identify potential determinants of final height SDS.

METHODS

Data collection

This study used data recorded in the ESPN/ERA-EDTA Registry. Within the registry, clinical data are collected annually as reported elsewhere [16,17]. Data obtained for the purpose of this study included: date of birth, sex, primary renal disease (PRD), date of start of RRT, treatment modality (haemodialysis (HD), peritoneal dialysis (PD) or Tx) and dates of change in treatment modality, donor source, height at start of RRT and at last follow-up. We included patients who started RRT at <19 years of age and reached documented final height between January 1, 1990 and December 31, 2011. This included data from the following 20 countries and periods of reaching final height: Belarus (2010), Czech Republic (2007-2010), Estonia (2010), Finland

(1992-2009), France (2004-2010), Greece (2010-2011), Hungary (2010-2011), Iceland (2009), Italy (1990-2011), Lithuania (2010-2011), the Netherlands (2008-2009), Norway (2008-2010), Poland (1991-2011), Portugal (2008-2010), Serbia (1997-2011), Slovakia (2010), Slovenia (2010), Spain (1990-2011), Switzerland (1990-2009) and UK (1992-2010).

Definition of variables

Height SDS was calculated according to recent national growth charts whenever available [18–25], or to newly developed Northern and Southern European growth charts [26] for those countries where recent growth reference data are unavailable. Height SDS values were calculated by the equation: SDS = (individual patient values – mean values for age and sex-matched healthy peers)/SDS values for age and sex-matched healthy peers.

Growth retardation was defined by a height SDS < –1.88 (i.e. the third percentile for height) and was categorized as moderate (–1.88 > SDS > –3.0) or severe (< –3.0 SDS). Final height was defined as the last height measurement available after 18 years of age, or, when not available, as the last height measurement when growth velocity per year was below 1 cm in boys > 17 years old and girls > 16 years old. Height at start of RRT was defined as first height available within 3 months after start of RRT or within 6 weeks for those who started RRT before 2 years of age.

To study the effect of height SDS change from start of RRT to final height measurement, we included only children with a potential for catch-up growth i.e. those <16 years old in this study. Time on RRT was defined as the time interval between start of RRT and either the last available height measurement or the age of 19, whichever occurred first. Renal diseases were grouped by primary renal disease code for paediatric patients, according to the ERA-EDTA Registry coding system [27].

Data analysis

Patient characteristics are presented as median and interquartile range (IQR) for continuous variables, and percentages for categorical variables. For comparison over time, only patients from countries with a complete follow-up of patients reaching final height over the last two decades were included.

To investigate the relationship between final height SDS and potential determinants univariable and multivariable linear regression analysis were used. Adjustments were made for possible confounders which were chosen based on a priori considerations and criteria for confounding [28]. Adjusted mean final height SDS was recalculated using the distribution in all cases. Variables included in adjusted analyses were age at start of RRT (0-<2 years, 2-<5 years, 5-<13 years, ≥ 13 years), period of start of RRT by decade (< 1990, 1990-1999, 2000-2010), country, sex, primary renal disease category, first modality of RRT (HD first, PD first or Tx first), percentage of lifetime and on RRT time on Tx, and height SDS at start of RRT. Statistical analyses were performed using SAS 9.2 software.

RESULTS

Baseline characteristics

Data were obtained from 1612 children on RRT from 20 countries who reached adult height between 1990 and 2011. Median age at start of RRT was 12.8 years, 53.8% were male and median age at final height measurement was 19.0 years (Table 1). Congenital anomalies of the kidney and urinary tract (CAKUT) were the most frequent underlying disease (40.4%) followed by glomerulonephritis (17.9%). Children received equally commonly PD (41.1%) and HD (41.4%) as initial RRT modality, whereas 17.5% started with a pre-emptive renal Tx. Median time on RRT was 5.7 years (IQR 2.9-9.4). At the time of final height measurement, 73.7% of patients had a functioning renal allograft, 17.2% were on HD and 9.1% on PD (Table 1).

Final height and prevalence of short stature

Boys reached a median final height of 168 cm (IQR 161-173); median final height SDS was –1.57 (IQR –2.56 to –0.81). Median final height in girls was 155 cm (IQR 149-161); median final height SDS for girls was –1.67 SDS (IQR –2.70 to –0.76). The difference between boys and girls was not significant (p=0.72). Overall, the median final height SDS was –1.65 (IQR –2.64 to –0.78); 57.4% had attained an adult height within the normal range, whereas 23.5% exhibited moderate (–1.88 > SDS > –3.0) and 19.1% severe (< –3 SDS) adult height deficits. At the time of final height measurement, body mass index (BMI) values were within the normal range in most patients with a median of 21.2 (IQR 19.2-24.0) in boys and 21.2 (IQR 19.0-24.4) in girls.

