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Navigating the Complexities of End-stage Renal Disease (ESRD) from Risk Factors to Outcome: Insights from the UK Biobank Cohort

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Summary

Background: The prevalence of end-stage renal disease (ESRD) is rising worldwide. Hyperglycaemia, hypertension, and dyslipidaemia are known risk factors. However, despite managing these risk factors optimally, ESRD cases are increasing. This study aims to explore the interactions of cardiorenal risk factors, socioeconomic, ethnic and cardiovascular comorbidities with ESRD outcomes.

Methods: This cross-sectional study used data from participants recruited between 2006 and 2010 in UK Biobank. Multivariable logistic regression models were fitted to analyse the risk factors for ESRD. Results are presented as adjusted odds ratio (aOR) and 95% confidence intervals (95% CI).

Findings: Among 502,408 study participants, 1191 (0.2%) were diagnosed with ESRD. Individuals diagnosed with diabetes before 40 had more than twice, and those with hypertension had 73% higher odds of ESRD, compared to those who were diagnosed between 40 and 60 years [aOR 2.26 (1.57 – 3.24)], and [aOR 1.73 (1.21 – 2.44)], respectively. In contrast to those without any cardiovascular disease (CVD), those with stroke, hypertension, myocardial infarction, and angina had higher odds of ESRD [aOR 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. Each additional year of diabetes duration increased ESRD odds by 2% [aOR 1.02 (1.01 - 1.03)]. Non-white ethnicity was linked to a 70% higher ESRD risk compared to white ethnicity [aOR 1.70 (1.23 - 2.31)], and individuals with diabetes had a 62% higher ESRD odds compared to those without [aOR 1.62 (1.36 - 1.93)]. The most socioeconomically deprived quintile had 83% higher ESRD risk [aOR 1.83 (1.48 - 2.26)] than the least deprived. Elevated HbA1c levels were also associated with higher ESRD risk [aOR 1.03 (1.02 - 1.03)], while each unit increase in high-density lipoprotein (HDL) decreased ESRD risk by 55% [aOR 0.45 (0.35 - 0.57)]. Proteinuria increased the ESRD odds 11-fold compared to microalbuminuria [aOR 11.0 (9.25 - 13.07), while normoalbuminuria reduced the odds by 76% [aOR 0.24 (0.20 - 0.28)].

Interpretation: Early onset of diabetes and hypertension is linked to higher odds of ESRD. Male gender, non-white ethnicity, higher HbA1c levels and prolonged hyperglycaemia are independently associated with ESRD. Microalbuminuria serves as a reliable early indicator of ESRD risk.

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Research in context

On August 9, 2024, using the MeSH term "end-stage renal disease (ESRD)" with the Boolean operator 'AND' combining "risk factors" we searched PubMed electronic database, without any language restrictions. The search identified 1000 journal articles, but none of them explored the interactions of different cardiorenal risk factors, socioeconomic deprivations, age of onset and duration of diabetes and hypertension, and ethnicity with ESRD outcomes.

In line with global increase in the prevalence of prediabetes and type 2 diabetes mellitus (T2DM), the incidence of chronic kidney disease (CKD) and ESRD are on the rise. Individuals with CKD are at a higher risk of ESRD and cardiovascular disease (CVD). It is one of the most expensive complications of metabolic deregulation, which needs renal replacement therapy (RRT) or transplant, putting enormous pressure on the health service budget.

Global diabetes management guidelines rely heavily on the United Kingdom Prospective Diabetes Study (UKPDS), which showed management of HbA1c, and blood pressure can reduce the risk of CKD and CVD. Despite managing these risk factors optimally, there is a disparity in ESRD outcomes based on ethnicity and socioeconomic backgrounds and between high-income and low- and middle-income countries (LMICs). The precise cause for these disparities is yet to be elucidated. Due to the evolving epidemiology of T2DM and the rising trend of ESRD and associated complications, the applicability of guidelines based on the UKPDS to meet the emerging challenges needs further evaluation.

Due to childhood obesity, rapid urbanisation and popularity of westernised fast-food culture in LMICs, a rapid rise in T2DM in children and adolescents have been observed. As there is no universal primary healthcare service available to detect T2DM at an early stage, an increasing number of people are presenting with established complications at a young age. For instance, while the mean age of RRT in the UK is 64 years, in Bangladesh, the mean age of RRT is 49 years, requiring an additional 15 years of RRT, which is unaffordable by majority of the population. The healthcare infrastructure in LMICs is unequipped to tackle this growing public health challenge.

The added value of this study

This study demonstrated the strong relationship between socioeconomic deprivation, BMI, young-onset diabetes and hypertension, CVD comorbidities and non-white ethnicities with ESRD. It also highlighted that microalbuminuria could be a sensitive marker for predicting ESRD. Compared to people with microalbuminuria, those with normoalbuminuria has a lower odds of ESRD, while those with proteinuria has a significantly higher odds. This study indicates that one of the contributing factors to the global rise in ESRD cases may be the younger onset of diabetes and hypertension and prolonged exposure to hyperglycaemia. Screening people for microalbuminuria, who develop diabetes and hypertension below the age of 40, and a holistic multifactorial management of cardiorenal risk factors may reduce the rising surge of ESRD worldwide. This is particularly important for the LMICs where there is no primary care cardiorenal risk management strategy in place.

Implications for all the available evidence

Due to the evolving nature of metabolic deregulation and vascular complications, applicability of management guidelines derived from the UKPDS needs urgent evaluation. Similarly, further research is needed to elucidate the drivers behind the ethnic and socioeconomic variation in renal health. Public health policy and practice need to be recalibrated to account for the emerging challenges of childhood diabetes, hypertension, and cardiovascular comorbidities. It needs a holistic multifactorial approach rather than a piece-meal glucocentric approach. Given the disproportionate impact of ESRD on the vulnerable communities of the society, it should be a global priority for public health intervention to reduce health inequity, premature mortality and morbidity.

Introduction

The rising prevalence of chronic kidney disease (CKD) and end-stage renal disease (ESRD) is a significant contributor 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 ESRD estimated between 4.9 and 7.1 million. [4] From 1990 to 2017, the age-standardised incidence of ESRD 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, ESRD became the 12th leading cause of global mortality in 2015, up from the 17th in 1990. [5] Notably, these data do not account for the cardiovascular mortality attributable to CKD and ESRD. 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 is in stark contrast to 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 ESRD is particularly pronounced in low- and middle-income countries (LMICs). [8] The impact of CKD and ESRD on health-related quality of life (HRQoL) is substantial, with costs rising exponentially 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 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% of the total cost. [11] The World Health Organization (WHO) has classed CKD as one of the priority non-communicable diseases (NCD) to tackle health inequalities. [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 ESRD. [14] Therefore, management of CVD risk factors such as hypertension, hyperglycaemia and dyslipidaemia were

principal therapeutic targets. However, in recent years, due to an epidemiological shift in the disease prevalence of T2DM and CKD, despite managing these risk factors, ESRD cases are rising. Notably, people from minority ethnic backgrounds are developing ESRD 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 ESRD at a younger age, require RRT for a longer duration, and die earlier than the white Indigenous population. [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 background and cardiorenal risk factors with ESRD outcomes from a global perspective.

