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Navigating the complexities of end-stage kidney disease (ESKD) from risk factors to outcome: insights from the UK Biobank cohort

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Abstract

Background The global prevalence of end-stage kidney disease (ESKD) is increasing despite optimal management of traditional risk factors such as hyperglycaemia, hypertension, and dyslipidaemia. This study examines the influence of cardiorenal risk factors, socioeconomic status, and ethnic and cardiovascular comorbidities on ESKD outcomes in the general population.

Methods This cross-sectional study analysed data from 502,408 UK Biobank study participants recruited between 2006 and 2010. Multivariable logistic regression models were fitted to assess risk factors for ESKD, with results presented as adjusted odds ratio (aOR) and 95% confidence intervals (95% CI).

Results A total of 1191 (0.2%) of the study participants reported ESKD. Diabetes increased ESKD risk by 62% [1.62 (1.36–1.93)], with early-onset diabetes (before age 40) conferring higher odds compared to later-onset (after age 40) [2.26 (1.57–3.24)]. Similarly, early-onset hypertension (before age 40), compared to later onset (after age 40), increased ESKD odds by 73% [1.73 (1.21–2.44)]. Cardiovascular comorbidities, including stroke, hypertension, myocardial infarction and angina, were strongly associated with ESKD [5.97 (3.99–8.72), 5.35 (4.38–6.56), 4.94 (3.56–6.78), and 4.89 (3.47–6.81)], respectively. Males were at 22% higher risk of ESKD than females [1.22 (1.04–1.43)]. Each additional year of diabetes duration increased ESKD odds by 2% [1.02 (1.01–1.03)]. Non-white ethnicity, compared to white and socioeconomically most deprived, compared to the least deprived quintiles, were at 70% and 83% higher odds of ESKD. Each unit of HbA1c rise increased the odds of ESKD by 2%. Compared to microalbuminuria, macroalbuminuria increased the odds of ESKD by almost 10-fold [9.47 (7.95–11.27)] while normoalbuminuria reduced the odds by 73% [0.27 (0.22–0.32)].

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Conclusions Early onset of diabetes and hypertension, male sex, non-white ethnicity, deprivation, poor glycaemic control, and prolonged hyperglycaemia are significant risk factors for ESKD. These findings highlight the complexity of ESKD and the need for multifactorial targeted interventions in high-risk populations.

Clinical trial number Not applicable.

Keywords Chronic kidney disease, Diabetes, End-stage kidney disease (ESKD), Renal replacement therapy (RRT)

Background

The rising prevalence of chronic kidney disease (CKD) and end-stage kidney disease (ESKD) are significant contributors to global mortality, morbidity and loss of quality-adjusted life-years (QALY) [1, 2]. It poses a significant global public health challenge [3]. As of 2019, CKD affected an estimated 13.4% of the global population (95% CI 11.7–15.1), with the number of individuals requiring renal replacement therapy (RRT) for ESKD estimated between 4.9 and 7.1 million [4]. From 1990 to 2017, the age-standardised incidence of ESKD treated with RRT increased by 43.1% (95% UI 40.5–45.8), and renal transplants saw a 34.4% increase (95% UI 29.7–38.9). Consequently, ESKD became the 12th leading cause of global mortality in 2015, up from the 17th in 1990 [5]. These data do not account for the cardiovascular mortality attributable to CKD and ESKD. Between 2005 and 2015, the global prevalence of CKD mortality increased by 31.7%, and diabetic kidney disease (DKD) increased by 39.5%, making it the third most significant increase in the primary cause of global deaths [6]. This trend starkly contrasts other non-communicable diseases (NCDs). For example, between 2005 and 2015, the QALY lost due to cardiovascular disease (CVD) and chronic obstructive pulmonary disease (COPD) fell by 10.2% and 3%, respectively [6].

Ethnic and socioeconomic disparities in kidney health are significant contributors to global health inequality [7]. The upward trend in the prevalence of ESKD is particularly pronounced in low- and middle-income countries (LMICs) [8]. The impact of CKD and ESKD on health-related quality of life (HRQoL) is substantial, with costs rising perpetually as the disease progresses. With the global rise in young-onset type 2 diabetes mellitus (T2DM), renal complications are developing at a younger age [9, 10]. In privately funded LMICs, the cost of RRT and renal transplant is often unaffordable, leading to premature mortality and morbidity. Globally, between 2022 and 2027, the 'Inside CKD' microsimulation projected that the annual direct cost of CKD and RRT would increase by 9.3%, from $372 billion to $406.7 billion. By 2027, patients receiving RRT are projected to constitute 5.3% of the CKD-diagnosed population but contribute 45.9% to the total cost [11]. The World Health Organization (WHO) has classed CKD as one of the priority NCDs to tackle global health inequality [12]. It is also a priority area for the United Nations Sustainable Development Goal (SDG) for the LMICs [13].

However, tackling kidney health inequalities is complex and requires a deeper understanding of its link with cardiometabolic risk factors, ethnicity, socioeconomic, cultural and lifestyle factors. Traditionally, people with CKD used to die of CVD before developing ESKD [14]. Therefore, management of CVD risk factors such as hypertension, hyperglycaemia and dyslipidaemia were principal therapeutic intervention targets. However, in recent years, due to an epidemiological shift in the disease prevalence of T2DM and CKD, despite managing these risk factors, ESKD cases are rising. Notably, people from minority ethnic backgrounds are developing ESKD at a younger age, requiring RRT for a longer duration. For instance, a recent observational study in East London showed that people from black and minority ethnic backgrounds were more likely to develop ESKD at a younger age, require RRT for a longer duration, and die earlier than those from white ethnicity [15]. Similar trends in kidney health inequalities in minority ethnicities are reported in the USA and globally [6, 16]. Therefore, a more holistic and comprehensive strategy is needed to understand the complex interplay of ethnicity, socioeconomic status and cardiorenal risk factors with ESKD outcomes.

This study examines the relationship between ESKD and risk factors, focusing primarily on the impact of cardiometabolic and socioeconomic factors on ESKD outcomes in the UK general population. The objectives are to raise awareness among public and primary care providers while informing public health policymakers to develop prevention strategies targeting key risk factors early in the disease trajectory.

Methods

Design and setting

In this cross-sectional study, we utilised pseudonymised data from UK Biobank, a population-based prospective cohort linked to general practice, secondary care, and mortality registry data from the Office for National Statistics (ONS). The UK Biobank is considered one of the most comprehensive global data sources for biomedical research [17]. The recruitment phase occurred between March 1, 2006, and December 31, 2010, when eligible participants aged 40–69 were invited to attend one of the

22 assessment centres across the UK. At these centres, participants completed a touchscreen-based questionnaire covering medical history, including smoking status, alcohol consumption, diet, and exercise. Trained research nurses collected anthropometric measurements, including height, weight, and blood pressure, and collected blood and urine samples for laboratory analysis [18]. The study employed a cross-sectional design, relying solely on baseline data from the UK Biobank without subsequent follow-up for incident ESKD cases.

