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Kidney-Function Trajectories From Young Adulthood to Midlife: Identifying Risk Strata and Opportunities for Intervention

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Introduction: Understanding normative patterns of change in kidney function over the life course may allow targeting of early interventions to slow or prevent the onset of kidney disease, but knowledge about kidney functional change before middle age is limited. This study used prospective longitudinal data from a representative birth cohort to examine common patterns of change from young to midadulthood and to identify risk factors and outcomes associated with poorer trajectories.

Methods: We used group-based trajectory modeling in the Dunedin study birth cohort ($n = 857$) to identify the following: (i) common kidney function trajectories between the ages 32 and 45 years, (ii) early-life factors associated with those trajectories, (iii) modifiable physical and psychosocial factors across adulthood associated with differences in trajectory slope, and (iv) links between trajectories and kidney-related outcomes at age 45 years.

Results: Three trajectory groups were identified and could be differentiated by age 32 years as follows: normal (58% of participants), low-normal (36%), and high-risk (6%) groups. Those from low socioeconomic backgrounds had higher odds of following a high-risk (vs. normal) trajectory. Modifiable factors (blood pressure, body mass index, inflammation, glycated hemoglobin, smoking, and socioeconomic status) across adulthood were associated with steeper age-related declines in kidney function, particularly among those in the low-normal and high-risk groups. Those in the low-normal and high-risk groups also had more adverse kidney-related outcomes at age 45 years.

Conclusion: The current findings could be used to inform the development of early interventions and point to socioeconomic conditions across the life course and health-related risk factors and behaviors in adulthood as kidney health promotion targets.

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Chronic kidney disease (CKD) represents a major public health burden that will continue to increase with our aging population. Globally, it has a prevalence of approximately 9% and is associated with significant socioeconomic inequities.[1] CKD is the 12th leading cause of death, and in 2017, CKD led to 35.8 million years of healthy life lost.[2] However, we do not yet have a clear understanding of the normative patterns of change in kidney function over the life course and the factors that influence such change. Improving our understanding of these patterns is likely to be important for differentiating healthy versus unhealthy kidney aging and for informing clinical and public health interventions to prevent or slow the onset of CKD. Population-based

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prospective longitudinal studies provide one of the best methods for characterizing normative age-related change in kidney function because they use representative samples and enable control of between-person differences and use of prospectively measured covariates.[3] They can also elucidate problematic patterns of change early in the life course, thereby affording the greatest public health benefit by identifying early intervention opportunities.[4] For example, by examining average patterns of change in kidney function from young adulthood to middle age in a US cohort, the Coronary artery Risk Development in Young Adults study has identified risk factors for accelerated age-related decline, such as race and obesity.[5,6] Nevertheless, to date, most studies of kidney aging have used repeated cross-sectional designs with different participants across age ranges,[7] or focused only on changes in kidney function after middle age.[8–13]

Given the scarcity of longitudinal, general-population data on common patterns of change in kidney function before middle age, the purpose of this study was to use data from a population-representative birth cohort to investigate normative patterns of change ("trajectories") in kidney function from age 32 to 45 years. Using data from the 5-decade "Dunedin study,"[14] the specific aims of this study were to use group-based trajectory modeling[15,16] to identify the following: (i) common trajectories of change; (ii) early-life factors linked to healthy or unhealthy trajectories; (iii) modifiable physical and psychosocial factors associated with differences in trajectory slope; and (iv) associations between trajectories and kidney-related outcomes at age 45 years. Previous longitudinal research has highlighted the potential utility of group-based trajectory modeling in public health research for identifying distinct common patterns of change and points of early intervention with key indicators of cardiovascular, metabolic, and oral health.[17–20] although some studies have used similar techniques to identify latent clusters of kidney-function trajectories and associated risk factors and outcomes, to date, they have been conducted only in clinical populations with established kidney disease[21,22] or older adult samples.[23] This study aimed to provide novel insights by examining kidney function trajectories from young to midadulthood in the general population, thereby providing the opportunity to elucidate potentially problematic trajectories years before disease onset.

METHODS

Study Design and Population

Participants were members of the Dunedin study, a longitudinal investigation of health and behavior in a representative birth cohort. Participants ($N = 1037$; 91% of eligible births; 52% male) were all individuals born between April 1972 and March 1973 in Dunedin, New Zealand, who were eligible based on residence in the province and who participated in the first assessment at age 3 years.[14] The cohort represented the full range of socioeconomic status in the general population of New Zealand's South Island and as adults matched the New Zealand National Health and Nutrition Survey on key adult health indicators and the New Zealand Census of citizens of the same age on educational attainment.[24,25] The cohort is primarily New Zealand European or White (93%), matching South Island demographics. Assessments were carried out at birth and at ages 3, 5, 7, 9, 11, 13, 15, 18, 21, 26, 32, 38, and most recently (completed April 2019) 45 years, when 94% ($n = 938$) of the 997 participants still alive took part. Attrition analyses showed that study members who participated at the age 45 years assessment phase were representative of the original cohort (Supplementary Figure S1). At each assessment, participants came to the research unit for interviews and examinations. The New Zealand Health and Disability Ethics Committee approved the study, and written informed consent was obtained from all participants.

Primary Kidney Function Measure

Glomerular filtration rate (GFR) indicates overall kidney function, but it is time consuming and expensive to measure GFR directly. Estimated GFR (eGFR) is a good proxy commonly used in clinical and research settings and can be calculated using the standardized CKD Epidemiology Collaboration equations that incorporate serum creatinine and/or cystatin C along with demographic variables.[26–28] In this study, our primary measure of kidney function was eGFR based on serum cystatin C. Cystatin C is known to produce more accurate estimates of GFR than creatinine because it is not influenced by highly variable factors such as hydration, diet, and muscle mass[26,29] and is therefore likely to be a better indicator of risk at the population level. Cystatin C was assayed from blood samples taken at ages 32, 38, and 45 years (details in Supplementary Materials) and transformed into eGFR using the CKD Epidemiology Collaboration equations.[26]

Early-Life Risk Factors

Sex

Sex was recorded as male or female at birth.