Table 1. Demographics and characteristics of the population (n=1612)

Variables		N (%)	Median (IQR)
Sex	Male	868 (53.8)	
	Female	744 (46.2)	
Primary renal disease	CAKUT	651 (40.4)	
	Glomerulonephritis	288 (17.9)	
	Hereditary nephropathy	117 (7.3)	
	Cystic kidney disease	189 (11.7)	
	Haemolytic uremic syndrome	48 (3.0)	
	Ischemic renal failure	22 (1.3)	
	Metabolic disorder	72 (4.5)	
	Vasculitis	54 (3.3)	
	Miscellaneous	93 (5.8)	
	Unknown or missing (12 missing)	78 (4.8)	
Age at start of RRT, years			12.8 (9.0 - 15.6)
Age at start of RRT, years	0-<2	70 (4.3)	
	2-<5	98 (6.1)	
	5-<13	540 (33.5)	
	13-<17	713 (44.2)	
	≥ 17	191 (11.9)	
Height SDS at start of RRT (n=915)			–1.56 (–2.75;–0.44)
Treatment modality at start of RRT (33 missing)	HD	648 (41.1)	
	PD	654 (41.4)	
	Tx	277 (17.5)	
Period of start of RRT	< 1990	224 (13.9)	
	1990-1999	693 (43.0)	
	2000-2011	695 (43.1)	
Age at time of final measurement, years			19.0 (18.1 - 19.0)
Number of RRT modalities	1	418 (25.9)	
	2	685 (42.5)	
	≥3	509 (31.6)	
Time on RRT at final height measurement, years	0-<2	269 (16.7)	
	2-<5	422 (26.2)	
	5-<10	542 (33.6)	
	10-<15	260 (16.1)	
	≥15	119 (7.4)	
% lifetime with functioning graft			15.9 (0.0-34.7)
Treatment modality at final height measurement (28 missing)	HD	272 (17.2)	
	PD	145 (9.1)	
	Tx	1167 (73.7)	

Longitudinal trends in final height

In the countries with complete follow-up information in the period 1990-2011 (n=981 patients), the overall proportion of patients with an adult height in the normal range rose from 49.6% in children who reached adulthood in 1990-1995 (median final height –1.90 SDS) to 62.2% among those reaching adulthood in 2006-2011 (median final height –1.41 SDS) (*P*=0.05) (Figure 1). Final height SDS improved significantly in both boys (from a median of –1.87 in 1990-1995 to –1.32 in 2006-2011) and girls (from a median of –2.15 in 1990-1995 to –1.67 in 2006-2011). The trend in final height change became more significant (from –2.06 in 1990-1995 to –1.33 SDS in 2006-2011) after adjustment for age at start of RRT and PRD. Furthermore, the improvement over time became clearer when stratifying by age and period of start of RRT. Adjusted final height increased significantly from –1.93 SDS (IQR –2.13 to –1.70) in children who started RRT before 1990, to –1.78 (IQR –2.01 to –1.53) in children starting RRT in 1990-1999, and to –1.61 (IQR –1.81 to –1.34) in those commencing RRT after 1999 (p <0.001) and the improvement in final height over time was seen within all categories of age at RRT start (Figure 2).

