on a low protein diet supplemented with keto analogs, relative to patients with an unrestricted diet. Beyond nutritional therapy and amino acid supplementation, intensive dialysis regimens or anti-inflammatory or antioxidant drugs could be other therapeutic tools to lower the carbamylation process in CKD patients.

Conclusion
The findings reported in the present study are highly original. They extend our knowledge on sortilin’s contributions to the cardiovascular complications of patients with CKD, particularly cardiovascular calcification, the potential deleterious role of post-translational modifications of molecules such as sortilin, and the importance of the carbamylation process in the pathogenesis of CKD complications in general (Figure 1). However, as always with interesting research, it opens the door for exciting new opportunities to explore unanswered questions, in this case questions regarding sortilin biology and actions to distinguish causal implication from an innocent bystander role. To cite but a few among the open questions: What is the relative contribution of different forms of sortilin (cellular, circulating, or vesicle-packed sortilin) in its actions in CKD? What is the molecular mechanism contributing to the release and post-translational modification of circulating sortilin in this condition? How can we reduce serum sortilin levels and inhibit the carbamylation process? Finally, will clinical intervention trials aimed to modify circulating carbamylated sortilin levels be able to prevent CAC or other cardiovascular complications of patients with CKD?

DISCLOSURE
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Modeling pulse wave velocity trajectories—challenges, opportunities, and pitfalls
Georg Heinze1, Jeppe Christensen1 and Maria C. Haller1,2

In this commentary, we discuss the analysis of trajectories of pulse wave velocity in a longitudinal cohort study of children with chronic kidney disease (the Cardiovascular Comorbidity in Children with Chronic Kidney Disease – Transplantation study). We revisit the analysis made by the study authors and unravel some additional limitations. We also reevaluate the implicit assumptions that were made in the chosen analysis and suggest extensions of the basic linear mixed model to obtain more differentiated answers to research questions in nephrology.

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see clinical investigation on page 585

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The analysis of the Cardiovascular Comorbidity in Children with Chronic Kidney Disease – Transplantation (4C-T) study suggests that the cardiovascular burden in girls with chronic kidney disease (CKD) is increased before and after kidney transplantation compared to boys. The authors used linear mixed models to analyze trajectories of pulse wave velocity z scores (PWVzs) over a period...
spanning from several years before transplantation to several years afterward.

Patients were selected for this analysis only if they had kidney transplantation during follow-up. Children with CKD who never were transplanted as they never progressed to end-stage kidney disease or children who received only dialysis as kidney replacement therapy (KRT) were not included. For this reason, all analyses on the “pre-KRT” and reported pre-transplant trajectories of PWVzs have to be interpreted with caution, as they describe only those children for whom it was already “known in advance” that the analysis era will end with KRT and transplantation. Hence, the key conclusion “that time acts differently on the cardiovascular burden between boys and girls during CKD” is probably not supported by the analyses, at least not for the period before KRT. To answer the question how time acts on the cardiovascular burden during CKD before kidney transplantation, one should have included children with CKD, irrespective of whether they were eventually transplanted, as this information is unknown at the time of decision making. The finding that pre-KRT PWVzs increased more rapidly in girls than in boys may well be a result of reverse causation: a more rapid increase in PWVzs in girls may just reflect their faster CKD progression, which is why they have been transplanted more likely. According to Table 1 of Sugianto et al.,¹ the underlying kidney disease in girls was more often non-congenital anomalies of the kidney and urinary tract, which could explain a faster CKD progression in genetic or glomerular diseases. This and other prognostic factors for transplantation could have been studied by fitting a prediction model (on the whole cohort of the 4C study) with PWVzs and estimated glomerular filtration rate as longitudinal markers, but this was not done.”