In this study, we explore the prevalence of ESRD in the UK Biobank cohort based on age, gender, ethnicity, socioeconomic background and cardiovascular comorbidities. We developed seven logistic regression models, incorporating different cardiometabolic risk factors in different ethnicities and socioeconomic backgrounds, to predict how cardiorenal risk factors were associated with ESRD outcomes.

Methods

Study design and data source

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 40–70 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 ESRD cases.

Ethics, public and patient involvement and software

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. There was no

formal involvement of the public and patients in this study. We used statistical software R version 4.4.2.

Outcome ascertainment, inclusion and exclusion criteria

Prevalent cases of ESRD were identified using self-administered questionnaires. For this study, people who reported ESRD at the first recruitment visit were the group of interest. All the study participants (n=502490) were eligible for inclusion. However, before the study began, 82 participants withdrew their consent, and they were excluded from the analyses, leaving a total of 502,408. A flow chart is included. (Supplementary material - figure 1)

Exposures and covariates

Smoking status was categorised into current smokers (those who smoked at the time of the questionnaire), 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 cigarette consumption, excluding other forms of nicotine use, such as e-cigarettes. 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 proteinuria (>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] which incorporate data on participants' postal codes, employment status, educational attainment, car ownership, and household income. Participants were stratified into five quintiles: most deprived, more deprived, moderately deprived, less deprived, and least deprived.

Statistical analyses

People who reported ESRD and those who did not were grouped into ESRD and non-ESRD 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 were assessed using histogram visual inspection and the Kolmogorov-Smirnov test. (Supplementary material – Figures 2-6) For significance testing, a two-way Student's t-test was applied to numerical variables with a parametric distribution, while the Wilcoxon test was used for non-parametric distributions.

Participants were categorised into two groups based on their questionnaire responses: ESRD and non-ESRD. The chi-squared test was used to assess the significance of differences in categorical variables between these groups. Multivariable logistic regression models were employed to identify the relationship between cardiorenal risk factors and ESRD. The results were expressed as adjusted odds ratios (aOR) with 95% confidence intervals (CI) and p-values indicating statistical significance. Missing data were handled using multiple imputation by chained equations (MICE). A bar chart and a missing data pattern graph showed that missingness at random (MAR) (see supplementary material – Figure 9). Logistic regression assumption multicollinearity was tested using variance inflation factor (VIF) which showed all the models satisfied this assumption (Supplementary Material 6). Statistical significance was determined at a p-value of <0.05.

Multivariate logistic regression models

Seven separate logistic regression models were constructed to explore ESRD predictors based on baseline characteristics and the binary outcome of ESRD.

- **Model 1** – In this model, sociodemographic profiles and smoking status were fitted with cardiorenal risk factors such as systolic blood pressure, cholesterol, BMI, and HbA1c.

- **Model 2** – It incorporated sociodemographic profiles, smoking and glycaemic status with cardiorenal risk factors of diastolic blood pressure (DBP), high-density lipoprotein (HDL) and BMI.
- **Model 3** – In this model, we used age, gender, BMI categories, albuminuria categories and hypertension status to predict ESRD outcomes.
- **Model 4** – In this model, we explored the odds of ESRD after adjusting for age, gender, age at diabetes and hypertension diagnosis, UAC values, and waist circumference.
- **Model 5** – In this model, we explored the relationship of different comorbidities with ESRD.
- **Model 6** – Covariates used in this model were diabetes and hypertension duration, smoking, albuminuria and BMI status

- **Model 7** – We fitted age, gender, ethnicity, and socioeconomic deprivation in this model to predict the odds of ESRD.

The results were visualised using forest plots displaying adjusted odds ratios and 95% confidence intervals and were reported using 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 final analysis included data from 502,408 participants who completed the questionnaire and consented to the use of their data for research purposes. The baseline characteristics of the participants are summarised in Table 1.

A hierarchical pattern was observed between patient-reported ESRD and socioeconomic deprivation levels. For instance, a higher prevalence of ESRD was noted in individuals from the most deprived quintile compared to those from the least deprived quintile. Generally, male participants exhibited significantly higher serum creatinine levels across all except the moderately deprived quintile. (Figure 1)

HbA1c levels of 73.9% of participants with ESRD were within the normoglycaemia range, 8.7% had prediabetes, and 17.4% fell within the diabetes range. The disparity in serum creatinine levels between males and females was most pronounced in the normoglycemic group and gradually decreased from prediabetes to diabetes. (Figure 2)

Among participants reporting ESRD, 47.7% were non-smokers, 41% were ex-smokers, and 10.7% were current smokers. In the non-smoker and ex-smoker categories, male participants had higher median creatinine levels. However, in the current smoker category, female participants exhibited higher serum creatinine levels. (Figure 3)

The scatter plot linear model showed that the relationship between HbA1c, and blood pressure with creatinine was not linear, suggesting that isolated management of either of the risk factors may not have an impact on the ESRD outcomes. (Supplementary materials - figures 7 – 9)

Table 1: Baseline characteristics of UK Biobank participants with and without ESRD

Variable name		ESRD (n=1191)	Non-ESRD (n= 501,217)	P value
Age (years) mean (SD)		58.97 (7.62)	57.04 (8.17)	<0.001
Sex – Male (%)		753 (63.2)	228329 (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)	471565 (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)	101160 (20.2)	<0.001
	Less deprived	194 (16.3)	100402 (20.1)	<0.001
	Moderately deprived	200 (16.8)	98968 (19.9)	<0.001
	More deprived	260 (21.9)	100238 (20.0)	<0.001
	Most deprived	367 (30.9)	99826 (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)	426721 (91.7)	<0.001
	Prediabetes	92 (8.7)	21208 (4.6)	<0.001
	Diabetes	185 (17.4)	17271 (3.7)	<0.001
BMI Status [n (%)]	**Underweight**	41 (3.5)	11663 (2.3)	<0.001
	Normal weight	259 (22.3)	153313 (30.8)	<0.001
	Overweight	462 (39.7)	211252 (42.4)	<0.001
	Obese	401 (34.5)	121911 (24.5)	<0.001
Smoking status [n (%)]	**Wish not to disclose**	7 (0.6)	2050 (0.4)	<0.001
	Non-smoker	567 (47.7)	272906 (54.5)	<0.001
	Ex-smoker	488 (41.0)	172535 (34.5)	<0.001
	Current smoker	127 (10.7)	52835 (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
Cardiovascular disease [n (%)]	**None**	260 (21.9)	350630 (70.1)	<0.001
	Hypertension	697 (58.6)	119442 (23.9)	<0.001
	Angina	78 (6.6)	11254 (2.2)	<0.001
	Stroke	48 (4.0)	6170 (1.2)	<0.001
	Heart attack	100 (8.4)	11505 (2.3)	<0.001

Model 1

Multivariable logistic regression fitted in Model 1 showed that the odds of ESRD increased by 83% in the most deprived and 49% in the more deprived, compared to the least deprived quintiles. Compared to females, the odds of ESRD in males were 48% higher. Each unit of increase in HbA1c and BMI increased the odds of ESRD by 3%. Each unit of total cholesterol reduced the risk of ESRD by 37%. Smoking status did not have a significant impact on the ESRD odds. (Figure 4)