Perinatal Risk

Perinatal information was taken from hospital records.[30] Perinatal risk was indicated for participants whose mothers had diabetes, prediabetes, or

hypertension (mild, moderate, or severe) during pregnancy or birth.

Birth Weight

Weight in kilograms was recorded at birth. In line with International Classification of Diseases–11 criteria, participants weighing <2.5 kg when they were born were counted as having low birth weight.[31]

Socioeconomic Status in Childhood

Socioeconomic status was measured repeatedly from birth through age 15 years using a scale developed by Elley and Irving that placed parents' occupations into 1 of 6 categories on the basis of the educational achievement and income associated with that occupation in the New Zealand Census (6 = highest status).[32] Consistent with previous Dunedin study work, we used the average across assessments from 0 to 15 years of the highest socioeconomic status of either parent to reflect the cumulative socioeconomic conditions that study members experienced across childhood (internal reliability alpha = 0.92).[33,34] Participants with an average score <3 (out of 6) were categorized as having low socioeconomic status in childhood.

Body Mass Index in Childhood

Height (to the nearest 1 mm) and weight (to the nearest 0.1 kg) at age 15 years were determined using calibrated scales, and body mass index (BMI; weight in kg/height in m^2) was computed.[35] Participants were counted as being overweight in childhood if their BMI at age 15 years was more than 1 standard deviation above the cohort mean for their sex.[36]

Familial Risk

Family medical history for study members' biological siblings, parents, and grandparents was collected from multiple informants when study members were aged 30 to 33 years.[37,38] Family history data were available for health problems that are closely related to CKD (heart disease,[39] hypertension,[40] and diabetes[41]), but CKD itself was not queried. Following previous Dunedin study work,[38] we calculated for each participant the proportion of first-degree relatives with heart disease, hypertension, and diabetes and then summed those proportions to obtain total familial risk scores for kidney-related health problems. Participants with a score in the highest quintile were counted as having high familial risk.

Time-Varying Covariates

Blood Pressure in Adulthood

Blood pressure at ages 32, 38, and 45 years was measured in a quiet room by trained assessors, with the study member in a seated position. A Hawksley random-zero sphygmomanometer (Hawksley and Sons, United Kingdom) was used at ages 32 and 38 years and an automatic BpTRU Vital Signs Monitor BPM 200 (BpTRU Medical Devices, Canada) at age 45 years. To ensure comparability over time, data at age 45 years were calibrated against the prior Hawksley readings to account for the change in equipment. High blood pressure was defined as systolic pressure of ≥130 mm Hg or taking antihypertensive medication.

BMI in Adulthood

BMI was measured at ages 32, 38, and 45 years in the same way as in childhood. High BMI was defined as exceeding 30 kg/m^2.[42]

Systemic Inflammation in Adulthood

We used the following 3 measures of systemic inflammation taken from serum collected at ages 32, 38, and 45 years: high-sensitivity C-reactive protein, fibrinogen, and white blood cells. High systemic inflammation was defined as exceeding the normal range for high-sensitivity C-reactive protein (>3 mg/l),[43] fibrinogen (>4 g/l),[44] or white blood cells (>11 × 10^9 cells/l).[45]

Glycated Hemoglobin in Adulthood

Glycated hemoglobin was measured in serum collected at ages 32, 38, and 45 years, and the concentration expressed as a percentage of total hemoglobin, as previously described.[46] To ensure comparability over time, data at age 45 years were calibrated against prior data up to age 38 years because of a change in assay method. Participants with a concentration ≥5.7% were counted as having high glycated hemoglobin.[47]

Smoking in Adulthood

At ages 32, 38, and 45 years, study members reported whether or not they currently smoked tobacco.

Alcohol Consumption in Adulthood

At ages 32, 38, and 45 years, study members reported their weekly alcohol consumption.[48] High alcohol consumption was defined as exceeding New Zealand Ministry of Health alcohol consumption guidelines (>10 alcoholic drinks per week for women or 15 for men; https://www.health.govt.nz/your-health/healthy-living/addictions/alcohol-and-drug-abuse/alcohol).

Socioeconomic Status in Adulthood

At ages 32, 38, and 45 years, study members' current or most recent (i.e., at the previous assessment phase) occupation was coded using a 6-point scale (6 = highest status) for occupations in New Zealand; those without current or recent occupation data were rated on the basis of their educational achievement according to criteria in the New Zealand Socioeconomic Index.[49,50]

Kidney-Related Outcomes at Age 45 Years

Metabolic Syndrome

Participants were counted as having metabolic syndrome at age 45 years if they had at least 3 of the following risk indicators based on the National Cholesterol Education Program expert panel on detection, evaluation, and treatment of high blood cholesterol in adults [adult treatment panel III], as previously described[51]: waist circumference >88 cm for women or >102 cm for men; systolic blood pressure ≥130 mm Hg or diastolic blood pressure ≥85 mm Hg; high-density lipoprotein ≤40 mg/dl for men or 50 mg/dl for women; triglycerides ≥2.26 mmol/l; or glycated hemoglobin ≥5.7%. Data for high-density lipoprotein and glycated hemoglobin at age 45 years were calibrated against prior data up to age 38 years because of changes in assay methods.

Albuminuria

Urine albumin and creatinine levels were assayed at age 45 years (details in Supplementary Materials). Albuminuria was indicated if participants had a urine albumin to creatinine ratio >3 g/mol.

