 doi:10.20944/preprints201912.0213.v1

*Article*

# Association of Short Stature with An Increased Risk of End-Stage Renal Disease in Type 2 Diabetic Patients: A Nationwide Population-Based Cohort Study

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**Abstract:** Short stature has been associated with increased various disease and all-cause death, but no reliable data exist the association between height and end-stage renal disease (ESRD) in diabetic patients. We investigated the relationship between short stature, development of ESRD, and mortality in type 2 diabetes. This study analyzed clinical data using the National Health Insurance Database in Korea. Height was stratified by five groups according to age and sex. Risk of ESRD and all-cause mortality was analyzed with Cox proportional hazards models. During a 6.9-year follow-up period, 220,457 subjects (8.4%) died and 28,704 subjects (1.1%) started dialysis. Short stature significantly increased the incidence of ESRD and all-cause mortality in the overall cohort analysis. In multivariable analysis, hazard ratios (HR) for development of ESRD comparing the highest versus lowest quartiles of adult height were 0.86 (95% confidence interval (CI), 0.83–0.89). All-cause mortality also decreased with highest height compared to patients with lowest height after fully adjusting for confounding variables (HR 0.79, 95% CI, 0.78–0.81). Adult height had an inverse relationship with newly diagnosed ESRD and all-cause in both males and females. Short stature is strongly associated with an increased risk of ESRD and all-cause mortality in type 2 diabetes.

**Keywords:** short stature; type 2 diabetes; end-stage renal disease; mortality

## 1. Introduction

Diabetic nephropathy is a major microvascular complication of type 2 diabetes mellitus (DM), and it is the major cause of end-stage renal disease (ESRD) in many countries of the world as well as Korea [1-3]. Identification of high-risk patients with type 2 DM who would benefit from intensive treatment and follow-up is very important to prevent or delay the development of ESRD. Advanced age, duration of diabetes, poor glycemic control, hypertension, dyslipidemia, obesity, ethnicity, and socioeconomic factors were established risk factors for chronic kidney disease in DM [4]. Despite efforts to control for these risk factors, the proportion of incident dialysis in diabetic patients is continuously rising. Further investigation is needed for risk stratification of the development of ESRD in DM.

Adult height is a cumulative outcome of nutritional environment and genetic factors during the early growth period. Short stature may be a marker of inadequate fetal growth and subsequent impaired growth in early childhood, factors that are related to certain metabolic diseases in adulthood [5]. Several epidemiologic studies have reported that short stature in the normal population is associated with adverse outcomes, including hypertension, microalbuminuria, impaired glucose tolerance, type 2 DM, and cardiovascular disease, such as myocardial infarction,

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ischemic heart disease, heart failure and stroke [6,7]. Short stature is also associated with proteinuria in both type 1 and type 2 DM [8,9], but no reliable data exist on the association between final adult height and development of ESRD in diabetic patients. Therefore, we investigated whether short adult stature is an independent risk factor of the development of ESRD in patients with type 2 diabetes.

Using a population-based cohort of the National Health Insurance Database in Korea, this study aimed to (1) examine whether the incidences of newly diagnosed ESRD and all-cause death were different with respect to adult height, and (2) determine whether short stature is associated with the development of ESRD and survival in patients with type 2 diabetes.

## 2. Materials and Methods

### *2.1. Data sources and study design*

This was a nationwide retrospective observational study using the Korean National Health Insurance (NHI) Claims Database of the Health Insurance Review Agency between 2009 and 2017. The national health insurance system (NHIS) biennially provides regular health check-ups to all members in the Republic of Korea. The Korean NHIS program covers a computerized database including all claims data, such as patient demographics, drug prescriptions, diagnostic disease codes (International Classification of Disease, 10th revision; ICD-10), insurer payment coverage, patient deductions, and claimed treatment details [10,11]. After the study protocol was approved by an official review committee, the NHIS database became available to researchers, and data are provided in anonymous form. The Institutional Review Board of the Catholic University of Korea, Yeoduio St. Mary's Hospital, approved the study protocol (SC19ZNDI0125).