Model 2

This model showed a positive relationship between male gender, socioeconomic deprivation, age, and BMI. Compared to females, the odds of ESRD were 48% higher in males; compared to the least deprived, the odds of ESRD were 96% higher in the most deprived and 50% higher in more deprived quintiles. The odds of ESRD in individuals with prediabetes and normoglycaemia, in comparison to those with diabetes, had 47% and 71% lower risk of ESRD, respectively. Each unit of increase in age and BMI was associated with a 2% increased risk, and each unit increase in HDL and DBP was associated with 55% and 2% lower risk of ESRD, respectively. The adjusted model did not demonstrate any statistically significant independent relationship between smoking status and ESRD. (Figure 5)

Model 3

This model showed that compared to people with microalbuminuria, those with proteinuria were at an 11-fold increased risk of ESRD. Likewise, individuals in the underweight category, compared to those in the normal weight category, were more than twice as likely to have ESRD. Likewise, males, compared to females, had a 39% increased risk of ESRD. Individuals without hypertension, compared to those with, were at 66%, and individuals with normoalbuminuria, compared with those with microalbuminuria, were at 76% lower risk of ESRD. Those with a BMI within the obesity category were at 28% lower risk of ESRD. Age and overweight category did not have any statistically significant relationship with ESRD. (Figure 6)

Model 4

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 ESRD, respectively. Individuals who developed diabetes above the age of 60 were 64% less likely to have ESRD 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 ESRD. (Figure 7)

Model 5

The adjusted model showed that compared to individuals with microalbuminuria, those with proteinuria had 9.47 times higher, and those with normoalbuminuria had 73% lower odds of ESRD. 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 ESRD. Compared to individuals without any cardiovascular disease, those with stroke, hypertension, myocardial infarction, and angina had 5.97, 5.35, 4.94-, and 4.89-times higher odds of ESRD. Male compared to female were 22%, and individuals with diabetes compared to those without were 62% higher risk of ESRD. (Figure 8)

Model 6

This model revealed that compared to people with microalbuminuria, those with proteinuria had 8.72 times higher, and those with normoalbuminuria were at 66% lower risk of ESRD. Each year of diabetes duration increased the odds of ESRD by 2%. Compared to individuals with normal weight, those with a BMI in the obesity range had 48% lower odds of ESRD. Hypertension duration and smoking status did not have any statistically significant relationship with ESRD. (Figure 9)

Model 7

This model showed that after adjusting for all the above confounding variables, the odds of ESRD in non-white ethnicity were 70% higher than in white ethnicity. Compared to females, males were at 44% higher risk of ESRD. Each year of increase in diabetes duration was associated with a 2% increased risk of ESRD. Duration of hypertension did not have any statistically significant association with ESRD. Age was negatively associated with ESRD. Interestingly, when ethnicity and deprivation were fitted in the same model, while ethnicity statistically significantly increased the risk of ESRD, deprivation was not a significant predictor of ESRD. (Figure 10)

Discussion

This study demonstrated that ESRD is a multifactorial disease, and significant variations exist in how cardiometabolic risk factors impact on the ESRD outcomes. Socioeconomic deprivation, non-white ethnicity, and male gender are independently associated with ESRD. Likewise, cardiovascular comorbidities, including hypertension, angina, myocardial infarction and stroke, increase the odds of ESRD. Younger age at the onset of diabetes (<40 years) and more prolonged exposure to hyperglycaemia predispose to ESRD. Compared to those with microalbuminuria, those with proteinuria had an 11-fold increased risk of ESRD, while those with normoglycaemia had a 76% lower risk. Female smokers had a higher creatinine value than male smokers, suggesting that female smokers may be at a higher risk of ESRD. HbA1c and BMI are independent predictors of ESRD. People with diabetes, compared to those without, were at a 62% higher risk of ESRD.

The strength of this study lies in its size and comprehensive analyses using appropriate methodology adjusting for potential confounders. To our knowledge, this is the first study that has investigated the interaction between social determinants of renal health and cardiorenal risk factors, using data from over half a million participants. However, this study has multiple limitations. Prevalent ESRD cases are obtained from self-reported questionnaires that are 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, 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. In this study, data were collected from the first visit, when the participants had already been diagnosed with ESRD and were under treatment. Therefore, the results may have been influenced by the disease, the treatment, or both.

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 ESRD is more frequent in males. [25] However, the inverse relationship between total cholesterol and ESRD is counterintuitive and contradicts current knowledge, which posits high cholesterol as a risk factor for ESRD. [26] The ESRD cohort in the UK Biobank was receiving secondary prevention drugs. It is likely that due to the drug treatment, the higher level of total cholesterol in this study was 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 ESRD risk in our study aligns with existing literature. [30]

An important finding of this study is the heightened risk of ESRD associated with young-onset diabetes. Model 4 showed that individuals who developed diabetes before 40, compared to those who developed it between 40 and 60, were 126% more likely to develop ESRD. Each additional year of diabetes duration increased ESRD risk by 2%. Current opinions are divided on why ESRD 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 the disease trajectory and progresses more rapidly than adult-onset T2DM. [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 ESRD. 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 20-35%. [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 albuminuria to proteinuria. [42] Although the precise mechanistic pathway is unknown, insulin therapy is associated with albuminuria, which is 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 is heavily reliant 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 33%. [44] Since then, a glucocentric management strategy has been adopted

worldwide. 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. The prevalence of microalbuminuria ten years after the diagnosis of T2DM was 25%. [45] In contrast, the Diabetes UK 2019 report suggested that a third of people may have already developed one or more microvascular complications when T2DM is diagnosed. [46]

T2DM is no longer an exclusive disease of middle-aged and older individuals. 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. [47] In young and adolescents, T2DM incidence has now surpassed type 1 diabetes mellitus (T1DM). [48] The complication rates in T2DM are reported to be significantly higher in young onset T2DM than in T1DM. [49, 50]

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 ESRD can be tackled on a global scale.

Conclusion

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

Conflict of Interest declaration

The NIHR funds lead author DK. He worked as a specialist adviser for the Quality Standard Advisory Committee (QSAC) of the National Institute for Health and Care Excellence (NICE). SdeL is the Director of RCGP, RSC and is the lead at the Clinical Informatics and Health Outcomes Research Group at the University of Oxford. He has received research funding through his University from AstraZeneca, GSK, Eli Lily, Moderna, MSD, Sanofi, Seqirus, and Takeda. He also served as an advisory board member for AstraZeneca, GSK, Sanofi, Seqirus, and Pfizer. Other authors declare no conflict of interest. This project received no external funding.

Author Contributions: DK led the study design, data access, extraction, curation, statistical analyses, and manuscript preparation. MN, AE, JM, and VA contributed to statistical analyses. NK and DA assisted with the literature review. SdeL and AS critically appraised the methodology, reviewed the manuscript and suggested corrections. All coauthors reviewed and provided feedback on the manuscript.

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Data sharing agreements – UK Biobank data can be obtained by application (www.ukbiobank.ac.uk).