Outcome ascertainment, inclusion and exclusion criteria

Prevalent cases of ESKD were identified using self-administered questionnaires. For this study, people who reported ESKD at the first recruitment visit were the group of interest. All the study participants ($n = 502490$) were eligible for inclusion. However, 82 participants withdrew their consent before the study began and were excluded from the analyses, leaving 502,408. A flow chart showing the study participants' selection process is included. (Supplementary material - Fig. 1). At the assessment visit, a qualified nurse checked the height, weight, blood pressure, and waist circumference and took urine, blood and saliva samples for analysis. They also verified the responses given by the participants in the touchscreen questionnaire.

Exposures and covariates

Smoking status was categorised into current smokers (those who smoked at the time of the assessment visit), ex-smokers (those who had regularly smoked in the past but had abstained for at least a year), and non-smokers (those who had never smoked). This classification focused solely on active cigarette consumption, excluding other forms of nicotine use, such as e-cigarettes and passive smoking. Participants reported the age at which they started and stopped smoking, allowing the calculation of smoking duration in years.

Urinary albumin concentration (UAC) was measured from spot urine samples. Using the Kidney Disease Improving Global Outcomes (KDIGO) guidelines, UAC values were categorised as normoalbuminuria (< 20 mg/L), microalbuminuria (20–200 mg/L), and macroalbuminuria (> 200 mg/L) [19]. Glycaemic status was defined using the International Expert Committee (IEC) criteria: HbA1c values of < 42 mmol/mol indicated normoglycaemia, 42–47 mmol/mol indicated prediabetes, and ≥ 48 mmol/mol indicated diabetes [20].

Body mass index (BMI) was calculated using the formula (weight in kg/height in m^2) and categorised into four groups: underweight (< 20 kg/m^2), normal weight (20–25 kg/m^2), overweight (> 25 – <30 kg/m^2), and obese (≥ 30 kg/m^2). Socioeconomic status was assessed using the Townsend deprivation indices [21], incorporating data on participants' postal codes, employment status, educational attainment, car ownership, and household income. For deprivation, participants were stratified into five quintiles: most deprived, more deprived, moderately deprived, less deprived, and least deprived. Diabetes and hypertension duration were calculated based on the age of diabetes and hypertension diagnoses and when the assessment visit was attended.

Statistical analyses

People who reported ESKD and those who did not were grouped into ESKD and non-ESKD groups to determine their cardiorenal and sociodemographic characteristics. Descriptive statistics were used to summarise the data, with categorical variables presented as frequencies and percentages. Numerical variables were reported as mean and standard deviation (SD) for normally distributed data or median and interquartile range (IQR) for non-normally distributed data. The normality of numerical data was assessed using histogram visual inspection and the Kolmogorov-Smirnov test. A two-way Student's t-test was applied to numerical variables with a parametric distribution for significance testing, while the Wilcoxon test was used for non-parametric distributions.

Participants were categorised into two groups based on their questionnaire responses: ESKD and non-ESKD. A Chi-squared test was used to assess the significance of differences in categorical variables between these groups. Missing data were handled using multiple imputations by chained equations (MICE). Multivariable logistic regression models were employed to identify the relationship between cardiorenal risk factors and ESKD, where ESKD was a binary outcome. In Model 1, adjustments were made for age, sex, HbA1c, body mass index (BMI), systolic blood pressure (SBP), cholesterol levels, deprivation status, and smoking status. Model 2 included adjustments for age, sex, urinary albumin concentration (UAC), waist circumference, and the ages at which diabetes and hypertension were diagnosed. Model 3 adjusted for sex, albuminuria, history of stroke, hypertension, myocardial infarction, angina, weight category, and diabetes status. Finally, Model 4 incorporated age, sex, ethnicity, duration of diabetes and hypertension, and deprivation status.

The results were expressed as adjusted odds ratios (aOR) with 95% confidence intervals (95% CI) and p-values indicating statistical significance. We fitted multivariable logistic regression models and presented the results using forest plots, displaying adjusted odds ratios and 95% confidence intervals. For reporting our findings, we followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [22].

Role of funding source
The funders were not involved in the conceptualisation, study design, data collection, analysis, or interpretation. AE had access to the complete dataset and verified its accuracy. DK had access to all data and took the final responsibility for the decision to submit the manuscript for publication.

Results

The analysis included data from 502,408 participants who completed the questionnaire and provided consent for their data to be used in research. Within the ESKD group, 63.2% were male, compared to 45.6% in the non-ESKD group. The mean age of study participants with ESKD was 59 years, while those without ESKD had a mean age of 57. Individuals from non-white ethnic backgrounds comprised 12.97% of the ESKD group, constituting only 5.76% of the study population.

In the non-ESKD group, the distribution across deprivation quintiles was relatively even. However, in the ESKD group, 70% belonged to the moderate to most deprived quintiles. Glycaemic status also differed between the groups, with 26.1% of the ESKD cohort having an HbA1c level within the diabetes or prediabetes range, compared to 8.3% in the non-ESKD group. Furthermore, 74.2% of individuals in the ESKD group were classified as overweight or obese, compared to 66.9% in the non-ESKD group. Smoking prevalence was higher among those with ESKD, with 51.7% identified as current or ex-smokers, compared to 45.1% in the non-ESKD cohort. Although creatinine levels are expected to be higher in males due to more muscle mass, within the ESKD cohort, female current smokers exhibited higher creatinine levels than males (Fig. 1).

The median age of diabetes diagnosis was 46 years in the ESKD group, compared to 54 years in the non-ESKD group. Likewise, the median age of hypertension diagnosis was 42 years in the ESKD group and 50 years in the non-ESKD group. The mean duration of diabetes and hypertension in the ESKD group was 17.16 and 19.28 years, respectively, whereas in the non-ESKD group, the mean duration was 10.63 and 14.42 years, respectively. Missing data was analysed using multiple imputations of chained equation (MICE), which showed that the missingness was at random (MAR) (supplementary material– Fig. 2). The logistic regression assumption of multicollinearity was tested using the variance inflation factor (VIF), which showed that all the models satisfied this assumption (supplementary material). Statistical significance was determined at a p-value of < 0.05. The baseline characteristics of the participants are summarised in Table 1.