Cystatin C–Based eGFR to Creatinine-Based eGFR Ratio

Serum cystatin C and creatinine were assayed at age 45 years (details in Supplementary Materials). Cystatin C–based eGFR ($eGFR_{cysC}$) and creatinine-based eGFR ($eGFR_{sCr}$) were calculated using the relevant CKD Epidemiology Collaboration equation.[26] Participants were counted as having a low $eGFR_{cysC}$ to $eGFR_{sCr}$ ratio (a risk factor for later frailty and mortality) if their $eGFR_{cysC}$ was more than 15 ml/min per 1.73 m^2 below their $eGFR_{sCr}$.[52]

Self-rated Health

Study members reported their general health using the following response options: excellent, very good, good, fair, or poor. Those who selected "fair" or "poor" were counted as having low self-rated health.

Life Satisfaction

Participants completed the 5-item Satisfaction with Life scale,[53] indicating how strongly they agreed on a 5-point scale (5 = strongly agree) with the statements: "In most ways my life is close to ideal," "The conditions of my life are excellent," "I am satisfied with my life," "So far I have gotten the important things I want in life," and "If I could live my life over, I would change almost nothing." The items were summed, and participants with scores in the lowest quintile were counted as having low life satisfaction.

Data Analysis

We used group-based trajectory modeling[15,16] to identify latent clusters of study members (trajectory groups) following statistically similar patterns of change in $eGFR_{cysC}$ from age 32 to 45 years. All analyses were conducted using Stata/IC 16 (StataCorp LLC, College Station, TX) and the traj plug-in[54] and checked via independent replication by 2 other analysts. Group-based trajectory modeling is a statistical technique for understanding clusters of common trajectories or risk strata, rather than 1 average trajectory or growth curve for the whole population. It is a type of finite mixture modeling that estimates the trajectory of each group, the shape of the trajectories, and the probability that an individual belongs to a particular group, given their individual trajectory. Individuals are "assigned" to the group for which they have the highest probability of belonging, but these categorizations of continuous data are not concrete. The probability that an individual belongs to a particular trajectory group can change when different covariates are included in the model, and thus, some individuals may be "reassigned" to a different group when the model changes. An important feature of group-based trajectory modeling is that the groups are not predetermined; they are identified in the data, and established criteria[15] are used to identify the best model, including the most appropriate number and shape of trajectories (see Supplementary Materials and Supplementary Tables S2 and S3 for model selection details).

We used group-based trajectory modeling because it is a readily interpretable analysis technique that allows for the possibility that clusters within the population tend to follow distinct kidney function trajectories from young adulthood to middle age, rather than 1 common path for the whole population (e.g., perhaps 1 cluster of individuals shows little age-related change in that early period of adulthood, whereas another shows accelerated decline). As demonstrated in previous longitudinal research with other health indicators such as BMI,[20] blood pressure,[19] glycated hemoglobin,[18] and caries,[17] group-based trajectory modeling also provides the opportunity to identify points in the life course at which trajectories might begin to diverge, thereby allowing interventions to be targeted as early as possible and have the greatest impact. Finally, group-based trajectory modeling enables the examination of potentially differential impacts of time-varying covariates in each of the groups (i.e., whether some risk factors have a greater impact on 1 group than another).

Three study members were excluded from our group-based trajectory analysis because they were extreme outliers at age 45 years, with clinician-diagnosed CKD and very low $eGFR_{cysC}$ (<10 ml/min per 1.73 m^2 for 2 study members; the third died between the ages 38 and 45 years assessment phases). Although group-based trajectory modeling can handle

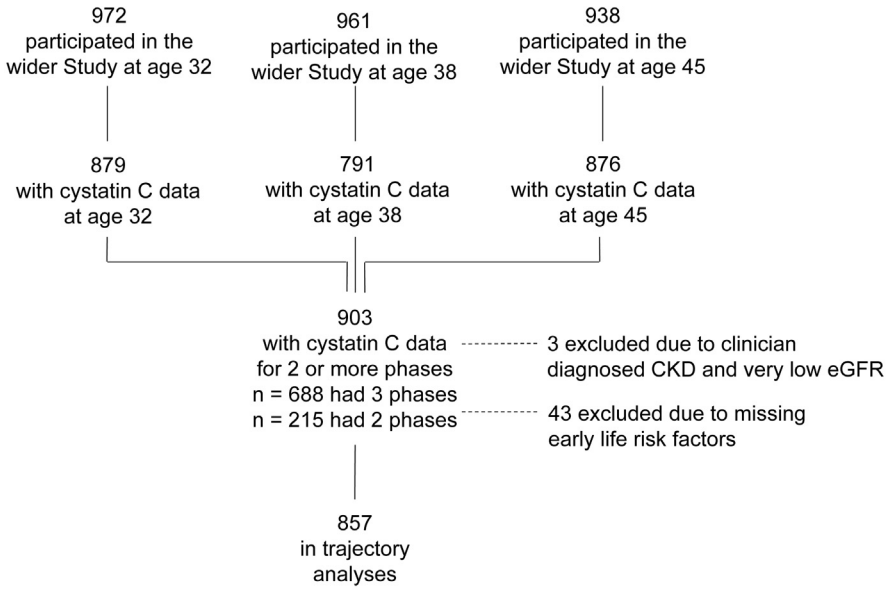

Figure 1. Summary of the number of study members who participated in the Dunedin study assessments at ages 32, 38, and 45 years, and the flow through to the 857 study members included in the current group-based trajectory analyses. See Supplementary Table S1 for retention in the study since its inception. CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate.

missing dependent variable data, we took a conservative approach by limiting our analyses to the 857 participants who had cystatin C data for at least 2 of the 3 modeled phases (32, 38, and 45 years) and available covariate data. Figure 1 summarizes the overall numbers of participants in the Dunedin Study at ages 32, 38, and 45 years and those included in the current analyses; retention of the Dunedin study cohort from its inception through to age 45 years is presented in Supplementary Table S1.