Nevertheless, the chosen study design is appropriate for analyses and conclusions concerning post-transplantation trajectories of PWVzs. Here the authors used linear mixed models to evaluate whether the steepness of the increase of PWVzs differed between boys and girls and to assess possible mediators of a slope difference. Linear mixed models are a family of (several) statistical methods to analyze dependent outcome data, that is, data where several observations of an outcome variable are available for the same individuals and hence extend methods for univariate outcomes. As explanatory variables, such models may incorporate variables that vary between individuals (such as sex or baseline characteristics) but also variables that vary within individuals (such as time since transplantation). Moreover, these models are able to incorporate 1 or several random effects to accommodate interindividual variation that the independent variables cannot explain.

In the present work, the authors used a basic parametrization of a linear mixed model and presented 3 models. Their “basic model” includes an interaction of time and sex to study if the slope differed between girls and boys. This model further uses a binary indicator of congenital anomalies of the

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**Figure 1 | Schematic of modeling trajectories (e.g., of pulse wave velocity z scores [PWVzs]) with a linear mixed model.** An individual’s expected trajectory is defined by intercept and slope. Both intercept and slope may depend on the individual’s values of baseline variables (fixed effects F that code known information about individuals). A linear mixed model also allows one to account for unknown information about individuals that may affect intercept and slope. This unknown information enters as random effects R. Variables (F or R) assumed to affect the intercept are included in the model. Variables (F or R) assumed to affect the slope are included in the model with their interaction with time (F × time, R × time).

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1. Sugianto et al. (2022)
kidney and urinary tract and time on dialysis as adjustment variables. The results show that girls have higher PWVzs post-transplantation than do boys, but the slope is similar between the sexes (0.12 z units per year in boys and 0.112 in girls). In the second, “prefinal,” model, the authors removed the interaction term but included diastolic blood pressure z scores and cholesterol as further adjustment variables. The third, “final,” model included an interaction of the pre-KRT estimated glomerular filtration rate slopes with sex, as well as 2 binary variables, 1 for girls and 1 for boys, indicating whether time from the first occurrence of estimated glomerular filtration rate ≤ 30 ml/min per 1.73 m² to transplantation was ≤ 1 year. Inclusion of these additional variables showed that the pre-KRT estimated glomerular filtration rate slopes affected post-transplantation PWVzs more in girls than in boys, and likewise that a shorter time to transplantation led to higher post-transplantation PWVzs, again more in girls than in boys. Neither the prefinal nor the final model indicates whether any variables also affected the speed of increase in PWVzs after transplantation, because interactions with time were not included and hence could not be evaluated.

By contrast, these models assumed (rather than revealed) that the slope of post-transplantation PWVzs was the same in girls and boys. All variables that were entered were assumed to affect the magnitude of all post-transplantation PWVzs similarly, whether measured immediately after KRT or years after KRT, but not their slope. In the title to Supplementary Table S5 of Sugianto et al., one finds the explanation that “covariates which...eliminate the association (p>0.05) between PWVzs and the interaction term [pre-KRT time*sex (girls)] were then further included in the backward selection process.” Such a binary view on significance usually leads to wrong conclusions, as a P value indicating nonsignificance does not indicate that the interaction becomes irrelevant or should even be eliminated from the model. Moreover, the models should have been extended to allow these variables to affect the slopes, by additionally including interaction terms of these variables with time post-KRT. The challenge in such extended models is then to interpret them correctly, and unfortunately this may be the reason why such models, although being powerful enough to study determinants of both magnitude and trends, are underused in the clinical literature. A further extension of such models allows the slope to vary between individuals in addition to the variation explained by the measured covariates. In this way, each individual is assigned their own slope, and the model adapts more appropriately to interindividual variation (Figure 1). Such random coefficient models are important to model longitudinal outcomes in nephrology to identify patients at high risk for a rapid decrease in kidney function, as slopes are not directly observable and hence should not be used as the target of modeling, as this would neglect the error made in estimating the slopes, which may even vary between individuals with different number of measurements. Moreover, the linear mixed model should be preferred because it appropriately takes into account all information from all patients, even those contributing only 1 measurement; performs a single-stage estimation; accommodates an unequal number of measurements per individual; and allows one to investigate which factors are associated with baseline values and slopes. Joint models are extensions of mixed models to accommodate informative dropout that cannot be explained by covariates.