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Figures

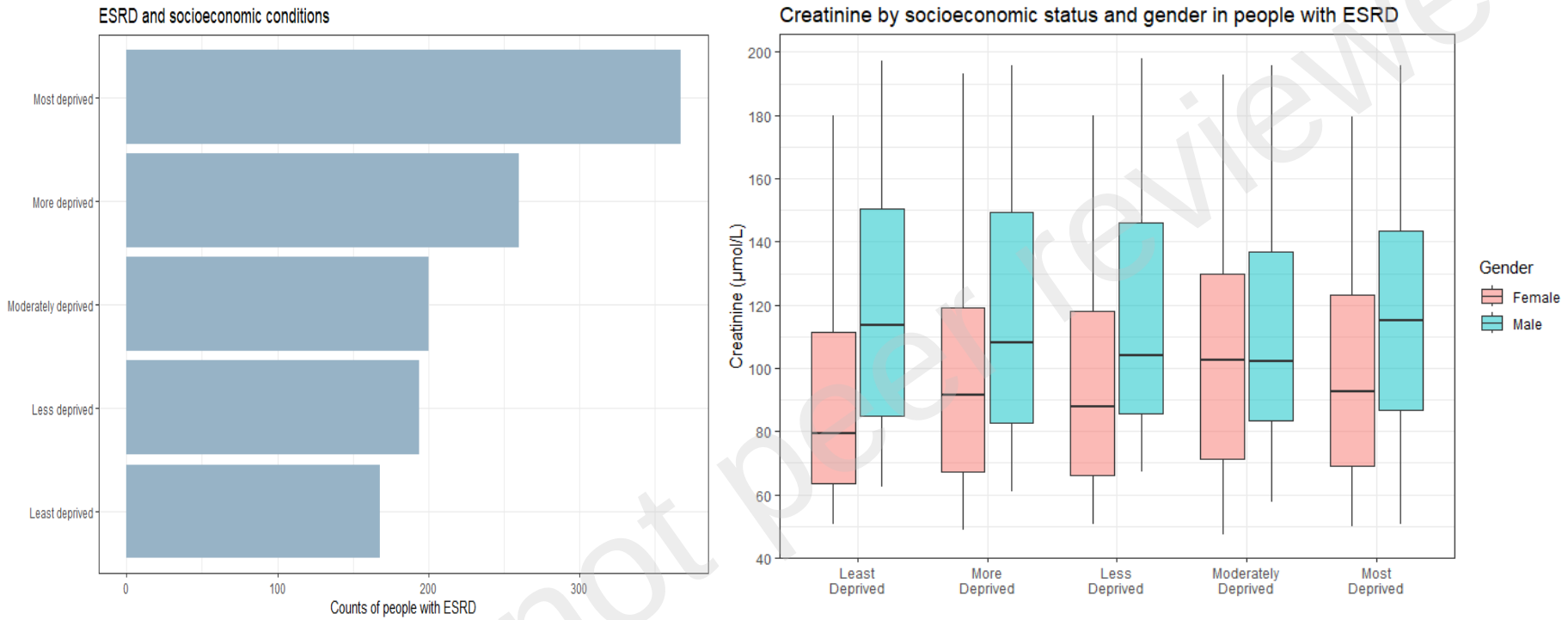


Figure 1: Distribution of people with ESRD based on gender, deprivation and serum creatinine

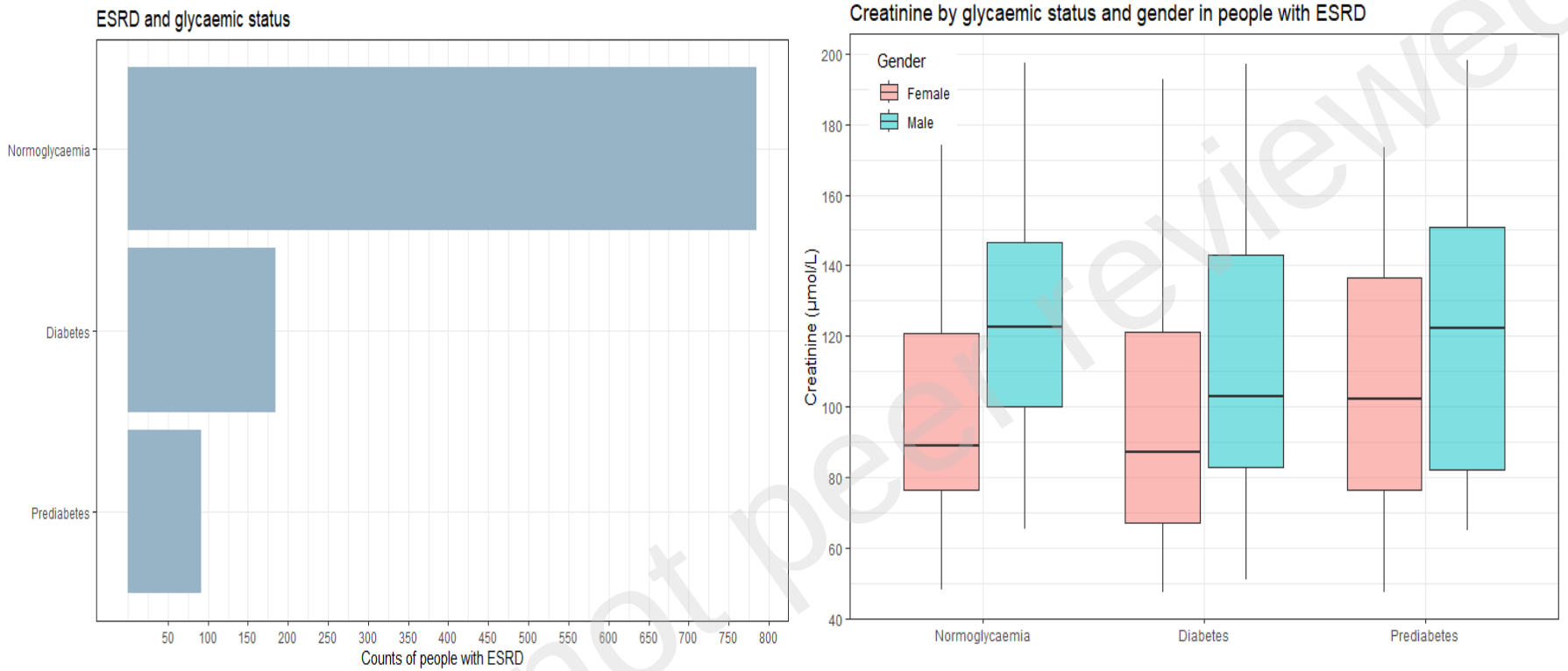


Figure 2: Distribution of people with ESRD based on gender, glycaemic status and serum creatinine