Model 1

Model 1 highlighted the impact of age, sex, BMI, blood pressure, smoking status and deprivation on the risk of ESKD. In this model, we fitted a multivariable logistic regression model using ESKD as a binary outcome and all the above as explanatory variables. Compared to the least deprived quintile, the odds of ESKD in the most deprived

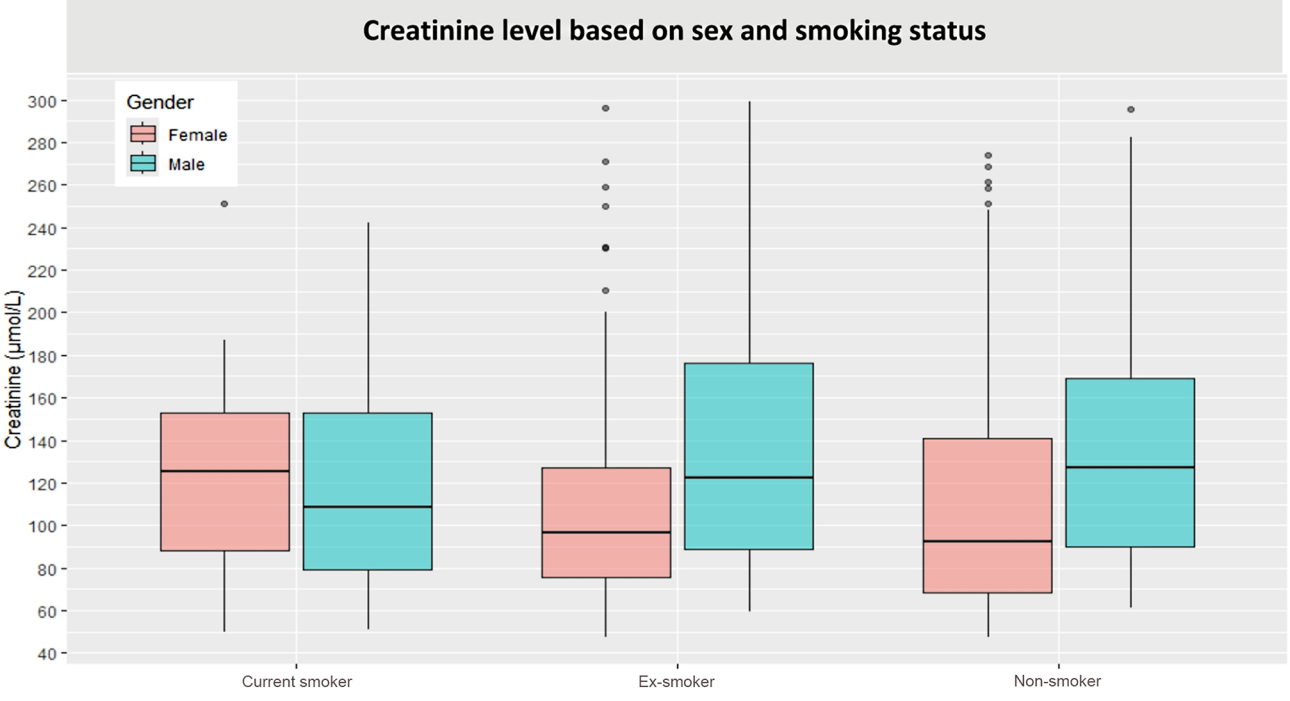

Fig. 1 Distribution of people with ESKD based on sex, smoking status and serum creatinine

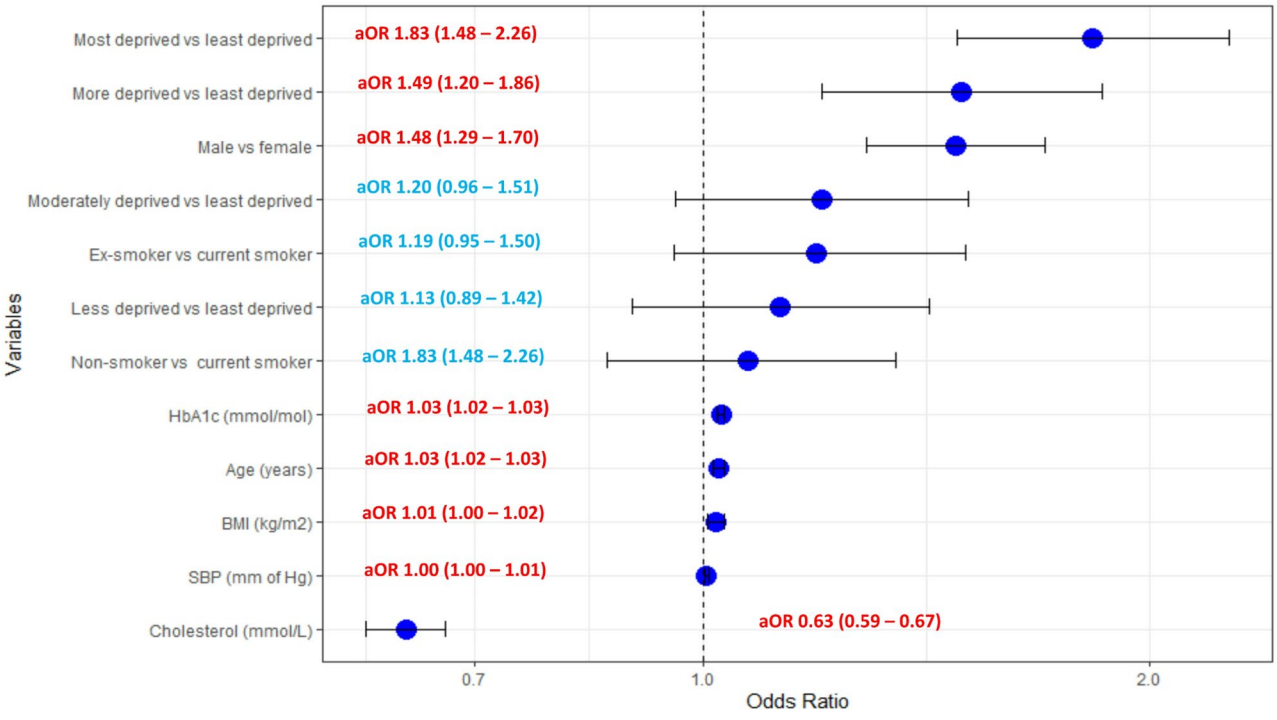

Fig. 2 Forest plot showing the predictors of ESKD (Model 1) (Red – statistically significant, turquoise – statistically insignificant)

quintile were 1.83 (1.48–2.26) and compared to females, the odds of ESKD in males were 1.48 (1.29–1.70). Each unit of rise in HbA1c, ageing, BMI and SBP increased the odds of ESKD, 1.03 (1.02–1.03), 1.03 (1.02–1.03), 1.01 (1.00–1.02), and 1.00 (1.00–1.01), respectively. Serum cholesterol negatively correlated with ESKD 0.63 (0.59–0.67). Smoking status did not have a statistically significant association with ESKD odds (Fig. 2).

Model 2

This model explored the relationship between diabetes and hypertension diagnoses, age, sex, UAC and waist circumference with ESKD. Compared to individuals who developed diabetes and hypertension between 40 and 60, those who developed below 40 were at 2.26- and 1.73 times higher odds of ESKD, respectively. Individuals who developed diabetes above the age of 60 were 64% less likely to have ESKD compared to those who developed it between 40 and 60 years. Age, male gender and hypertension diagnosis above 60 did not have any statistically significant relationship with ESKD. Individuals who developed diabetes above 60, compared to those who developed between 40 and 60, had a lower risk of ESKD, 0.36 (0.20–0.63) (Fig. 3).