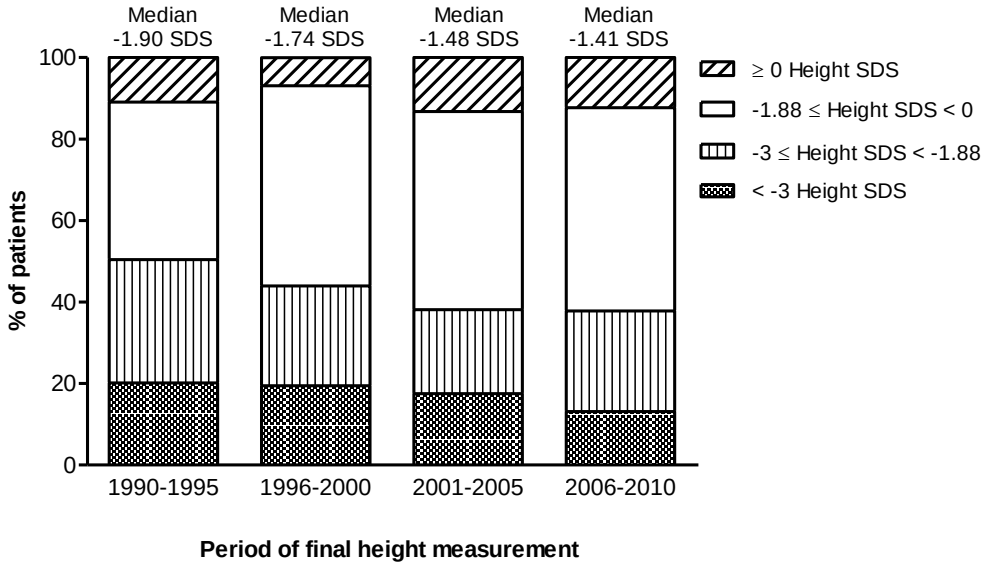

Figure 1. Distribution of height SDS by period of reaching adulthood (n=1612)
Abbreviations: SDS standard deviation score

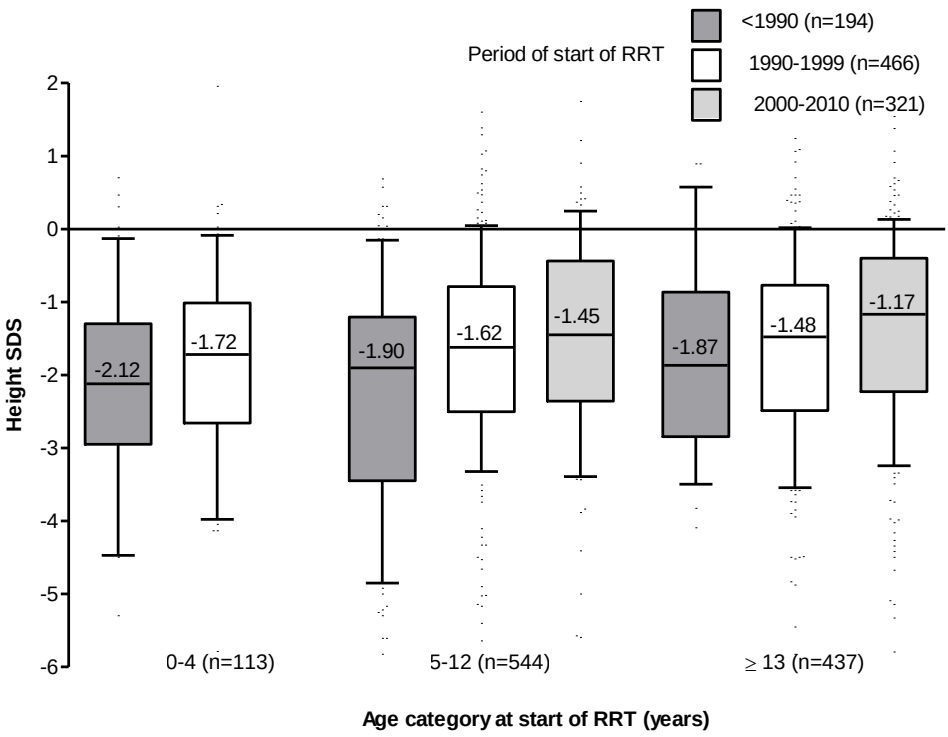

Figure 2. Changes in final height SDS over time according to age and period of start of RRT (n=981)

The horizontal line in the middle of the box represents the median, the bottom and top of the box represent the lower and upper quartiles, respectively, and the ends of the whiskers represent the 10th and the 90th percentiles.
Abbreviations: SDS standard deviation score; RRT renal replacement therapy

A height measurement at start of RRT was available for 566 patients (58%) in patients from countries with complete follow-up information. The adjusted height SDS change by year spent on RRT from start of RRT to final height measurement did not significantly differ by the period of start of RRT. In the early period of RRT (before 1990) height SDS change was –0.04/year on RRT (95% CI: –0.10 to + 0.02/year on RRT), whereas it was –0.11/year on RRT (95% CI: –0.26 to +0.05/year on RRT) in a more recent period of RRT (2001-2006). When we selected only those patients who started RRT before 16 years of age (children with growth potential), there was a significant improvement over time in the change in height SDS from start of RRT to final height SDS (Figure 3). Although not significantly, height SDS at start of RRT improved over time, it was –1.65 in the early period of RRT and –1.32 when starting RRT from 2001-2006 (*P*=0.37).