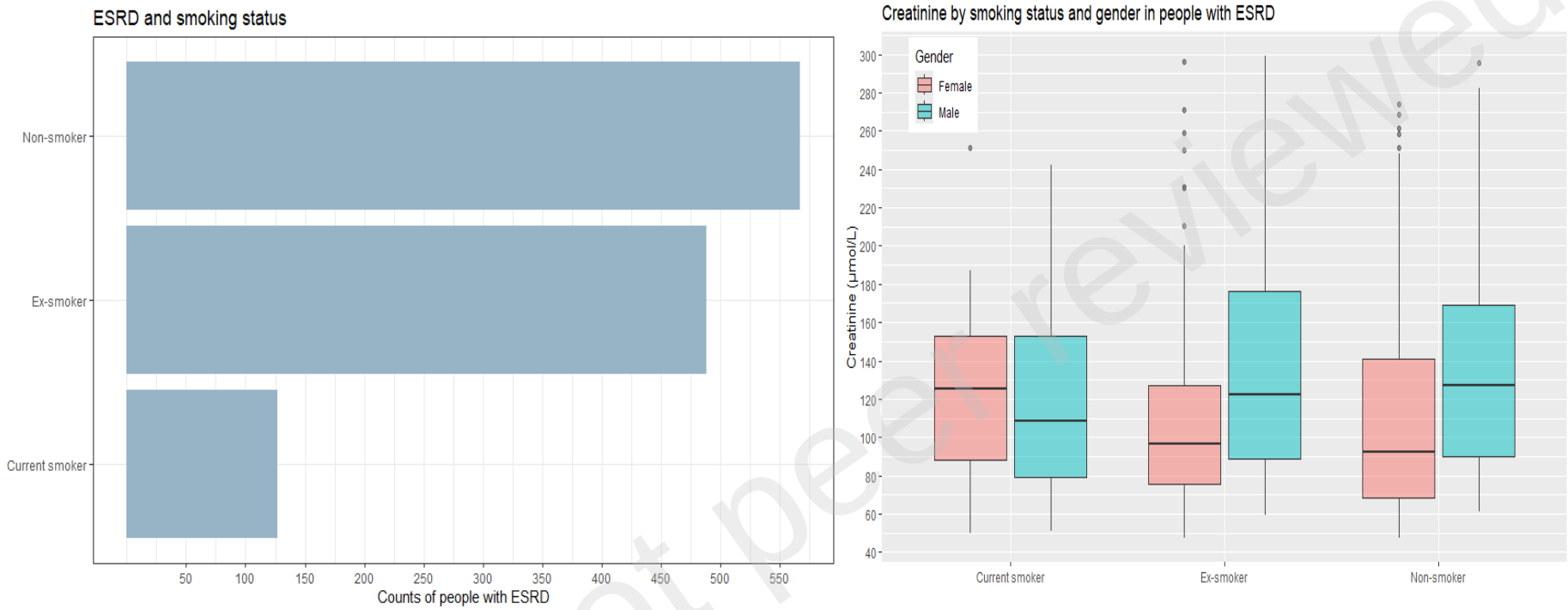
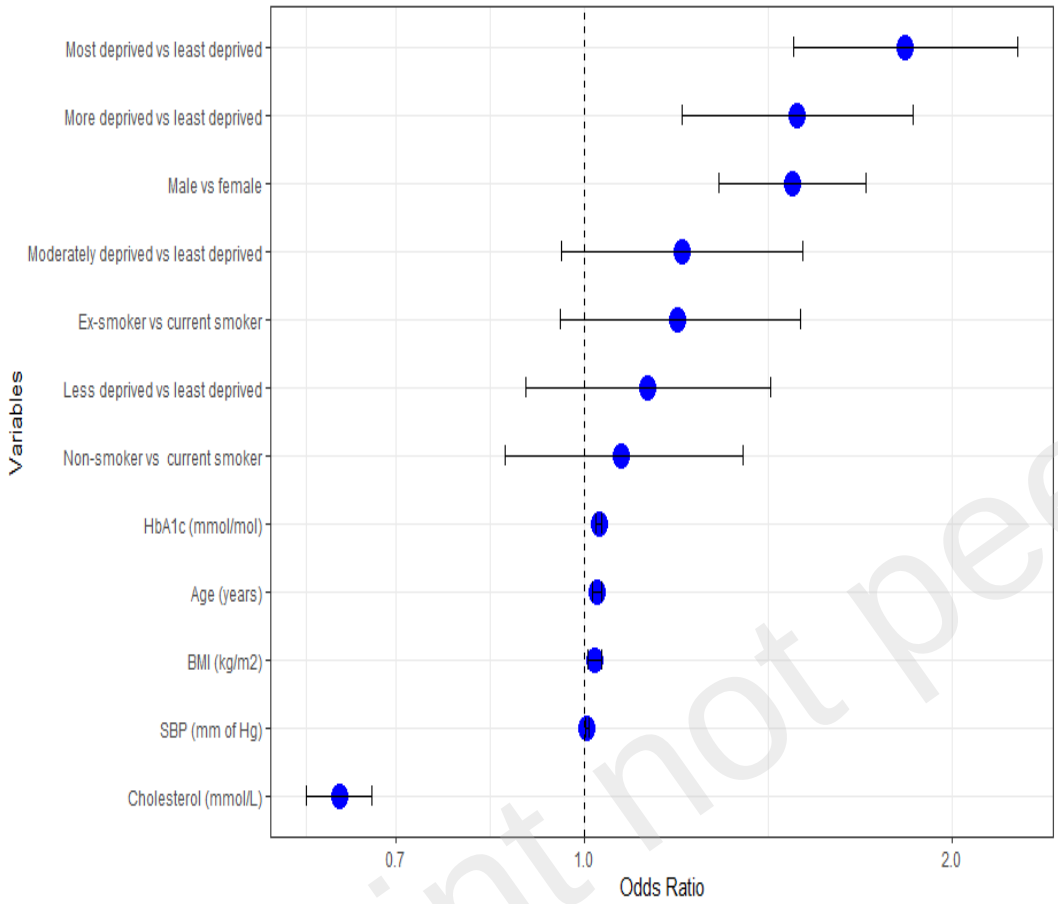


Figure 3: Distribution of people with ESRD based on sex, smoking status and serum creatinine