Model 3

This multivariable logistic regression model showed that compared to individuals with microalbuminuria, those with macroalbuminuria had 9.47 times higher, and those with normoalbuminuria had 73% lower odds of ESKD [9.47 (7.95–11.27) and 0.27 (0.22–0.32)], respectively. Likewise, in comparison to individuals with normal weight, those in the underweight quartile were 2.21 times higher, and those who were in the overweight and obese quartile were 20% and 45% lower risk of ESKD. Compared to individuals without, those with stroke, hypertension, myocardial infarction, and angina had higher odds of ESKD [5.97 (3.99–8.72), 5.35 (4.38–6.56), 4.94 (3.56–6.78), and 4.89 (3.47–6.81)], respectively. Males, compared to females, were at 22%, and individuals with diabetes, compared to those without, were at 62% higher risk of ESKD (Fig. 4).

Model 4

This model showed that after adjusting for sex, age, deprivation, ethnicity, diabetes and hypertension duration, the odds of ESKD in non-white ethnicity were 70% higher than in white ethnicity. Compared to females, males were at 44% higher risk of ESKD. Each year of increase in diabetes duration was associated with a 2% increased risk of ESKD. Duration of hypertension did not have any statistically significant association with ESKD. Intriguingly, when age, ethnicity and deprivation were fitted in the same model, ethnicity statistically significantly increased the risk, ageing reduced the risk, and deprivation was not a significant predictor of ESKD (Fig. 5).

Table 1 Baseline characteristics of UK Biobank participants with and without ESKD

Variable name		ESKD (*n* = 1191)	Non-ESKD (*n* = 501,217)	*P* value
Age (years) mean (SD)		58.97 (7.62)	57.04 (8.17)	< 0.001
Sex – Male (%)		753 (63.2)	228,329 (45.6)	< 0.001
UAC (mg/L) [median (IQR)]		86.20 (18.40, 446.20)	11.50 (8.40, 19.40)	< 0.001
Cholesterol (mmol/L) [mean (SD)]	Total cholesterol	4.99 (1.23)	5.69 (1.14)	< 0.001
	HDL	1.28 (0.40)	1.45 (0.38)	< 0.001
	LDL	3.05 (0.88)	3.56 (0.87)	< 0.001
	Triglyceride	0.65 (0.34)	0.69 (0.30)	< 0.001
Creatinine (micromole/L) [(mean (SD)]		193.09 (189.78)	72.03 (15.06)	< 0.001
HbA1c (mmol/mol) [mean (SD)]		41.42 (13.94)	36.12 (6.75)	< 0.001
BMI (kg/m^2) [mean (SD)]		28.73 (5.82)	27.43 (4.80)	< 0.001
Ethnicity n (%)	White	1044 (87.65)	471,565 (93.86)	< 0.001
	Black	50 (4.20)	8,008 (1.59)	< 0.001
	Asian	53(4.45)	11,399 (2.27)	< 0.001
	Mixed	4 (0.33)	2,950 (0.59)	< 0.001
	Other	38 (3.19)	6,397 (1.27)	< 0.001
Deprivation quintiles (%)	Least deprived	168 (14.1)	101,160 (20.2)	< 0.001
	Less deprived	194 (16.3)	100,402 (20.1)	< 0.001
	Moderately deprived	200 (16.8)	98,968 (19.9)	< 0.001
	More deprived	260 (21.9)	100,238 (20.0)	< 0.001
	Most deprived	367 (30.9)	99,826 (19.9)	< 0.001
SBP (mm of Hg) [mean (SD)		143.69 (21.83)	139.73 (19.69)	< 0.001
DBP (mm of Hg) [mean (SD)		81.10 (11.48)	82.21 (10.70)	0.001
Glycaemic status (HbA1c-based) [n (%)]	Normoglycaemia	785 (73.9)	426,721 (91.7)	< 0.001
	Prediabetes	92 (8.7)	21,208 (4.6)	< 0.001
	Diabetes	185 (17.4)	17,271 (3.7)	< 0.001
BMI Status [n (%)]	Underweight	41 (3.5)	11,663 (2.3)	< 0.001
	Normal weight	259 (22.3)	153,313 (30.8)	< 0.001
	Overweight	462 (39.7)	211,252 (42.4)	< 0.001
	Obese	401 (34.5)	121,911 (24.5)	< 0.001
Smoking status [n (%)]	Wish not to disclose	7 (0.6)	2050 (0.4)	< 0.001
	Non-smoker	567 (47.7)	272,906 (54.5)	< 0.001
	Ex-smoker	488 (41.0)	172,535 (34.5)	< 0.001
	Current smoker	127 (10.7)	52,835 (10.6)	< 0.001
Waist circumference (cm) [mean (SD)]		97.17 (15.55)	90.30 (13.48)	< 0.001
Age diabetes diagnosed (year) [median (IQR)]		46 (35, 55)	54 (45, 60)	< 0.001
Age hypertension diagnosed (year) [median (IQR)]		42 (32, 52)	50 (41, 58)	< 0.001
Diabetes duration (years) [mean (SD)]		17.16 (14.49)	10.63 (13.53)	< 0.001
Hypertension duration (years) [mean (SD)]		19.28 (16.82)	14.42 (17.60)	< 0.001
Cardiovascular disease [n(%)]	None	260 (21.9)	350,630 (70.1)	< 0.001
	Hypertension	697 (58.6)	119,442 (23.9)	< 0.001
	Angina	78 (6.6)	11,254 (2.2)	< 0.001
	Stroke	48 (4.0)	6170 (1.2)	< 0.001
	Heart attack	100 (8.4)	11,505 (2.3)	< 0.001

Discussion

This study highlighted the multifactorial nature of end-stage kidney disease (ESKD) and revealed substantial variations in how cardiometabolic risk factors influence ESKD outcomes. Descriptive analyses indicated that the ESKD group had a higher proportion of males, individuals with higher deprivation scores, those with overweight and obesity, and current or former smokers compared to the non-ESKD group. While males are physiologically expected to have higher creatinine levels, our findings showed that female smokers had higher creatinine levels than male smokers. Additionally, individuals with ESKD who also had diabetes and hypertension were diagnosed with these conditions at a younger age and had a longer duration of disease compared to those without ESKD.