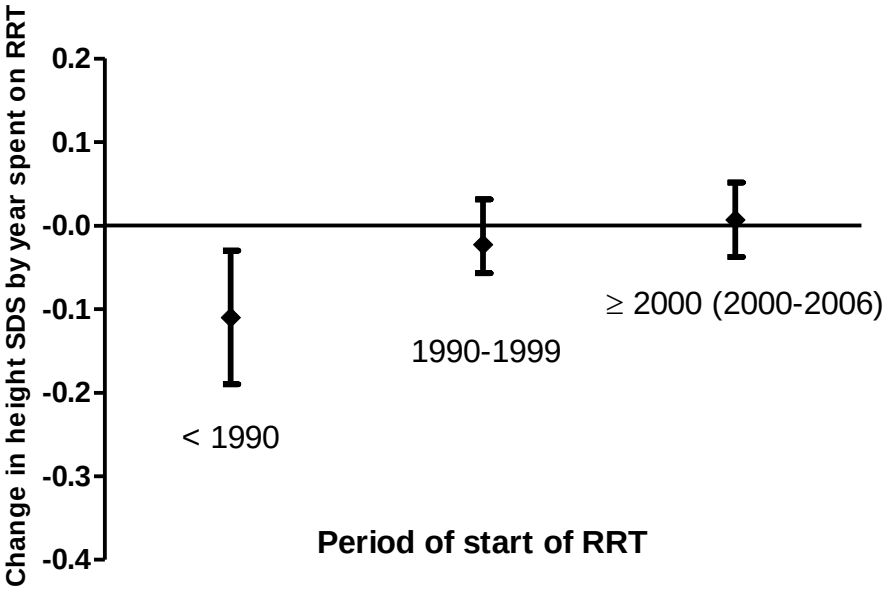

Figure 3. Mean yearly change in height SDS from start of RRT to final height measurement by period of start of RRT (n=458)
In patients who started RRT <16 years, the change in height SDS between start of RRT and final height SDS significantly improved (p=0.02). Analyses were adjusted for age at start of RRT.
Abbreviations: SDS standard deviation score; RRT renal replacement therapy

Factors associated with final height

Older age at start of RRT (i.e. children ≥ 13 years at start of RRT vs. other age categories), a more recent period of start of RRT (2000-2010 and 1990-1999 vs. RRT < 1990), the percentages of lifetime on Tx and RRT time on Tx, and a higher height SDS at time of RRT start were independently associated with a significantly higher adjusted final height SDS (Tables 2 and 3). For 49.4% of the children commencing RRT before the age of 13 years, the final height SDS was below -1.88. Furthermore, after adjustment for sex, age and period of start of RRT, patients with CAKUT were significantly shorter at final height as compared to those with glomerulonephritis, cystic kidney diseases, hereditary nephropathy, HUS, vasculitis, and children in the group miscellaneous aetiologies, while patients with metabolic disorders were significantly shorter than those with CAKUT (Table 2). In the subgroup of patients with cystinosis or oxalosis (n=66), the adjusted final height SDS was –2.54 (IQR –2.91 to –2.16).

Pre-emptive Tx as initial RRT modality was associated with a significantly better adult height SDS as compared to PD and HD, but after adjustment for time on Tx no significant differences between initial treatment modalities were found (Table 2).

Table 2. Factors associated with final height SDS: categorical variables (n=1612)