To identify the most parsimonious set of trajectory groups, we tested different combinations of trajectory groups (2, 3, or 4 groups) and shapes (zero-order, linear, or quadratic). These analyses excluded covariates to characterize the observed trajectories in the population, averaged across the factors that might influence individual variation around the estimated trajectory path for a particular group.[15] Once the most parsimonious set of trajectory groups was identified, we examined 2 covariate types to understand their relationships with the trajectories as follows: early-life risk factors (perinatal risk, low birth weight, low childhood socioeconomic status, childhood overweight, and familial risk) that could be associated with the probability of following a particular trajectory, and time-varying covariates across ages 32 to 45 years (blood pressure, BMI, systemic inflammation, glycated hemoglobin, smoking, alcohol consumption, and socioeconomic status) that could be associated with within-group differences in trajectory slope. We conducted univariate analyses with each early-life risk factor or time-varying covariate on its own before constructing the following 3 multivariable models: (i) an early-life model that included early-life risk factors associated ($P < 0.1$) with trajectory group membership in a multinomial logistic regression model that included all putative risk factors, (ii) an adult model that included time-varying covariates that were associated ($P < 0.1$) with a change in trajectory slope for any group, and (iii) a life course model that included both the early-life risk factors and time-varying covariates in adulthood.

Finally, to test the broad validity of the observed trajectory groups, we used logistic regression analyses to examine associations between trajectory group

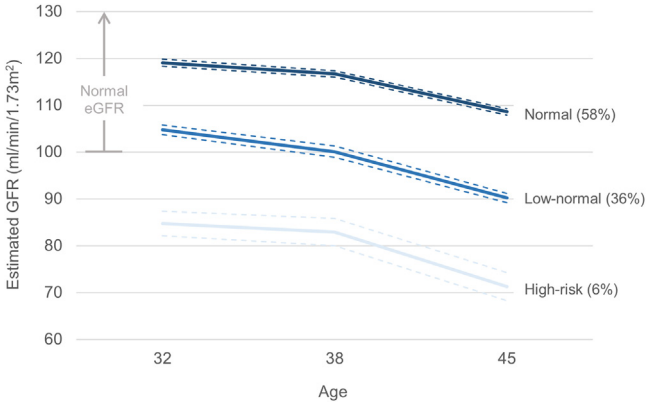

Figure 2. Estimated glomerular filtration rate (based on serum cystatin C) and associated 95% confidence intervals (dashed lines) for the 3 trajectory groups identified in the Dunedin study (derived from the model without risk factors or time-varying covariates to show the observed patterns in the population). Individual trajectories are shown in Supplementary Figure S2. eGFR, estimated glomerular filtration rate.

Table 1. Associations between early-life risk factors and cystatin C–based estimated glomerular filtration rate trajectory group membership

	Univariate[a]					Multivariable early-life model[b]				Multivariable life course model[c]			
						BIC[d] = −9095.24				BIC = −8903.64			
Early life risk factor	BIC	*N*	*n* (%)[e]	OR	95% CI	*N*	*n* (%))[e]	OR	95% CI	*N*	*n* (%)[e]	OR	95% CI
Sex (% female)	−9101.41												
High-risk trajectory group		47	23 (49%) (23)	1.15	(0.61, 2.19)								
Low-normal trajectory group		312	53% (164)	1.24	(0.89, 1.72)								
Normal trajectory group		498	48% (241)	Ref									
Perinatal risk	−9101.91												
High-risk trajectory group		46	5 (11%) (5)	1.53	(0.57, 4.11)								
Low-normal trajectory group		311	28 (9%) (28)	1.11	(0.61, 1.99)								
Normal trajectory group		500	40 (8%) (40)	Ref									
Low birth weight[f]	−9101.75												
High-risk trajectory group		48	1 (2%)	0.43	(0.06, 3.20)								
Low-normal trajectory group		310	14 (5%) (14)	0.83	(0.38, 1.82)								
Normal trajectory group		499	27 (5%) (27)	Ref									
Low child socioeconomic status[6]	−9092.96												
High-risk trajectory group		47	20 (43%)	4.05	(2.10, 7.82)[i]	48	20 (42%)	3.58	(1.83, 7.01)[i]	103	28 (27%)	1.87	(1.03, 3.41)[g]
Low-normal trajectory group		309	69 (22%)	1.66	(1.08, 2.53)[g]	307	69 (22%)	1.57	(1.02, 2.42)[g]	380	75 (20%)	1.31	(0.80, 2.16)
Normal trajectory group		501	76 (15%)	Ref		502	76 (15%)	Ref		374	62 (17%)	Ref	
Childhood overweight[f]	−9096.72												
High-risk trajectory group		47	12 (26%)	3.05	(1.43, 6.51)[h]	48	12 (25%)	2.61	(1.21, 5.66)[g]	103	23 (22%)	1.87	(0.96, 3.64)
Low-normal trajectory group		308	54 (18%)	1.75	(1.09, 2.81)[g]	307	55 (18%)	1.72	(1.06, 2.79)[g]	380	51 (13%)	1.19	(0.67, 2.11)
Normal trajectory group		502	54 (11%)	Ref		502	53 (11%)	Ref		374	46 (12%)	Ref	
High familial risk[f]	−8837.86												
High-risk trajectory group		44	12 (27%)	1.62	(0.76, 3.45)								
Low-normal trajectory group		300	57 (19%)	1.06	(0.69, 1.64)								
Normal trajectory group		487	90 (18%)	Ref									