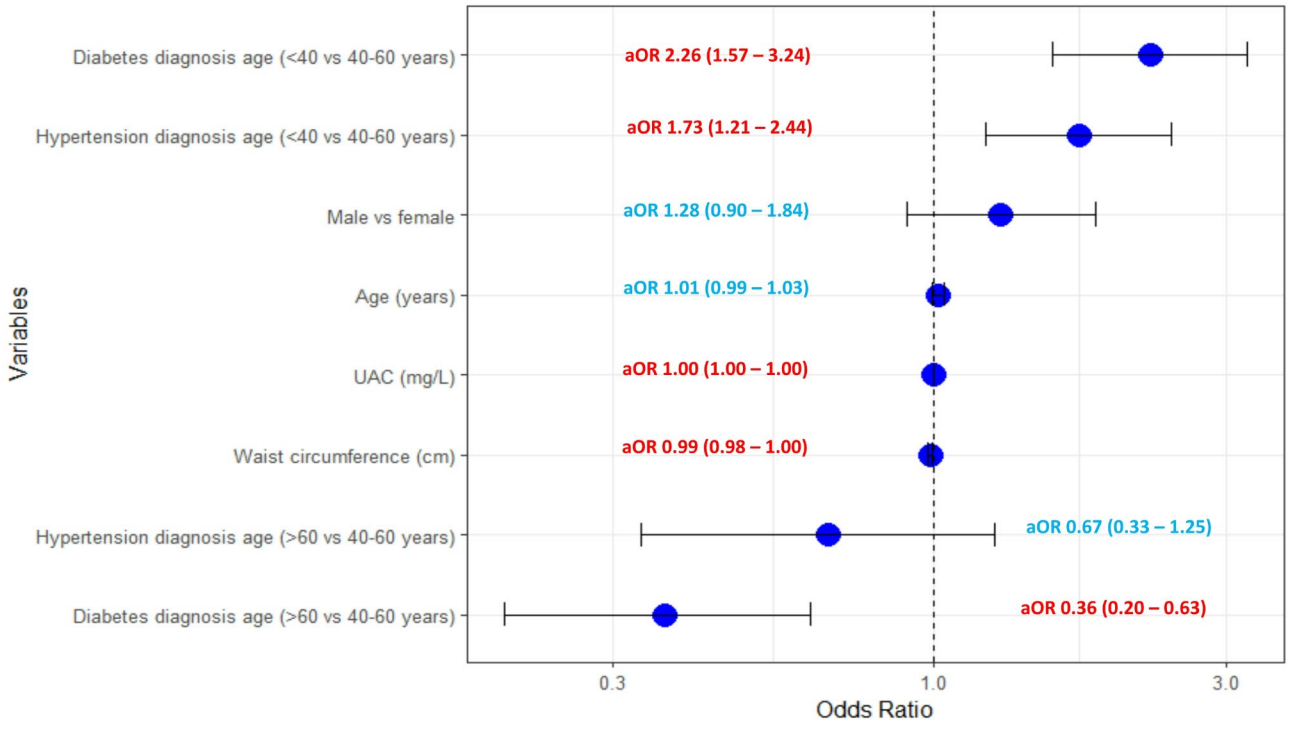

Fig. 3 Forest plot showing the predictors of ESKD (Model 2) (Red – statistically significant, turquoise – statistically insignificant)

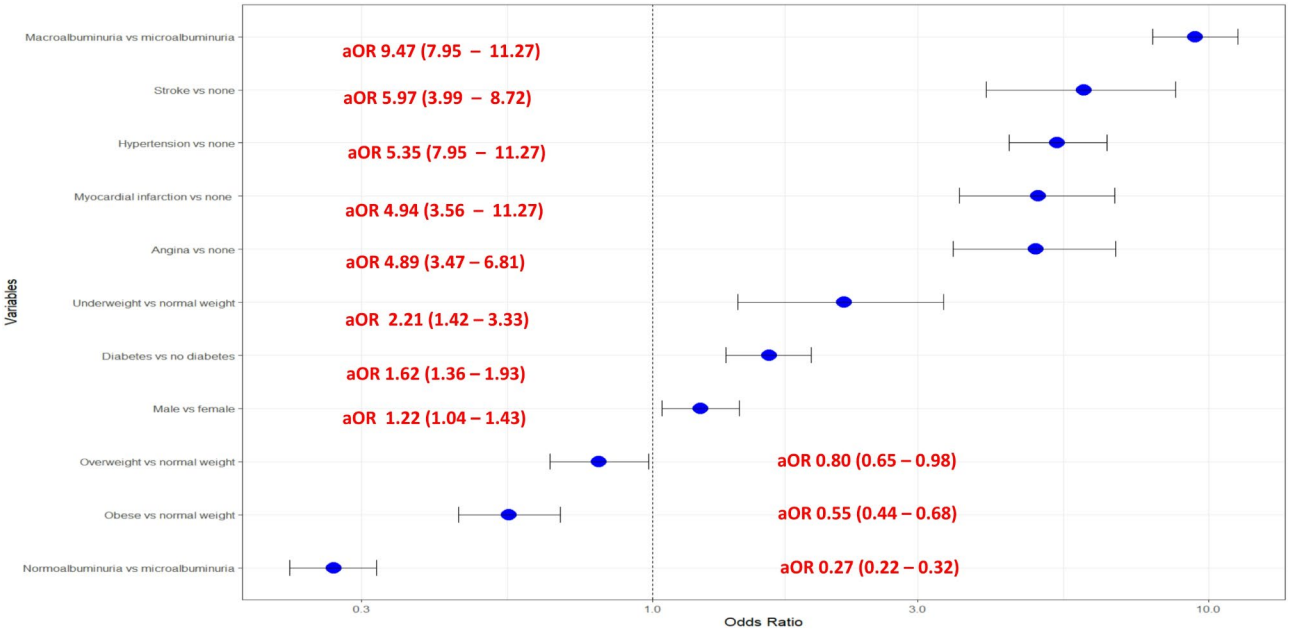

Fig. 4 Forest plot showing the predictors of ESKD (Model 3) (Red – statistically significant)

Exploratory analyses revealed that socioeconomic deprivation, non-white ethnicity, and male gender are independently associated with ESKD. Likewise, cardiovascular comorbidities, including hypertension, angina, myocardial infarction and stroke, increased the odds of ESKD. Younger age at the onset of diabetes (< 40 years) and more prolonged exposure to hyperglycaemia predispose to ESKD. The strength of this study lies in its size and comprehensive analyses using appropriate methodology adjusting for potential confounders. This study uses data from the general population and represents patients encountered in primary care settings. This study can raise awareness among primary care physicians and the public to understand the complexity of ESKD and