Variable	Unadjusted		Adjusted#	
	Mean final height SDS (95% CI)	P value*	Mean final height SDS (95% CI)	P value*
Sex			Adjusted for [1, 2]	
Boys	–1.80 (–1.91; – 1.70)	Reference	–1.79	
Girls	–1.77 (–1.92 ;–1.62)	0.68	–1.79 (–1.93 - –1.64)	0.94
Age at start of RRT (years)			Adjusted for [2, 3, 4]	
≥ 17	–1.49 (–1.60; –1.39)	Reference	–1.48	Reference
13-<17	–1.55 (–1.79; –1.30)	0.08	–1.60 (–1.85 - –1.35)	0.33
5-<13	–2.03 (–2.27; –1.78)	< 0.0001	–1.95 (–2.21 - –1.69)	0.0003
2-<5	–2.26 (–2.63; –1.89)	< 0.0001	–2.17 (–2.57 - –1.78)	0.0005
0-<2	–2.16 (–2.58; –1.75)	< 0.0001	–2.16 (–2.60 - –1.71)	0.0029
Period of start of RRT			Adjusted for [1, 4]	
< 1990	–2.40 (–2.60; –2.20)	Reference	–2.17	Reference
1990-1999	–1.84 (–2.06; –1.61)	< 0.001	–1.76 (–1.99 - –1.53)	0.0005
2000-2010	–1.54 (–1.86; –1.32)	< 0.001	–1.70 (–1.95 - –1.44)	0.0003
Treatment at start of RRT			Adjusted for [1, 2, 3, 4]	
PD	–1.91 (–2.02; –1.79)	Reference	–1.86	
HD	–1.73 (–1.89; –1.56)	0.03	–1.81 (–1.99 - –1.62)	0.52
Tx	–1.65 (–1.86; –1.43)	0.02	–1.57 (–1.80 - –1.41)	0.006
Primary renal disease			Adjusted for [1, 2, 3]	
CAKUT	–2.00 (–2.12; –1.88)	Reference	–2.01	Reference
Glomerulonephritis	–1.52 (–1.73; –1.31)	< 0.0001	–1.56 (–1.77 - –1.36)	<0.0001
Hereditary nephropathy	–1.46 (–1.76; –1.16)	0.0004	–1.30 (–1.60 - –1.01)	<0.0001
Cystic kidney disease	–1.75 (–2.00; –1.51)	0.05	–1.70 (–1.95- –1.46)	0.01
HUS	–1.41 (–1.86; –0.96)	0.01	–1.28 (–1.72 - –0.84)	0.001
Vasculitis	–1.19 (–1.61; –0.77)	0.0002	–1.33 (–1.74 - –0.92)	0.001
Metabolic disorder	–2.59 (–2.93; –2.22)	0.002	–2.55 (–2.91 - –2.19)	0.003
Miscellaneous	–1.59 (–1.89; –1.29)	0.008	–1.61 (–1.90 - –1.31)	0.008

* Difference from reference population

Adjustment for possible confounding factors: [1] age at start of RRT; [2] period of RRT; [3] sex; [4] PRD

Abbreviations: SDS standard deviation score, RRT renal replacement therapy, PD peritoneal dialysis, HD haemodialysis, Tx renal transplantation, CAKUT congenital anomalies of the kidney and urinary tract, HUS haemolytic uremic syndrome, PRD primary renal disease

Table 3. Factors associated with final height SDS: continuous variables (n=1612)

Variable	Unadjusted		Adjusted#	
	Mean final height SDS (95% CI)	P value	Mean final height SDS (95% CI)	P value
Height at start of RRT			Adjusted for [1, 2, 3, 4]	
Per 1 SDS increase	+0.38(0.34; 0.43)	< 0.0001	+0.37 (0.32 ; 0.41)	< 0.0001
% lifetime RRT			Adjusted for [1, 2, 3, 4, 5]	
Per 10% increase	–0.09 (–0.12; –0.06)	<0.0001	+ 0.04 (–0.01; 0.09)	0.11
% lifetime with functioning graft			Adjusted for [1, 2, 3, 4, 5]	
Per 10% increase	+0.008 (–0.03; 0.04)	0.64	+0.19 (0.15; 0.24)	< 0.0001
% RRT time with functioning graft				
Per 10% increase	+0.06 (0.04; 0.08)	< 0.0001	+0.10 (0.07; 0.12)	< 0.0001
Years with functioning graft				
Per additional year	+0.004 (–0.01; 0.02)	0.62	+0.10 (0.08; 0.12)	< 0.0001
% RRT time on dialysis				
Per 10% increase	–0.06 (–0.08; –0.04)	< 0.0001	–0.10 (–0.12; –0.08)	< 0.0001
Years on dialysis				
Per additional year	–0.16 (–0.19; –0.13)	< 0.0001	–0.14 (–0.17; –0.11)	< 0.0001

Adjustment for possible confounding factors: [1] age at start of RRT; [2] period of RRT; [3] sex; [4] PRD; [5] initial RRT modality
Abbreviations: SDS standard deviation score, RRT renal replacement therapy, PRD primary renal disease

DISCUSSION

This Europe-wide adult height study, the first of its kind since early reports by the ERA-EDTA registry [29], demonstrates the size of the problem of growth failure in children with ESRD. Around 50% of the children requiring RRT before their 13th birthday grew to a final height below the third percentile. A fifth of patients with childhood-onset ESRD attained an adult height more than 3 SD below the mean, a degree of stunting highly likely to impact on social integration and quality of life [5,6,30]. These growth outcomes are in keeping with data of the NAPRTCS registry [8]; the slightly better mean adult height SDS figures in the North American Registry (–1.46 vs. –1.65 in this study) are largely explained by differences of the reference datasets [26] whereas absolute heights were almost identical to even slightly better as compared to the NAPRTCS (girls 154 cm, boys 166 cm) and our registry (girls 155 cm, boys 168 cm).