BIC, Bayesian information criterion; CI, confidence interval; OR, odds ratio; Ref, reference.
[a]Model includes each potential risk factor on its own.
[b]Multivariable early-life model includes childhood socioeconomic status and childhood overweight.
[c]Multivariable life course model includes early-life risk factors (childhood socioeconomic status and childhood overweight) and time-varying covariates in adulthood (blood pressure, body mass index, systemic inflammation, glycated hemoglobin, smoking, and socioeconomic status).
[d]BIC; higher values indicate better model fit.
[e]Number and percentage with that risk factor in each trajectory group. The sample sizes differ slightly between the univariate models, and between the univariate and multivariable models because adding different covariates to the model can change individuals' probabilities of belonging to a particular trajectory group. Hence, when the model changes, some individuals may be assigned to a different trajectory group.
[f]Sensitivity analyses with continuous versions of these variables revealed the same overall pattern of results.
[g]$P \leq 0.05$.
[h]$P \leq 0.01$.
[i]$P \leq 0.001$.

membership and the probability of poor kidney-related outcomes at age 45 years (metabolic syndrome, albuminuria, low $eGFR_{cysC}$-to-$eGFR_{sCr}$ ratio, low self-rated health, and low life satisfaction).

We used predominantly categorical covariates to facilitate interpretation, but to ensure that the pattern was not misleading or distorted by instances of small cell sizes, we conducted sensitivity analyses in which all univariate and multivariable analyses were repeated with continuous versions of the relevant early-life risk factors (birth weight, childhood socioeconomic status, childhood BMI, and familial risk), time-varying covariates in adulthood (blood pressure, BMI, individual inflammation indicators, glycated hemoglobin, and socioeconomic status), and kidney-related outcomes at age 45 years (urine albumin-to-creatinine ratio, $eGFR_{cysC\text{-}to\text{-}eGFRsCr}$ ratio, self-rated health, and life satisfaction). The overall patterns of results across the univariate and multivariable analyses were consistent, and therefore, we report only the primary categorical analyses here. Further sensitivity analyses showed that the overall pattern of results was consistent when the model was restricted to the 688 study members with cystatin C data for all 3 assessment phases, although the reduced sample size meant that there were some differences in the observed *P* values and statistical significance.

RESULTS

Identifying Trajectory Groups

The base model with the best overall fit included the following 3 groups, all with quadratic trajectories: (i) normal (58% of participants; $n = 499$), (ii) low-normal (36%; $n = 311$), and (iii) high-risk (6%; $n = 47$). Figure 2 shows estimated $eGFR_{cysC}$ for each trajectory group at ages 32, 38, and 45 years and illustrates 3 points. First, there is separation between the groups: at

Table 2. Distribution of time-varying covariates in each cystatin C–based estimated glomerular filtration rate trajectory group

Age	32	38	45
Time-varying covariate	% or mean (95% CI)	% or mean (95% CI)	% or mean (95% CI)
High blood pressure (%)			
High-risk trajectory group	24% (13, 39)	24% (13, 39)	31% (19, 46)
Low-normal trajectory group	14% (10, 18)	24% (19, 29)	30% (25, 35)
Normal trajectory group	19% (16, 23)	22% (18, 26)	27% (24, 32)
High body mass index (%)			
High-risk trajectory group	37% (24, 52)	40% (26, 55)	58% (43, 72)
Low-normal trajectory group	21% (16, 26)	29% (24, 35)	40% (35, 46)
Normal trajectory group	13% (10, 17)	19% (16, 23)	27% (23, 31)
High systemic inflammation (%)			
High-risk trajectory group	39% (25, 56)	37% (23, 53)	34% (21, 50)
Low-normal trajectory group	28% (23, 33)	30% (25, 36)	32% (27, 38)
Normal trajectory group	18% (14, 22)	17% (13, 20)	20% (16, 24)
High glycated hemoglobin (%)			
High-risk trajectory group	11% (4, 27)	26% (14, 43)	51% (35, 67)
Low-normal trajectory group	9% (6, 13)	20% (16, 25)	44% (38, 50)
Normal trajectory group	6% (4, 8)	14% (11, 18)	32% (28, 37)
Smoking (%)			
High-risk trajectory group	55% (40, 69)	50% (35, 65)	43% (29, 58)
Low-normal trajectory group	39% (33, 44)	30% (26, 36)	30% (25, 35)
Normal trajectory group	21% (17, 25)	15% (12, 19)	13% (10, 16)
High alcohol consumption (%)			
High-risk trajectory group	36% (23, 51)	26% (15, 41)	21% (12, 36)
Low-normal trajectory group	26% (22, 32)	29% (24, 34)	30% (25, 35)
Normal trajectory group	27% (24, 32)	27% (26, 31)	33% (29, 37)
Socioeconomic status (mean)			
High-risk trajectory group	2.8 (2.4, 3.1)	3.1 (2.6, 3.5)	2.9 (2.5, 3.4)
Low-normal trajectory group	3.1 (2.9, 3.2)	3.6 (3.5, 3.8)	3.6 (3.4, 3.7)
Normal trajectory group	3.4 (3.3, 3.5)	3.9 (3.8, 4.1)	4.0 (3.9, 4.1)

CI, confidence interval.
Trajectory groups are based on the model without risk factors or time-varying covariates to show the observed patterns in the population.

each assessed age, mean $eGFR_{cysC}$ was significantly different across groups, with levels highest in the normal group, intermediate in the low-normal, and lowest in the high-risk group at each age. Second, mean $eGFR_{cysC}$ in the high-risk group was abnormal or approaching abnormal levels as early as age 32 years. Third, the average rate of decline in the normal group (0.81 ml/min per 1.73 m^2 per year of age) was consistent with estimates from previous research in healthy populations,[7,55] whereas higher rates were observed in the low-normal and high-risk groups (1.12 and 1.04 ml/min per 1.73 m^2 per year, respectively).