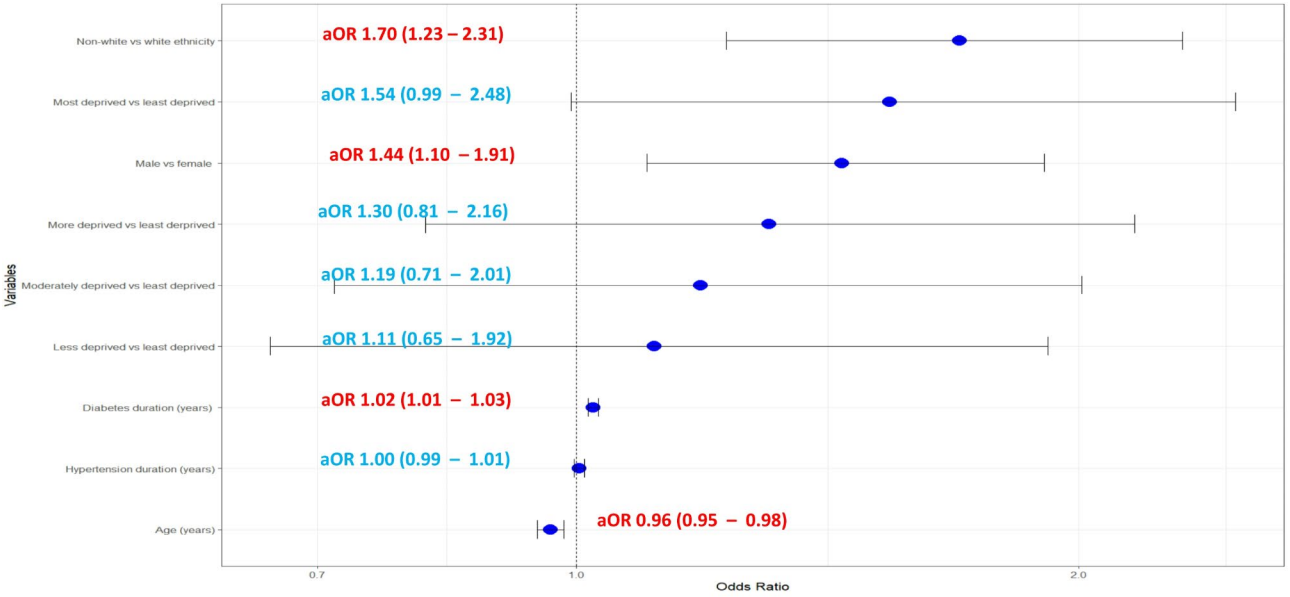

Fig. 5 Forest plot showing the predictors of ESKD (Model 4) (Red – statistically significant, turquoise – statistically insignificant)

how they can work together to reduce the risk and prevent the rising surge of ESKD.

However, this study has multiple limitations. Prevalent ESKD cases are obtained from self-reported questionnaires at a single time point, which is open to recall bias. Likewise, as we relied on the questionnaire for diabetes diagnosis, which did not specify the types of diabetes, stratified analysis was not possible. Although the albumin creatinine ratio (ACR) is the gold standard for defining microalbuminuria, the UK Biobank did not put ACR as a separate variable, which led us to use UAC, which is less reliable. The cross-sectional design of this study can only suggest an association and no temporal relationship can be ascertained. This study collected data from the first visit when the participants had already been diagnosed with ESKD and were under treatment. Therefore, the results may have been influenced by the disease, the treatment, or both. Almost 94% of the study participants were of white ethnicity, which limits the generalisability of this study. Moreover, the participants were volunteers, so the findings may not be comparable to the real-world population.

The positive relationship between older age, HbA1c, BMI, and male gender demonstrated in this study is in keeping with current literature [23–25]. Previous studies reported that although the prevalence of CKD is higher in females, progression to ESKD is more frequent in males [25]. However, the inverse relationship between total cholesterol and ESKD is counterintuitive and contradicts current knowledge, posing high cholesterol as a risk factor for ESKD [26]. The ESKD cohort in the UK Biobank was receiving secondary prevention drugs. Due to the drug treatment, this study's higher level of total cholesterol was likely made up of a lower level of triglycerides and LDL and a higher level of HDL cholesterol. Previous research suggests that triglycerides and glycoxidized LDL cholesterol may be more detrimental to renovascular endothelium than total cholesterol, potentially explaining the protective effect observed [27–29]. The negative correlation between HDL levels and ESKD risk is extensively reported in existing literature [30].

An important finding of this study is the heightened risk of ESKD associated with young-onset diabetes. Current opinions are divided on why ESKD risk is higher in people with young-onset T2DM compared to adult onset. Some experts concede that young-onset T2DM is a more aggressive disease phenotype that causes micro- and macrovascular complications at an early stage of disease trajectory and progresses more rapidly than adult-onset [31]. In contrast, others believe that prolonged exposure to hyperglycaemia, regardless of the age of diabetes onset is more detrimental to renal function [32]. This study showed that both early onset and more prolonged exposure to hyperglycaemia increase the risk of ESKD. These findings have significant implications for public health policy and practice.

Young-onset T2DM poses unique challenges that extend beyond deregulated glucose homeostasis. In adult-onset T2DM, the annual rate of pancreatic β-cell decline is approximately 7% [33, 34], while in young-onset T2DM, it is between 20 and 35% [35, 36]. Although treatment with insulin or metformin improves insulin resistance in adults, pancreatic β-cell function continues to decline in young-onset T2DM despite being on insulin and metformin [37]. Due to the rapid decline in pancreatic β-cell in individuals with young-onset T2DM,

oral hypoglycaemic drugs often become ineffective and require earlier initiation of insulin therapy [38]. Due to a physiological surge in circulating insulin antagonist hormones such as growth hormone (GH), sex hormones and cortisol during puberty [39], young and adolescents with T2DM require higher doses of insulin to maintain euglycaemia [40, 41]. However, maintaining euglycaemia does not always prevent vascular complications. Frequent glycaemic oscillations and oxidative stress associated with insulin therapy can lead to renovascular endothelial damage, evidenced by a faster progression from microalbuminuria to macroalbuminuria in those who are on insulin [42]. Although the precise mechanistic pathway is unknown, insulin therapy is associated with microalbuminuria, an early sign of renovascular disease [43]. Poor response to oral hypoglycaemic drugs and earlier initiation of insulin may explain more aggressive renal disease phenotype in young-onset T2DM.

Global T2DM management strategy heavily relies on the findings of the United Kingdom Prospective Diabetes Study (UKPDS). This landmark study ran for twenty years, from 1977 to 1997, in 23 UK clinical sites. It first showed that reducing HbA1c by 1% would reduce microvascular complications by 37%. [44] Since then, a glucocentric management strategy has been adopted worldwide to prevent vascular complications. However, the epidemiology of T2DM has evolved since UKPDS, necessitating a fresh look at the emerging challenges. In the UKPDS cohort, the mean age of study participants at the diagnosis of T2DM was 52 years [45] and the prevalence of microalbuminuria ten years after the diagnosis of T2DM was 25%.] [46]. In contrast, the Diabetes UK 2019 report suggested that a third of people may have already developed one or more microvascular complications, including microalbuminuria, when T2DM is diagnosed [47].