A total of 2,706,223 subjects aged ≥ 20 years with type 2 DM who underwent an initial baseline health checkup by the NHIS between 2009 and 2012 were recruited. A total of 35,134 subjects who were less than 30 years old were excluded because they were more likely to have type 1 DM. Patients with missing data (n = 40,638) and with a diagnosis of ESRD before the index year (n = 8,941) were also excluded to avoid the confounding effect of preexisting ESRD (Figure 1). Because adult height is affected by age and sex, subjects were divided into quintiles depending on adult height for each age group (20–39 years, 40–49 years, 50-59 years, 60-69 years, and ≥ 70 years) and sex. The quintiles from ten different age and sex groups were merged into a single quintile. The reference values for each quintile according to age and sex groups are shown in Table S1.

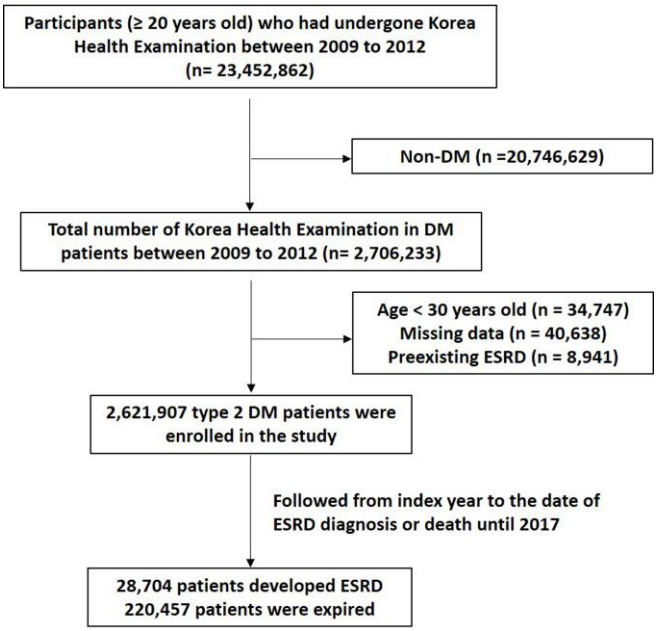


**Figure 1.** Flow chart of patient inclusion in the study.

### *2.2 Data collection*

 doi:10.20944/preprints201912.0213.v1

Data were analyzed for all participants at baseline and included age, sex, height, weight, body mass index (BMI), waist circumference, blood pressure (BP), fasting glucose, estimated glomerular filtration rate (eGFR), and triglyceride after an overnight fast. Quality control of laboratory tests was performed according to the South Korean Association of Laboratory Quality Control. The presence of hypertension, DM, hyperlipidemia, chronic kidney disease (CKD), and lifestyle behaviors, such as physical activities, smoking, and alcohol consumption, were evaluated using standardized self-reporting questionnaires. Smoking status was classified as non-smoker or current smoker, and alcohol consumption was classified as non-drinker or heavy drinker (≥ 30 g/day) based on a question about frequency of alcohol intake. CKD was defined as eGFR less than 60 mL/min/1.73m$^2$. Low income level was defined as the lowest 25% of income earners.

*2.3. Definition of type 2 diabetes mellitus, end-stage renal disease, and mortality*

The diagnostic criteria of type 2 DM in all participants were as follows: (1) at least one claim per year under ICD-10 codes for type 2 DM (E11-E14), or (2) fasting glucose level ≥ 126 mg/dL. All participants visited outpatient or inpatient care diagnosed with type 2 DM and accepted at least one prescription of anti-diabetic drugs. The primary endpoint was newly diagnosed ESRD or all-cause mortality during follow-up period. Detection of ESRD was defined as the combination of ICD-10 codes for renal replacement therapy (N18-19) and special medical aid codes for performance of hemodialysis or peritoneal dialysis (hemodialysis: O7011-O7020 or V001, peritoneal dialysis: O7071-O7075 or V003). Patients with ESRD are registered as special medical aid beneficiaries, and all expenses for medical care provided to dialysis patients are reimbursed by the Korean Health Insurance Review and Assessment Service. Therefore, all ESRD patients in the whole population of South Korea could be recognized and analyzed. Subjects with acute kidney injury who simultaneously had both an acute renal failure code and a dialysis code and subjects who had a continuous renal replacement therapy code or an acute peritoneal dialysis code were excluded. Claims data were merged with national mortality data from the National Statistical Office for analysis.