Early-Life Risk Factors

Perinatal risk, low birth weight, low childhood socioeconomic status, childhood overweight, and familial risk were considered potential early-life factors that could be associated with a higher risk of following a less healthy trajectory. The distribution of each risk factor in the 3 trajectory groups and the odds of following a low-normal or high-risk (vs. normal) trajectory are shown in Table 1. In univariate analyses, growing up in a low socioeconomic household or being overweight in childhood were associated with higher odds of following a less healthy trajectory (i.e., being in the low-normal or high-risk groups). Multinomial regression with all covariates in the same model indicated that low socioeconomic status and overweight were the risk factors with notable associations ($P < 0.1$) with trajectory group. In the multivariable early-life model including childhood socioeconomic status and childhood overweight, both risk factors remained significantly associated with trajectory group membership. In the life course model including early-life risk factors and time-varying covariates, low childhood socioeconomic status was significantly associated with likelihood of assignment to the high-risk group (compared with the normal group; see Table 1). Thus, the overall pattern of effects was similar across the early-life and life course models, although the effect sizes tended to be smaller in the life course model and there were some differences in statistical significance. Indeed, the life course model may have underestimated associations between the early-life factors (childhood socioeconomic status and overweight) and kidney function trajectories in adulthood, given that many of the time-varying covariates included in the model are possible mediators of early-life factor kidney function relationships.

Time-Varying Covariates in Adulthood

Blood pressure, BMI, systemic inflammation, glycated hemoglobin, smoking, alcohol consumption, and socioeconomic status between the ages 32 and 45 years were considered potential time-varying covariates. The prevalence of each covariate in each trajectory group at ages 32, 38, and 45 years is shown in Table 2. The estimated difference in trajectory slope per unit change in each time-varying covariate for each group is shown in Table 3. For the binary covariates (high blood pressure, high BMI, high systemic inflammation, high glycated hemoglobin, high alcohol consumption, and smoking), slope difference indicates the difference in trajectory slope between those with versus without that risk factor. For the continuous variable (socioeconomic status), slope difference indicates the difference in trajectory slope with each step up on the 6-point socioeconomic scale. In univariate analyses, all potential time-varying covariates except high alcohol consumption were associated ($P < 0.1$) with a change in trajectory slope in one or more groups. In the multivariable adult model including blood pressure, BMI, systemic inflammation, glycated hemoglobin, smoking, and socioeconomic status from age 32 to 45 years, high blood pressure, BMI, and systemic inflammation were

Table 3. Associations between time-varying covariates and differences in cystatin C–based estimated glomerular filtration rate trajectory slope in the high-risk, low-normal, and normal trajectory groups

		Univariate[a]		Multivariable adult model[b]		Multivariable life course model[c]	
				BIC[d] = −8894.60		BIC = −8903.64	
Time-varying covariate	BIC	Slope difference[e]	95% CI	Slope difference	95% CI	Slope difference	95% CI
High blood pressure[f]	−8985.69						
High-risk trajectory group		−1.48	(−5.48, 2.52)	−3.33	(−6.66, 0.01)[g]	−3.30	(−6.64, 0.04)[g]
Low-normal trajectory group		−1.83	(−3.59, −0.08)[g]	−1.66	(−3.29, −0.04)[g]	−1.63	(−3.28, 0.01)[g]
Normal trajectory group		0.51	(−0.70, 1.73)	0.65	(−0.79, 2.09)	0.65	(−0.78, 2.07)
High body mass index[f]	−8967.47						
High-risk trajectory group		−2.66	(−6.97, 1.66)	−3.62	(−7.01, −0.22)[g]	−2.81	(−6.43, 0.80)
Low-normal trajectory group		−3.79	(−5.62, −1.97)[h]	−4.60	(−6.35, −2.86)[h]	−4.22	(−6.02, −2.41)[h]
Normal trajectory group		−1.30	(−2.65, 0.05)	−0.89	(−2.52, 0.74)	−0.78	(−2.42, 0.86)
High systemic inflammation[f]	−8970.94						
High-risk trajectory group		−8.72	(−12.38, −5.06)[h]	−5.19	(−8.51, −1.87)[i]	−5.16	(−8.68, −1.63)[i]
Low-normal trajectory group		−4.39	(−5.94, −2.83)[h]	−3.90	(−5.45, −2.34)[h]	−3.77	(−5.34, −2.19)[h]
Normal trajectory group		−1.51	(−2.81, −0.21)[g]	−1.23	(−2.79, 0.33)	−1.21	(−2.75, 0.34)
High glycated hemoglobin[f]	−8959.65						
High-risk trajectory group		−3.73	(−7.96, 0.51)	−3.01	(−6.24, 0.23)	−3.29	(−6.63, 0.04)[g]
Low-normal trajectory group		−2.03	(−3.82, −0.23)[g]	−0.82	(−2.53, 0.89)	−0.83	(−2.55, 0.88)
Normal trajectory group		−0.49	(−1.87, 0.89)	−0.22	(−1.86, 1.41)	−0.25	(−1.87, 1.36)
Smoking	−9066.06						
High-risk trajectory group		−6.51	(−10.42, −2.61)[i]	−5.56	(−9.00, −2.13)[i]	−5.12	(−8.69, −1.56)[i]
Low-normal trajectory group		−5.56	(−7.29, −3.82)[h]	−6.86	(−8.60, −5.13)[h]	−6.69	(−8.48, −4.90)[h]
Normal trajectory group		−3.36	(−4.89, −1.83)[h]	−2.49	(−4.25, −0.73)[i]	−2.48	(−4.22, −0.74)[i]
High alcohol consumption	−9086.84						
High-risk trajectory group		0.44	(−3.75, 4.63)				
Low-normal trajectory group		0.12	(−1.49, 1.72)				
Normal trajectory group		0.85	(−0.30, 2.00)				
Socioeconomic status	−9078.73						
High-risk trajectory group		1.99	(0.67, 3.31)[i]	1.41	(0.38, 2.44)[i]	1.40	(0.32, 2.47)[g]
Low-normal trajectory group		0.80	(0.29, 1.32)[i]	0.53	(0.02, 1.04)[g]	0.45	(−0.07, 0.96)
Normal trajectory group		0.28	(−0.12, 0.68)	0.15	(−0.31, 0.62)	0.12	(−0.34, 0.58)