Kidney health inequality is a leading contributor to global health inequality. In the last 20 years, the global prevalence of younger onset T2DM has increased substantially, particularly in LMICs. (9) For example, in Bangladesh and India, the prevalence of T2DM among individuals aged 5–19 has doubled over the past 20 years [48]. In young and adolescents, T2DM incidence has surpassed type 1 diabetes mellitus (T1DM) [49]. The vascular complication rates are reported to be significantly higher in young onset T2DM than adult onset and T1DM [50, 51]. The risk is significantly higher in people from the black and minority ethnic background and they develop ESKD at a younger age [52]. Alarmingly, the median age of RRT initiation in Bangladesh is 49 years, compared to 64 years in the UK [53]. Therefore, public health policy needs realignment to reduce kidney health inequality.

The impending epidemic of young-onset T2DM and vascular complications are predictable. While high-income countries have already prioritised this and allocated resources to research and manage this epidemic, LMICs are unprepared. Urgent action is needed to develop an effective and affordable public health policy by which the emerging challenges of the rising trend of ESKD can be tackled on a global scale.

Conclusion

ESKD is a multifactorial condition predisposed by diabetes, hypertension, socioeconomic deprivation and cardiovascular comorbidities. Early-onset diabetes and hypertension significantly increase ESKD risk. Screening high-risk groups of people for microalbuminuria and individually tailored, targeted management may reduce the rising surge of ESKD cases worldwide. Supporting LMICs in prioritising renal health for public health policy is pivotal in preventing avoidable mortality and morbidity.

Supplementary Information

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Supplementary Material 1

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Author contributions

DK - Conceptualised, collected data, analysed data, undertook statistical analyses and prepared the draft manuscript. AE, MN, JO and VA - Oversaw the statistical analyses. RB, UK - commented on the methodology and analyses. SS - Offered clinical input. BZ, SK, HR, SI and AV - Read and commented on the draft manuscript. NK and DA - Conducted literature review. SdeL, RB and AS - Supervised the project. All authors read the manuscript before submission.

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Data availability

UK Biobank data can be obtained by application (www.ukbiobank.ac.uk).

Declarations

Ethics approval and consent to participate

The UK Biobank received ethical approval from the National Information Governance Board for Health and Social Care (NIGB) and the Northwest Multicentre Research Ethics Committee (11/NW/03820). There was no formal involvement of the public and patients in this study. All participants gave informed consent to participate in the study and data sharing. This study was conducted adhering to the principle of the Declaration of Helsinki.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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References

1. Nguyen NTQ, Cockwell P, Maxwell AP, Griffin M, O'Brien T, O'Neill C. Chronic kidney disease, health-related quality of life and their associated economic burden among a nationally representative sample of community dwelling adults in England. PLoS ONE. 2018;13(11):e0207960.
2. Hossain MP, Goyder EC, Rigby JE, El Nahas M. CKD and poverty: a growing global challenge. Am J Kidney Dis. 2009;53(1):166–74.
3. Alebiosu CO, Ayodele OE. The global burden of chronic kidney disease and the way forward. Ethn Dis. 2005;15(3):418–23.
4. Lv J-C, Zhang L-X. Prevalence and disease burden of chronic kidney disease. In: Liu B-C, Lan H-Y, Lv L-L, editors. Renal fibrosis: mechanisms and therapies. Singapore: Springer Singapore; 2019. pp. 3–15.
5. Cockwell P, Fisher L-A. The global burden of chronic kidney disease. Lancet. 2020;395(10225):662–4.
6. Wang H, Naghavi M, Allen C, Barber RM, Bhutta ZA, Carter A, et al. Global, regional,and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980–2015: a systematic analysis for the Global Burden of Disease Study 2015. The Lancet. 2016;388(10053):1459– 544.
7. Yu Y, Zhang M, Tang Y, Zhai C, Hu W, Yu G et al. Global disease burden attributable to kidney dysfunction, 1990–2019: A health inequality and trend analysis based on the global burden of disease study. Diabetes Res Clin Pract. 2024:111801.
8. George C, Mogueo A, Okpechi I, Echouffo-Tcheugui JB, Kengne AP. Chronic kidney disease in low-income to middle-income countries: the case for increased screening. BMJ Global Health. 2017;2(2):e000256.
9. Xie J, Wang M, Long Z, Ning H, Li J, Cao Y et al. Global burden of type 2 diabetes in adolescents and young adults, 1990–2019: systematic analysis of the global burden of disease study 2019. BMJ. 2022:e072385.
10. Dart AB, Martens PJ, Rigatto C, Brownell MD, Dean HJ, Sellers EA. Earlier onset of complications in youth with type 2 diabetes. Diabetes Care. 2014;37(2):436–43.
11. Chadban S, Arıcı M, Power A, Wu M-S, Mennini FS, Arango Álvarez JJ, et al. Projecting the economic burden of chronic kidney disease at the patient level (Inside CKD): a microsimulation modelling study. eClinicalMedicine. 2024;72:102615.
12. Tunstall-Pedoe H. Preventing Chronic Diseases. A Vital Investment: WHO Global Report. Geneva: World Health Organization, 2005. pp 200. CHF 30.00. ISBN 92 4 1563001. Also published on http://www.who.int/chp/chronic_disease_report/en. Oxford University Press; 2006.
13. Luyckx VA, Tonelli M, Stanifer JW. The global burden of kidney disease and the sustainable development goals. Bull World Health Organ. 2018;96(6):414.
14. Thompson S, James M, Wiebe N, Hemmelgarn B, Manns B, Klarenbach S, et al. Cause of death in patients with reduced kidney function. J Am Soc Nephrol. 2015;26(10):2504.
15. Mathur R, Dreyer G, Yaqoob MM, Hull SA. Ethnic differences in the progression of chronic kidney disease and risk of death in a UK diabetic population: an observational cohort study. BMJ Open. 2018;8(3):e020145.
16. Norris K, Nissenson AR. Race, gender, and socioeconomic disparities in CKD in the united States. J Am Soc Nephrol. 2008;19(7):1261–70.
17. Bycroft C, Freeman C, Petkova D, Band G, Elliott LT, Sharp K, et al. The UK biobank resource with deep phenotyping and genomic data. Nature. 2018;562(7726):203–9.
18. Sudlow C, Gallacher J, Allen N, Beral V, Burton P, Danesh J, et al. UK biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. PLoS Med. 2015;12(3):e1001779.
19. Levey AS, Eckardt K-U, Tsukamoto Y, Levin A, Coresh J, Rossert J, et al. Definition and classification of chronic kidney disease: A position statement from kidney disease: improving global outcomes (KDIGO). Kidney Int. 2005;67(6):2089–100.
20. International Expert Committee report on the. Role of the A1C assay in the diagnosis of diabetes. Diabetes Care. 2009;32(7):1327–34.
21. Morse S, Vogiatzakis IN. Resource use and deprivation: geographical analysis of the ecological footprint and Townsend index for England. Sustain [Internet]. 2014;6(8):4749. 71 pp.].
22. Von Elm E, Altman DG, Egger M, Pocock SJ, GÃ¸tzsche PC, Vandenbroucke JP. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. Lancet (London England). 2007;370(9596):1453.
23. Hsu C-y, Iribarren C, McCulloch CE, Darbinian J, Go AS. Risk factors for end-stage renal disease: 25-year follow-up. Arch Intern Med. 2009;169(4):342–50.
24. Sheen YJ, Sheu WHH. Risks of rapid decline renal function in patients with type 2 diabetes. 2014;5:835–46.
25. Cobo G, Hecking M, Port FK, Exner I, Lindholm B, Stenvinkel P, et al. Sex and gender differences in chronic kidney disease: progression to end-stage renal disease and haemodialysis. Clin Sci. 2016;130(14):1147–63.
26. Fox CS, Muntner P. Trends in diabetes, high cholesterol, and hypertension in chronic kidney disease among US adults: 1988–1994 to 1999–2004. Diabetes Care. 2008;31(7):1337–42.
27. Wang Y-X, Wang A-P, Ye Y-N, Gao Z-N, Tang X-L, Yan L et al. Elevated triglycerides rather than other lipid parameters are associated with increased urinary albumin to creatinine ratio in the general population of China: a report from the reaction study. Cardiovasc Diabetol. 2019;18(1).
28. Bjornstad P, Maahs DM, Wadwa RP, Pyle L, Rewers M, Eckel RH, et al. Plasma triglycerides predict incident albuminuria and progression of coronary artery calcification in adults with type 1 diabetes: the coronary artery calcification in type 1 diabetes study. J Clin Lipidol. 2014;8(6):576–83.
29. Shiu SWM, Tan KCB, Wong Y, Leng L, Bucala R. Glycoxidized LDL increases lectin-like oxidised low density lipoprotein receptor-1 in diabetes mellitus. 2009;203:522–7.
30. Zoppini G, Targher G, Chonchol M, Perrone F, Lippi G, Muggeo M. Higher HDL cholesterol levels are associated with a lower incidence of chronic kidney disease in patients with type 2 diabetes. 2009;19:580–6.
31. Lascar N, Brown J, Pattison H, Barnett AH, Bailey CJ, Bellary S. Type 2 diabetes in adolescents and young adults. Lancet Diabetes Endocrinol. 2018;6(1):69–80.
32. Wu T, Ding L, Andoh V, Zhang J, Chen L. The mechanism of Hyperglycemia-Induced renal cell injury in diabetic nephropathy disease: an update. Life (Basel). 2023;13(2).
33. Kahn SE, Lachin JM, Zinman B, Haffner SM, Aftring RP, Paul G, et al. Effects of Rosiglitazone, glyburide, and Metformin on Î²-cell function and insulin sensitivity in ADOPT. Diabetes. 2011;60(5):1552–60.
34. Matthews DR, Cull CA, Stratton IM, Holman RR, Turner RC. UKPDS 26: sulphonylurea failure in Nonâ insulin dependent diabetic patients over six years. Diabet Med. 1998;15(4):297–303.
35. Group TS. Effects of Metformin, Metformin plus Rosiglitazone, and Metformin plus lifestyle on insulin sensitivity and β-cell function in today. Diabetes Care. 2013;36(6):1749–57.
36. Bacha F, Gungor N, Lee S, Arslanian SA. Progressive deterioration of β-cell function in obese youth with type 2 diabetes. Pediatr Diabetes. 2013;14(2):106–11.