*2.4. Statistical analyses*

Data for continuous variables are described as mean ± standard deviation or median value (interquartile range). Data for categorical variables are described as numbers and percentages. Incidence rates of ESRD and all-cause mortality were calculated as the number of incident cases divided by the entire follow-up period and expressed per 1,000 person-years. The strength of the association between adult stature and primary endpoint were assessed using the hazard ratio (HR) and 95% confidence interval (CI) calculated by Cox proportional-hazards regression analysis. Three models were model 1 adjusted for age, sex, and BMI; Model 2 adjusted for age, sex, BMI, smoking, alcohol intake, regular exercise, and low income; and Model 3 adjusted for age, sex, BMI, smoking, alcohol intake, regular exercise, low income, hyperlipidemia, hypertension, CKD, insulin use, OHA, and DM duration > 5 years. All statistical analyses were performed using SAS version 9.4 software (SAS Institute, Cary, NC, USA). Statistical significance was set as $p < 0.05$.

## 3. Results

*3.1. Baseline characteristics*

Baseline characteristics of the study population according to five groups of adult height levels are shown in Table 1. The study cohort consisted of 2,621,907 patients with type 2 DM who were detected between 2009 and 2012 and followed until 2017. Mean age of the total population was 57.9 ± 11.9 years. Among all subjects, 1,575,271 subjects (60.1%) were male, 1,498,762 (57.2%) had hypertension, 1,118,407 (42.7%) had hyperlipidemia, and 291,461 (11.1%) were diagnosed with CKD. Subjects in lower quintiles of adult height were older and more likely to be men. Weight circumference was lowest in the shorter groups, and adult BMI was also lower in the shorter groups. Lower quintiles of adult height had fewer heavy drinkers, fewer physical activities, and lower incomes. Systolic BP showed negative relationships with height. Shorter subjects had a lower

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proportion of diabetes duration longer than 5 years, and they used oral hypoglycemic agents (OHA) and insulin injection less frequently. Shorter stature was also associated with lower baseline levels of blood fasting glucose and triglyceride. Baseline levels of eGFR increased gradually as heights of the subjects decreased. Because of the large sample size, *p* values for trend were < 0.001 for all variables. During a mean follow-up period of 6.9 years, 28,704 (1.1%) subjects were newly diagnosed with ESRD and 220,457 (8.4%) subjects died. The total number of deaths gradually increased from subjects with the highest to the lowest adult height.