At first glance the analysis of longitudinal trends in height outcomes appears disappointing, with a global height gain of 0.49 SDS, i.e. 2.5 cm, between the patients attaining adult height before 1995 and those who did after 2005. However, this modest improvement was clearly related to changes in population characteristics, as an increasing fraction of children with early-onset ESRD due to severe renal malformations and/or multisystem disease was admitted to paediatric RRT programs and survived to adulthood over time. Also, patients with

congenital malformations and inherited metabolic disorders achieved a significantly smaller adult height than patients with disorders typically manifesting in later childhood. When adjusting for the age at RRT start and primary renal diagnosis, a more significant 0.73 SDS increase in adult height over time became apparent.

Multivariable analysis revealed several factors related to the timing and choice of RRT which appear critical for final height outcomes in childhood-onset ESRD. The most important predictor of an acceptable final height was a late need for RRT during the paediatric age. However, height SDS did not change significantly between onset of RRT and final measurement. The overall impact of the RRT on final height was neutral throughout the observation period, among the overall population. Moreover, height at start of RRT increased by 0.4 SDS from the early period to the more recent years of starting RRT. This would suggest that the observed moderate improvement of final height over time was mainly due to better growth management during the pre-ESRD period and any strategies to prevent or correct CKD-associated growth failure [31–34] are most likely to be effective before ESRD has occurred. However, when studying only those patients with a greater "growth potential" on RRT, namely only the patients younger than 16 years old at start of RRT, the change between height at start and final height measurement significantly improved over time (Figure 3). This finding that height SDS no longer declines after RRT also suggests overall improvement in the care of ESRD over the years.
Regarding the choice of RRT once required, the fraction of childhood lifetime spent on dialysis adversely predicted final height. This finding is consistent with reported longitudinal data on growth on dialysis demonstrating a decrease in height SDS over time [1,8], and the negative impact of the fractional lifetime spent on dialysis on adult height previously noted in patients on long-term recombinant human Growth Hormone (rhGH) therapy [32]. Conversely, the time spent with a functioning allograft was positively associated with final height outcome.

In our study, no data on dose and duration rhGH were available to estimate its impact on final height but we found that only a small proportion population (approximately 20%) has been treated by rhGH while on RRT. Although previous reports suggested a positive effect of rhGH on final height in children with CKD [32,35] and support its use during RRT, it is noteworthy that the currently approved European indication for the drug is limited to patients on dialysis and allograft recipients with impaired glomerular filtration rate.
Further research will be required to develop optimization strategies that will facilitate better growth outcomes in this challenging population.
This study has several limitations. The lack of detailed data on treatments such as steroids, supplemental feeding, and rhGH precluded an assessment of the relative impact of these therapies on final height. We also did not have sufficient information on ethnicity, syndromic short stature and comorbidities that influence growth and final height [36] neither have data

on pubertal status or mid parental height. Also, one might imagine that children who died are more likely shorter than those who survived and reached final height [4]. Finally, although adult height has been assessed at an average age of 19 years, some patients might not have reached their definite final height at last measurement. Indeed, delayed puberty has been associated with late growth after the age of 18 in children with ESRD [11,37]. This finding, however, has not been reported in more recent studies reporting normal puberty post Tx [38]. The strengths of the study include the large data set, the long-term follow-up including complete coverage of sequential RRT modalities, and the rather detailed patient characterization allowing a comprehensive analysis of potential effectors of final height. Even if we cannot fully ascertain case completeness in the ESPN/ERA-EDTA registry, most national registries have specific procedures insuring data quality and coverage.

In conclusion, although more and more challenging paediatric patients have been accepted into RRT programs, including neonates and children with severe comorbidities, final height has consistently improved over the years. New approaches are needed to improve longitudinal growth and adult height prognosis after childhood-onset ESRD.

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