37. Effects of treatment. Of impaired glucose tolerance or recently diagnosed type 2 diabetes with Metformin alone or in combination with insulin glargine on β-cell function: comparison of responses in youth and adults. Diabetes. 2019;68(8):1670–80.
38. Copeland KC, Silverstein J, Moore KR, Prazar GE, Raymer T, Shiffman RN, et al. Management of newly diagnosed type 2 diabetes mellitus (T2DM) in children and adolescents. Pediatrics. 2013;131(2):364–82.
39. Hindmarsh P, Di Silvio L, Pringle PJ, Kurtz AB, Brook CGD. Changes in serum insulin concentration during puberty and their relationship to growth hormone. Clin Endocrinol. 1988;28(4):381–8.
40. Hannon TS, Janosky J, Arslanian SA. Longitudinal study of physiologic insulin resistance and metabolic changes of puberty. Pediatr Res. 2006;60(6):759–63.
41. Arslanian S, Bacha F, Grey M, Marcus MD, White NH, Zeitler P. Evaluation and management of Youth-Onset type 2 diabetes: A position statement by the American diabetes association. Diabetes Care. 2018;41(12):2648–68.
42. Ma RC, Wong C, Wang C, So W, Loo K, Wong SC, et al. Relationship between glucose variability, glycaemic control, oxidative stress and peripheral blood mononuclear cell NF-kappa B activity in patients with type 1 and Insulin-Treated type 2 diabetes. Diabetes. 2010;59:A65–A.
43. Skrha J, Soupal J, PrÃ¡znÃ½ M. Glucose variability, HbA1c and microvascular complications. Reviews Endocr Metabolic Disorders. 2016;17(1):103–10.
44. Stratton IM, Adler AI, Neil HAW, Matthews DR, Manley SE, Cull CA, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. BMJ. 2000;321(7258):405–12.
45. Turner RC, Holman RR, Matthews DR, Oakes SF, Bassett PA, Stratton IM, et al. UK prospective diabetes study (UKPDS). 8. Study design, progress and performance. Diabetologia. 1991;34(12):877–90.
46. Adler AI, Stevens RJ, Manley SE, Bilous RW, Cull CA, Holman RR, et al. Development and progression of nephropathy in type 2 diabetes: the united Kingdom prospective diabetes study (UKPDS 64). Kidney Int. 2003;63(1):225–32.
47. Diabetes UK. Report -Â https://www.diabetes.org.uk/professionals/position-statements-reports/statistics. 2019.
48. Praveen PA, Kumar SR, Tandon N. Type 2 diabetes in youth in South Asia. Curr Diab Rep. 2015;15:1–10.
49. Bloomgarden ZT. Type 2 diabetes in the young: the evolving epidemic. Diabetes Care. 2004;27(4):998–1010.
50. Al-Saeed AH, Constantino MI, Molyneaux L, D'Souza M, Limacher-Gisler F, Luo C, et al. An inverse relationship between age of type 2 diabetes onset and complication risk and mortality: the impact of Youth-Onset type 2 diabetes. Diabetes Care. 2016;39(5):823–9.
51. Dabelea D, Stafford JM, Mayer-Davis EJ, D'Agostino R Jr., Dolan L, Imperatore G et al. Association of type 1 diabetes vs type 2 diabetes diagnosed during childhood and adolescence with complications during teenage years and young adulthood. (1538–3598 (Electronic)).
52. Norton JM. Chapter 4 - Social determinants of Racial and socioeconomic disparities in CKD and ESRD. In: Cukor D, Cohen SD, Kimmel PL, editors. Psychosocial aspects of chronic kidney disease. Academic; 2021. pp. 49–88.
53. Kar S, Islam MF. Global Dialysis perspective. Bangladesh Kidney360. 2023;4(10):e1472–5.

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