BIC, Bayesian information criterion; CI, confidence interval.
[a]Model includes each potential time-varying covariate on its own.
[b]Multivariable adult model includes blood pressure, body mass index, systemic inflammation, glycated hemoglobin, smoking, and socioeconomic status at ages 32, 38, and 45 years.
[c]Multivariable life course model includes early-life risk factors (childhood socioeconomic status, childhood overweight) and time-varying covariates in adulthood (blood pressure, body mass index, systemic inflammation, glycated hemoglobin, smoking, and socioeconomic status).
[d]BIC; higher values indicate better model fit.
[e]Slope difference = In each group, the difference in trajectory slope per unit change in the time-varying covariate. For the binary variables (high blood pressure, high body mass index, high systemic inflammation, high glycated hemoglobin, high alcohol consumption, smoking), slope difference indicates the difference in trajectory slope between those with versus without that risk factor. For the continuous variable (socioeconomic status), slope difference indicates the difference in trajectory slope with each step up on the 6-point socioeconomic scale.
[f]Sensitivity analyses with continuous versions of these variables revealed the same overall pattern of results.
[g]$P \leq 0.05$.
[h]$P \leq 0.001$.
[i]$P \leq 0.01$.

associated with a downward shift in $eGFR_{cysC}$ trajectory for those in the high-risk and low-normal groups; smoking was associated with a downward shift in trajectory for all 3 groups; and higher socioeconomic status was associated with an upward shift in trajectory for the high-risk and poor-normal groups. The results were similar for the life course model including early-life risk factors and time-varying covariates, albeit with some differences in statistical significance. Specifically, high blood pressure and systemic inflammation were associated with a downward shift in $eGFR_{cysC}$ trajectory for those in the high-risk and low-normal groups, high BMI was associated with a downward shift for those in the low-normal group, high glycated hemoglobin was associated with a downward shift for those in the high-risk group, smoking was associated with a downward shift in trajectory for all 3 groups, and higher socioeconomic status was associated with an upward shift in trajectory for the high-risk group only (see Table 3).

Kidney-Related Outcomes at Age 45 Years

Prevalence of 4 outcomes at age 45 years incremented with trajectory group (Table 4). Those in the high-risk and low-normal groups were more likely than those in the normal group to have metabolic syndrome, a low $eGFR_{cysC}$-to-$eGFR_{sCr}$ ratio, low self-rated health, and low life satisfaction at age 45 years. There was a small numeric trend but no statistically significant group difference in albuminuria at 45 years.

Table 4. Proportion of participants who met criteria for each kidney-related outcome at age 45 years and the odds of meeting criteria for each outcome in each $eGFR_{cysC}$ trajectory group

Outcome at age 45 yr	% (95% CI)	Univariate odds ratio (95% CI)
Metabolic syndrome		
High-risk trajectory group	42% (28, 57)	2.66 (1.40, 5.07)[a]
Low-normal trajectory group	30% (25, 35)	1.55 (1.12, 2.16)[a]
Normal trajectory group	21% (18, 25)	Ref
Albuminuria[b]		
High-risk trajectory group	9% (3, 22)	1.62 (0.54, 4.84)
Low-normal trajectory group	8% (5, 11)	1.34 (0.76, 2.37)
Normal trajectory group	6% (4, 8)	Ref
Low $eGFR_{cysC}$-to-$eGFR_{sCr}$ ratio[b]		
High-risk trajectory group	48% (33, 63)	71.36 (26.06, 195.45)[c]
Low-normal trajectory group	13% (10, 18)	12.12 (5.07, 28.98)[c]
Normal trajectory group	1% (1, 3)	Ref
Low self-rated health[b]		
High-risk trajectory group	24% (14, 39)	7.60 (3.37, 17.16)[c]
Low-normal trajectory group	13% (10, 18)	3.64 (2.09, 6.34)[c]
Normal trajectory group	4% (3, 6)	Ref
Low life satisfaction[b]		
High-risk trajectory group	47% (33, 61)	3.82 (2.04, 7.16)[c]
Low-normal trajectory group	34% (29, 39)	2.22 (1.60, 3.09)[c]
Normal trajectory group	19% (15, 22)	Ref

CI, confidence interval; $eGFR_{cysC}$; cystatin C–based estimated glomerular filtration rate; $eGFR_{sCr}$; creatinine-based eGFR; Ref, reference.
[a] $P \leq 0.01$.
[b] Sensitivity analyses with continuous versions of these variables revealed the same overall pattern of results.
[c] $P \leq 0.001$.
Trajectory groups are based on the model without risk factors or time-varying covariates to show the observed patterns in the population.

DISCUSSION

This study used prospective longitudinal data to examine normative patterns of change in kidney function from young to midadulthood in a general population cohort. We identified 3 trajectory groups (normal, low-normal, and high-risk), which differentiated early in adulthood those who seem to be at risk of kidney function problems later in life. Average rates of decline per year of age in the normal group were consistent with previous research in healthy populations[7,55] and indicate that those in the low-normal and high-risk groups showed slightly accelerated decline. Low socioeconomic status and overweight in childhood were associated with higher odds of following a high-risk trajectory. Modifiable physical and psychosocial factors across adulthood including blood pressure, BMI, systemic inflammation, glycated hemoglobin, smoking, and lower socioeconomic status were associated with accelerated age-related declines in $eGFR_{cysC}$, with the size of these effects tending to increment with trajectory risk group. The risk for negative kidney-related outcomes at age 45 years also incremented with trajectory risk group, with participants in the low-normal and high-risk trajectory groups more likely to have metabolic syndrome (clustered cardiovascular risk factors), low $eGFR_{cysC}$-to-$eGFR_{sCr}$ ratio (a risk factor for later frailty and mortality),[52] low self-rated health, and low life satisfaction.