Most deprived vs least deprived 1.83 (1.48-2.26); p-value <0.001

More deprived vs least deprived 1.49 (1.20 – 1.86); p-value <0.001

Male vs female 1.48 (1.29 – 1.70); p-value <0.001

Moderately deprived vs least deprived 1.20 (0.96 – 1.51); p-value 0.115

Ex-smoker vs current smoker 1.19 (0.95 – 1.50); p-value 0.128

Less deprived vs least deprived 1.13 (0.89 – 1.42); p-value 0.309

Non-smoker vs current smoker 1.07 (0.86 – 1.35); p-value 0.545

HbA1c (mmol/mol) 1.03 (1.02 – 1.03); p <0.001

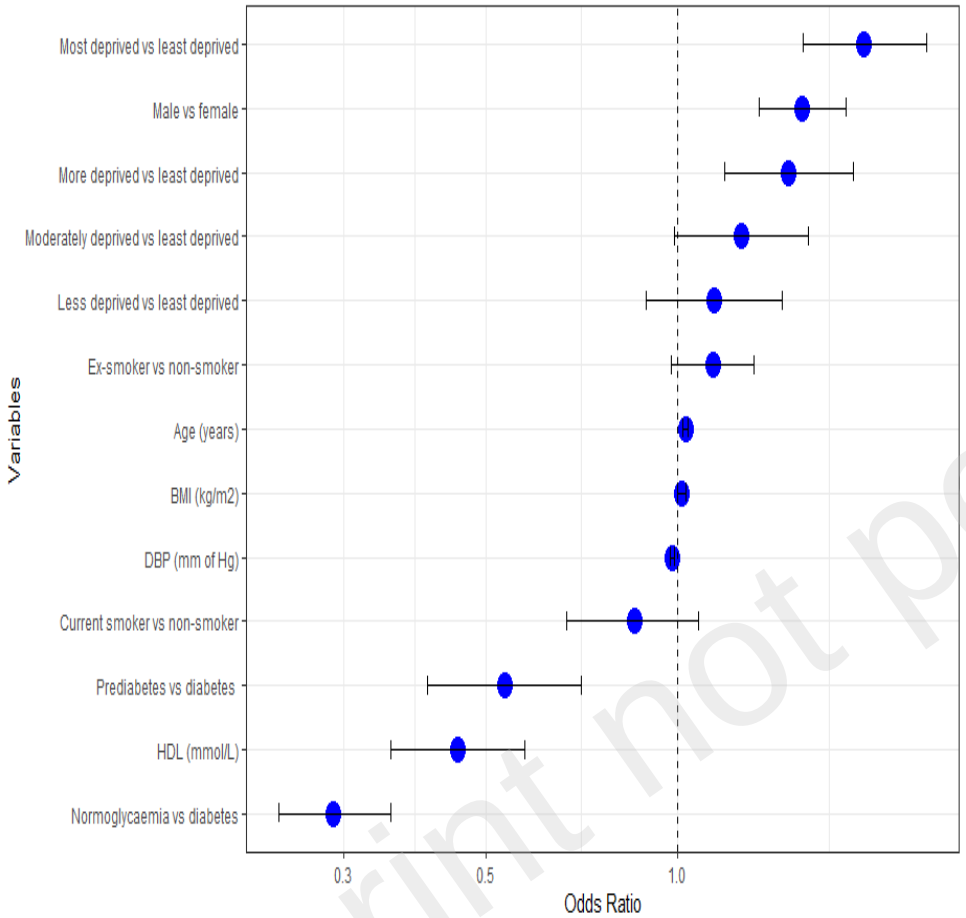
Age (years) 1.03 (1.02 – 1.03); p<0.001

BMI (kg/m^2) 1.01 (1.00 – 1.02); p-value <0.001

SBP (mm of Hg) 1.00 (1.00 – 1.01); p-value 0.013

Cholesterol (mmol/L) 0.63 (0.59 – 0.67); p-value <0.001

Figure 4: Forest plot showing the predictors of ESRD (Model 1) (Bold italic – statistically significant)



Most deprived vs least deprived 1.96 (1.57 – 2.46); p-value <0.001

Male vs female 1.48 (1.29 – 1.70); p-value <0.001

More deprived vs least deprived 1.50 (1.19 – 1.90); p-value <0.001

Moderately deprived vs least deprived 1.25 (0.99 – 1.60); p-value 0.062

Less deprived vs least deprived 1.14 (0.89 – 1.46); p-value 0.289

Ex-smoker vs non-smoker 1.13 (0.97 – 1.31); p-value 0.097

Age (years) 1.02 (1.01 – 1.03); p-value <0.001

BMI (kg/m^2) 1.02 (1.01 – 1.03); p-value 0.038

DBP (mm of Hg) 0.98 (0.97 – 0.99); p-value <0.001

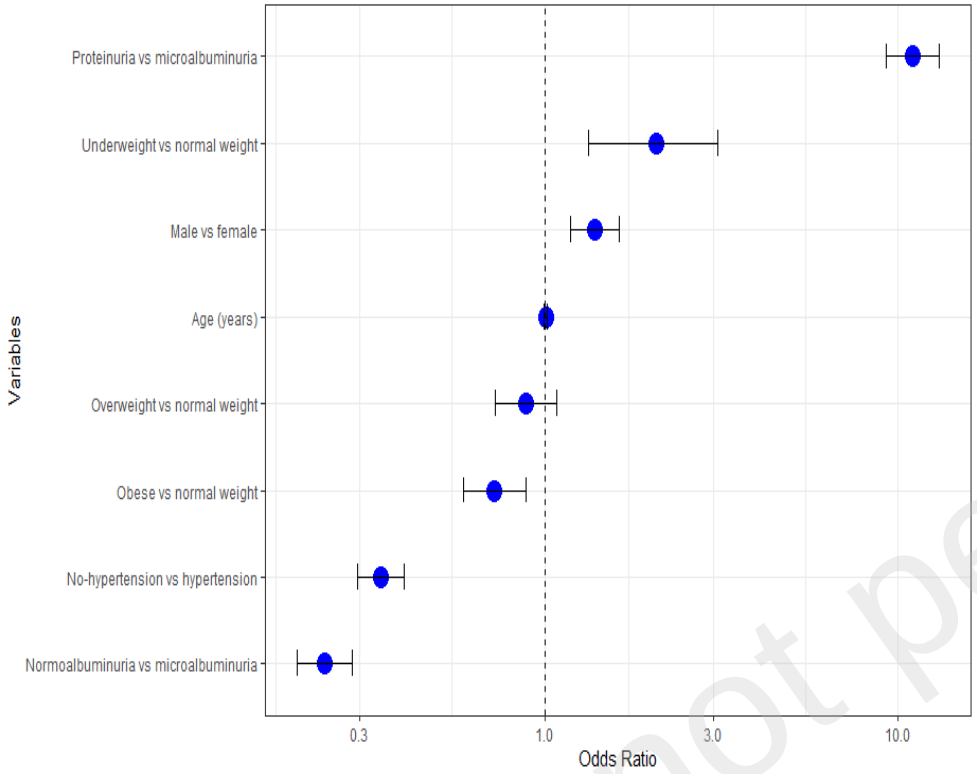
Current smoker vs non-smoker 0.85 (0.67 – 1.07); p-value 0.180

Prediabetes vs diabetes 0.53 (0.40 – 0.70); p-value <0.001

HDL (mmol/L) 0.45 (0.35 – 0.57); p-value <0.001

Normoglycaemia vs diabetes 0.29 (0.23 – 0.35); p-value <0.001

Figure 5: Forest plot showing the predictors of ESRD (Model 2) (Bold italic – statistically significant)