Statistical methodology has seen substantial development in recent decades, but unfortunately, many of these methodological developments are ignored in practice, probably because researchers, reviewers, and editors are reluctant to adopt new methodology, even if simple methods are not sufficient to analyze complex data. The series “XYZ of Statistics” in Kidney International, other statistical series in medical journals, or global collaborations such as the STRATOS (STRengthening Analytical Thinking for Observational Studies) initiative were initiated to change this by providing guidance to researchers dealing with the complexities of modern medical data.

**DISCLOSURE**

All the authors declared no competing interests.

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Sex differences in cardiovascular disease burden in children with chronic kidney disease

Ashlene M. McKay¹ and Chia Wei Teoh¹,²

Cardiovascular disease is the leading cause of death in children and adults with chronic kidney disease. In this issue, Sugianto et al. demonstrated signs of increased cardiovascular damage (vascular stiffness) in children with chronic kidney disease and highlighted an increased susceptibility of girls, especially in the context of declining kidney function and longer transplant wait times. Understanding the determinants leading to these differences are essential to address the disparity in outcomes in children with chronic kidney disease.

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see clinical investigation on page 585

In the general population, women have a longer life expectancy than do men, an effect that has been attributed to biological and behavioral differences. Estrogen is considered to be "protective," and women generally have less risk-taking behavior and seek and engage in health care services more than men do. However, there is an increasing appreciation of sex-specific differences in disease epidemiology, pathophysiology, and its outcomes. Evidence from population-based studies suggest that sex differences exist in patients with chronic kidney disease (CKD).¹ CKD affects more women than men, but men tend to progress more rapidly to kidney failure and have a higher preponderance to initiate kidney replacement therapy. Like in the general population, mortality is higher in men during predialysis CKD, with cardiovascular disease being a leading cause of death. However, the survival advantage of women is significantly diminished in patients on kidney replacement therapy, including those with kidney transplants. While on kidney replacement therapy, women also suffer from a higher symptom burden and poorer health-related quality of life. Although biological differences play an important role, these differences may be amplified by sociocultural and socioeconomic factors—men and women may manifest and cope with disease differently and likely experience differences in health care delivery.

Despite advances in CKD care over the past 5 decades, children with CKD have a drastically reduced life expectancy as compared with their age-matched healthy peers: up to 40 to 55 years less in children treated with dialysis and up to 12 to 20 years less in children with kidney transplants.² Similar to the adult population with CKD, the leading cause of death in children with CKD is cardiovascular disease. In a retrospective cohort study of >14,000 children (aged 2–19 years) with end-stage kidney disease from the US Renal Data System, girls were found to have a 36% higher mortality rate than boys³—particularly striking when considering the overall higher mortality rates observed in boys in the general pediatric population. Additionally, girls had a 33% higher risk of cardiovascular mortality, adding to the growing body of evidence that girls with CKD may be at an increased risk of adverse cardiovascular consequences. A study of the prospective multicenter Chronic Kidney Disease in Children cohort (N = 725 children) demonstrated that girls with CKD had higher rates of left ventricular hypertrophy than did boys at the same CKD stage and that adiposity, a known cardiovascular risk factor, had a greater effect on left ventricular mass index z scores in girls than in boys.⁴

In this issue, Sugianto et al. demonstrated an increased burden of cardiovascular changes in 255 children (girls: n = 80) with CKD who underwent kidney transplantation and highlighted important sex differences between boys and girls.⁵ The study population was part of the Cardiovascular Comorbidity in Children with Chronic Kidney Disease Study, a prospective multicenter European cohort study following ~700 children with CKD (with a median follow-up of 6 years), aiming to understand the causes and outcomes of cardiovascular disease in children with CKD. The primary end point was sex- and height-adjusted standardized pulse wave velocity z scores (PWVzs), a measure of vascular stiffness, that has been shown to correlate well with cardiovascular disease outcomes in the general population and in adults with CKD. The study found that PWVzs increased in children with CKD of both sexes throughout the study period; however, PWVzs were higher and increased more rapidly over time in girls. Comparatively, healthy children

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