The current findings highlight risk strata in the general population that could be used to inform early interventions to prevent or slow the onset of CKD. The strata identified here also underscore the need for public health attention and investment into the prevention of CKD. Approximately 6% of people appeared to be at high-risk; as a group, they had relatively poor kidney function as early as age 32 years, showed further declines to age 45 years, and had a poor kidney-related health profile including a relatively high prevalence of clustered cardiovascular risk factors at age 45 years. Although small, this group represents significant individual and public health cost, especially given the risk CKD poses for ischemic heart disease and stroke.[2] The second group, comprising approximately one-third (36%) of the cohort, followed a low-normal trajectory. These people seem more likely than those following a normal trajectory to go on to develop reduced kidney function. Despite relatively normal function in early adulthood, by middle age, they showed signs of impairment consistent with stage 2 CKD (eGFR 60−90 ml/min per 1.73 m^2). The kidney-related health profile of the low-normal group was worse than that for those following a normal trajectory, with outcomes intermediate between the high-risk and normal groups. Taken together, these 2 risk strata make up a sizable proportion (approximately 42%) of the population that could benefit from early intervention efforts.

Alongside previous research,[56–58] the current findings point to modifiable physical and psychosocial factors across adulthood (in this study, from ages 32–45 years) that could be used to guide public health interventions aimed at preventing or slowing age-related decline in kidney function. Our findings support the idea that across young adulthood to midlife, interventions aimed at reducing hypertension, BMI, systemic inflammation, glycated hemoglobin, and smoking and improving socioeconomic status may help slow age-related declines in kidney function. Moreover, they show something akin to a dose-response relationship in which the associations between time-varying covariates and kidney function were stronger for those following a low-normal (than normal) trajectory, and in the case of blood pressure, systemic inflammation, glycated hemoglobin, and socioeconomic status, stronger still for those following a high-risk trajectory. Thus, interventions that reduce modifiable risk factors as early as possible in the life course could have the greatest benefit for those most at risk of developing CKD.

This study extends previous research by examining early life and time-varying covariates in relation

to the developmental course of kidney function from young to midadulthood, rather than kidney functional outcomes at a single time point. However, we did observe some unexpected results. We did not find statistically significant associations between kidney function trajectories and some factors that have previously been linked to impaired kidney function, including early-life risk factors (low birth weight, other perinatal risk factors, familial risk[59-61]) and proteinuria[62] in adulthood. It is possible that these links were not yet evident in our general population (as opposed to clinical) cohort at age 45 years but may become more so as study members age, a larger proportion show evidence of CKD and comorbid conditions, and trajectories diverge. It is also possible that we did not have sufficient power to detect some of the smaller observed effects, particularly in the high-risk group.

The main strengths of this study include the use of prospective longitudinal data from a representative general population cohort followed with high retention[14] from birth to middle age, the consistent collection and analysis of kidney biomarker data from young to midadulthood, and the use of group-based trajectory modeling to elucidate putative risk strata and identify possible points of early intervention. There are also some limitations that should be taken into account. Although we were able to consider inequities associated with socioeconomic circumstances in childhood, we could not consider the same in relation to ethnicity because of low ethnic diversity in the Dunedin study. We were limited to examining $eGFR_{cysC}$ trajectories across the 3 assessment points in adulthood for which cystatin C data could be obtained (ages 32, 38, and 45 years). Given this limited window, it is important to note the possibility that kidney function trajectories might diverge earlier in life than was evident here. Moreover, albuminuria data were only available at age 45 years; therefore, we could not examine concurrent change in $eGFR_{cysC}$ and albuminuria. To provide further insight into the normative patterns of change in kidney function across the life course and the earliest possible points of intervention, future longitudinal research should seek to investigate kidney function across a wider age range (ideally, from childhood through to older adulthood), in ethnically diverse samples, and with multiple biomarkers. Note also that the trajectories are approximations of reality and may not generalize to other indicators of kidney function or other populations. Future research should seek to replicate these findings in different cohorts to further validate the risk strata identified here.

General population data on within-person change in kidney function are rare, particularly early in adulthood. By identifying common patterns of change in kidney function from young to midadulthood and correlated early-life risk factors and time-varying covariates across adulthood, the current findings can help to inform the development and early implementation of public health interventions aimed at protecting kidney health and preventing disease before it manifests. Future research is needed to confirm the trajectories identified here. Nevertheless, the current findings provide information that could be used in development and targeting of early interventions. In particular, they point to socioeconomic circumstances across the life course and health-related risk factors and behaviors in adulthood as important kidney health promotion targets.

DISCLOSURE

All the authors declared no competing interests.

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SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary References.

Assay Details.

Figure S1. Distribution of childhood SES, ACEs, self-control, and IQ among the full cohort of Dunedin study members and those who at age 45 were deceased, alive, seen (i.e., participated in that assessment phase), or MRI scanned.

Figure S2. Individual estimated glomerular filtration rate (based on serum cystatin C) trajectories for participants assigned to the high-risk, low-normal, and normal trajectory groups (derived from the model without any risk factors or time-varying covariates).

Table S1. Participant retention in the Dunedin study, birth to age 45 years.

Table S2. Goodness-of-fit (BIC) statistics by trajectory group configurations (number and shape).

Table S3. Model statistics for the selected trajectory model (3 groups; all quadratic trajectories).

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