Proteinuria vs microalbuminuria 11.00 (9.25-13.07); p-value <0.001

Underweight vs normal weight 2.06 (1.33 - 3.09); p-value <0.001

Male vs female 1.39 (1.19 - 1.63); p-value <0.001

Age (years) 1.00 (1.00 - 1.02); p-value = 0.061

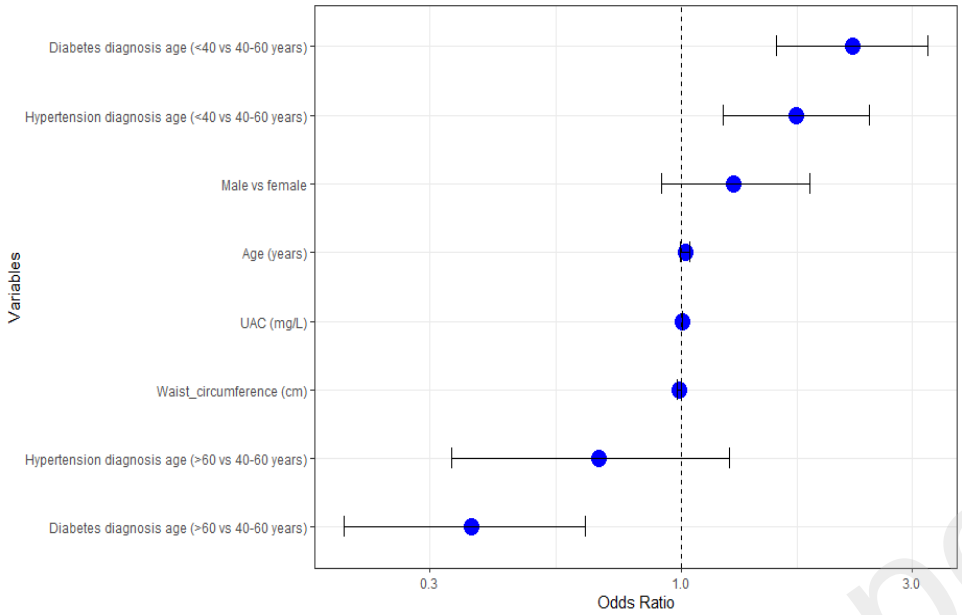
Overweight vs normal weight 0.88 (1.00 - 1.02); p-value = 0.237

Obese vs normal weight 0.72 (0.59 - 0.89); p-value = 0.001

No hypertension vs hypertension 0.34 (0.29 - 0.40); p-value <0.001

Normoalbuminuria vs microalbuminuria 0.24 (0.20 - 0.28); p-value <0.001

Figure 6: Forest plot showing the predictors of ESRD (Model 3) (Bold italic – statistically significant)



Diabetes diagnosis age (<40 vs 40-60 years) 2.26 (1.57-3.24); p-value <0.001

Hypertension diagnosis age (<40 vs 40-60 years) 1.73 (1.21-2.44); p-value <0.001

Male vs female 1.28 (0.90-1.84); p-value 0.168

Age (years) 1.01 (0.99-1.03); p-value 0.180

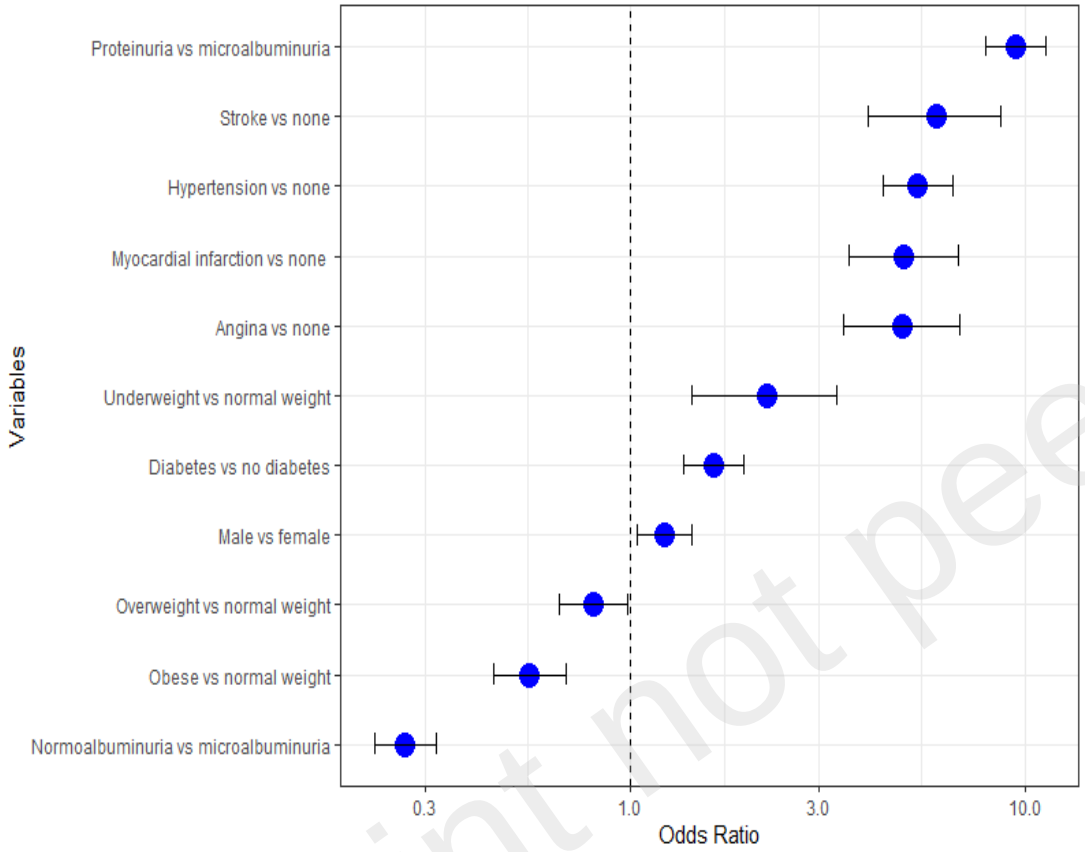
UAC (mg/L) 1.00 (1.00 – 1.00); p-value <0.001

Waist circumference (cm) 0.99 (0.98-1.00); p-value <0.001

Hypertension diagnosis age (>60 vs 40-60 years) 0.67 (0.33-1.25); p-value 0.241

Diabetes diagnosis age (>60 vs 40-60 years) 0.36 (0.20- 0.63); p-value <0.001

Figure 7: Forest plot showing the predictors of ESRD (Model 4) (Bold italic – statistically significant)



Proteinuria vs microalbuminuria 9.47 (7.95 -11.27); p <0.001

Stroke vs none 5.97 (3.99 -8.72); p <0.001

Hypertension vs none 5.35 (4.38 -6.56); p <0.001

Myocardial infarction vs none 4.94 (3.56 – 6.78); p <0.001

Angina vs no angina 4.89 (3.47 – 6.81); p <0.001

Underweight vs normal weight 2.21 (1.42 – 3.33); p <0.001

Diabetes vs no diabetes 1.62 (1.36 – 1.93); p <0.001

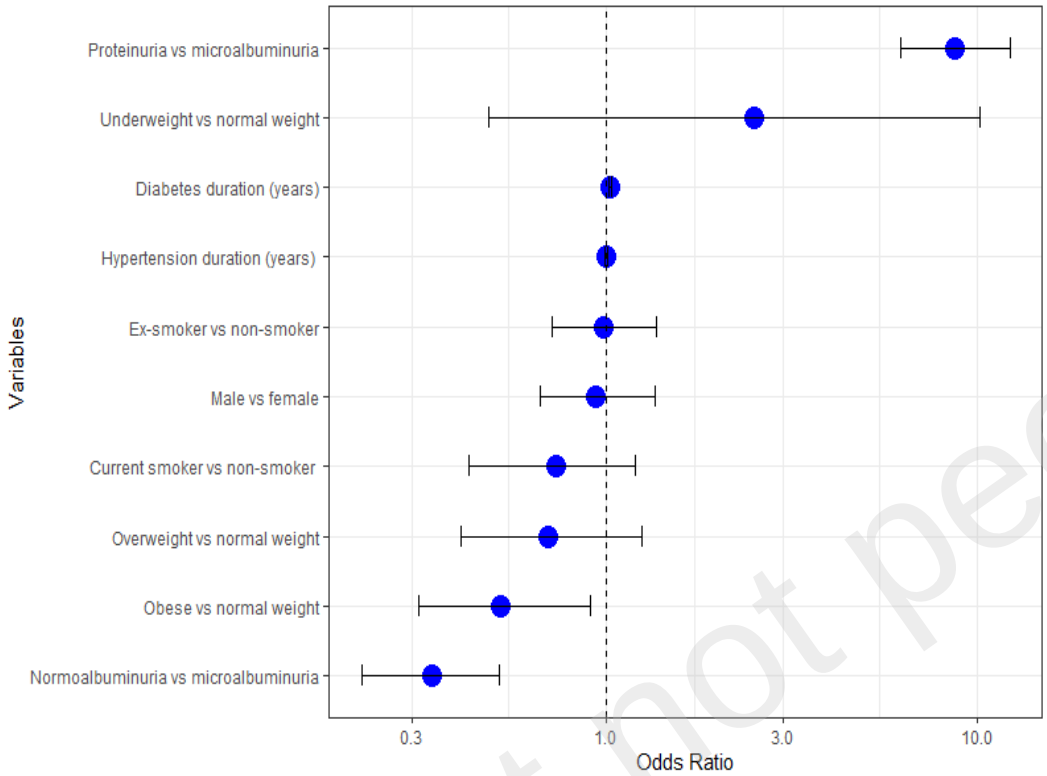
Male vs female 1.22 (1.04 – 1.43); p = 0.015

Overweight vs normal weight 0.80 (0.65 – 0.98); p = 0.031

Obese vs normal weight 0.55 (0.44 – 0.68); p <0.001

Normoalbuminuria vs microalbuminuria 0.27 (0.22 – 0.32); p <0.001

Figure 8: Forest plot showing the predictors of ESRD (Model 5) (Bold italic – statistically significant)



Proteinuria vs microalbuminuria 8.72 (6.24 – 12.25); p <0.001

Underweight vs normal weight 2.50 (0.48 – 10.19); p = 0.226

Diabetes duration 1.02 (1.01 – 1.03); p <0.001

Hypertension duration 1.00 (0.99 – 1.01); p = 0.632

Ex-smoker vs non-smoker 0.99 (0.71 – 1.37); p = 0.935

Male vs female 0.94 (0.66 – 1.35); p = 0.731

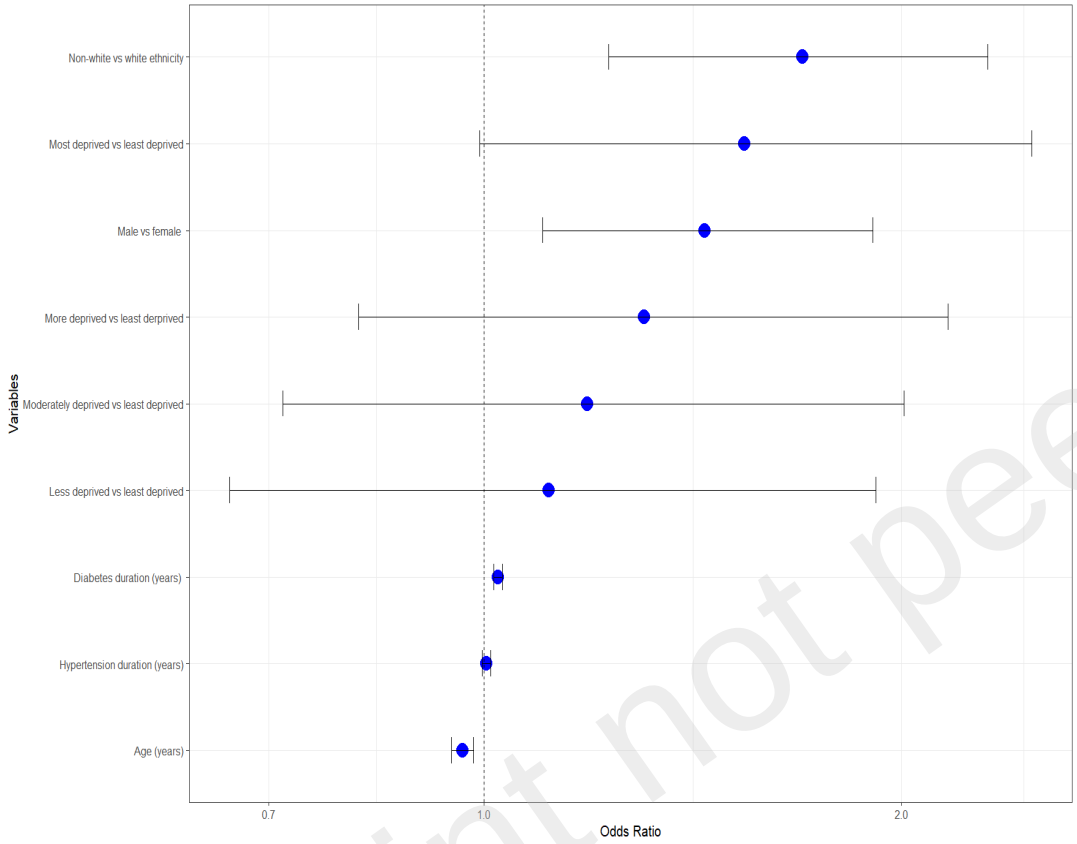
Current smoker vs non-smoker 0.73 (0.43 – 1.20); p = 0.235

Overweight vs normal weight 0.69 (0.40 – 1.25); p = 0.204

Obese vs normal weight 0.52 (0.31 – 0.91); p = 0.015

Normoalbuminuria vs microalbuminuria 0.34 (0.22 – 0.52); p <0.001

Figure 9: Forest plot showing the predictors of ESRD (Model 6) (Bold italic – statistically significant)



Non-white vs white 1.70 (1.23-2.31); p <0.001

Most deprived vs least deprived 1.54 (0.99-2.48); p=0.063

Male vs female 1.44 (1.10-1.91); p<0.001

More deprived vs least deprived 1.30 (0.81-2.16); P= 0.283

Moderately deprived vs least deprived 1.19 (0.71 – 2.01); p = 0.512

Less deprived vs least deprived 1.11 (0.65-1.92); p = 0.692

Diabetes duration (years) 1.02 (1.01- 1.03); p<0.001

Hypertension duration (years) 1.00 (0.99-1.01); p = 0.217

Age (years) 0.96 (0.95-0.98); p <0.001

Figure 10: Forest plot showing the predictors of ESRD (Model 7) (Bold italic – statistically significant)