**Table 1.** Baseline characteristics across the quintiles of height in diabetic patients of cohort (n = 2,621,907)

| | Height (Quintile) | | | | | *p*-value |
|---|---|---|---|---|---|---|
| | Q1 (n = 513,054) | Q2 (n = 541,528) | Q3 (n = 500,279) | Q4 (n = 514,133) | Q5 (n = 552,913) | |
| **Height** | 154.6 ± 7.7 | 158.8 ± 7.4 | 163.2 ± 7.1 | 165.2 ± 7.7 | 169.7 ± 8.2 | < 0.001 |
| **Male (cm)** | 160.0 ± 3.6 | 164.9 ± 2.6 | 1680.0 ± 2.4 | 171.1 ±2.5 | 175.9 ± 3.7 | < 0.001 |
| **Female (cm)** | 146.2 ± 3.6 | 151.0 ± 2.6 | 154.1 ± 2.6 | 156.3 ± 2.7 | 160.8 ± 3.6 | < 0.001 |
| **Age (year)** | 58.5 ± 12.0 | 58.7 ± 12.2 | 57.2 ± 11.9 | 57.3 ± 11.7 | 57.7 ± 11.7 | < 0.001 |
| **Age (year, n (%))** | | | | | | < 0.001 |
| **30-39** | 31,707 (6.2) | 37,664 (7.0) | 34,214 (6.8) | 28,295 (5.5) | 33,985 (6.1) | |
| **40-64** | 317,008 (61.8) | 320,841 (59.2) | 321,877 (64.4) | 336,872 (65.5) | 355,430 (64.3) | |
| **65-** | 164,339 (32.0) | 183,023 (33.8) | 144,188 (28.8) | 148,966 (29.0) | 163,498 (29.6) | |
| **Sex (male, n (%))** | 310,139 (60.4) | 303,613 (56.1) | 329,224 (65.8) | 307,942 (59.9) | 324,353 (58.7) | < 0.001 |
| **Body mass index (kg/m²)** | 25.0 ± 3.4 | 25.1 ± 3.4 | 25.1 ± 3.3 | 25.1 ± 3.3 | 25.1 ± 3.3 | < 0.001 |
| **Waist circumference (cm)** | 83.3 ± 8.2 | 84.5 ± 8.3 | 85.6 ± 8.3 | 86.3 ± 8.5 | 87.6 ± 8.7 | < 0.001 |
| **Social history** | | | | | | |
| **Current Smoker (n (%))** | 130,767 (25.5) | 129,658 (23.9) | 139,420 (27.9) | 134,630 (26.2) | 139,534 (25.2) | < 0.001 |
| **Alcohol intake (n, (%))** | | | | | | < 0.001 |
| **No** | 473,305 (92.3) | 500,510 (92.4) | 453,430 (90.6) | 467,421 (90.9) | 501,773 (90.8) | |
| **Heavy** | 39,749 (7.7) | 41,018 (7.6) | 46,849 (9.4) | 46,712 (9.1) | 51,140 (9.2) | |
| **Regular exercise (n (%))** | 221,411 (43.2) | 246,434 (45.5) | 246,671 (49.3) | 256,317 (49.9) | 281,236 (50.9) | < 0.001 |
| **Low income (n (%))** | 126,869 (24.7) | 122,835 (22.7) | 109,293 (21.9) | 109,607 (21.3) | 114,428 (20.7) | < 0.001 |
| **Past medical history** | | | | | | |
| **Hypertension (n (%))** | 295,180 (57.5) | 314,170 (58.0) | 281,922 (56.4) | 291,485 (56.7) | 315,905 (57.1) | < 0.001 |
| **Hyperlipidemia (n (%))** | 215,819 (42.1) | 235,027 (43.4) | 208,563 (41.7) | 221,489 (43.1) | 237,509 (43.0) | < 0.001 |
| **CKD (n (%))** | 54,889 (10.7) | 62,957 (11.6) | 52,410 (10.5) | 56,631 (11.0) | 64,574 (11.7) | < 0.001 |
| **DM control** | | | | | | |
| **DM duration > 5 yrs (n (%))** | 152,335 (29.7) | 168,934 (31.2) | 151,300 (30.2) | 159,929 (31.1) | 179,766 (32.5) | < 0.001 |
| **Insulin use (n, (%))** | 40,172 (7.8) | 44,281 (8.2) | 39,437 (7.9) | 41,993 (8.2) | 48,202 (8.7) | < 0.001 |
| **OHA use (n, (%))** | 202,542 (39.5) | 220,201 (40.7) | 197,858 (39.6) | 207,451 (40.4) | 227,797 (41.2) | < 0.001 |
| **Systolic BP (mmHg)** | 129.3 ± 16.1 | 129.2 ± 15.8 | 129.0 ± 15.6 | 129.0 ± 15.5 | 128.9 ± 15.3 | < 0.001 |
| **Diastolic BP (mmHg)** | 79.0 ± 10.3 | 78.9 ± 10.2 | 79.2 ± 10.2 | 79.1 ± 10.1 | 79.1 ± 10.1 | < 0.001 |
| **Glucose (mg/dL)** | 143.5 ± 44.1 | 143.0 ± 43.5 | 144.5 ± 43.6 | 144.2 ± 43.6 | 144.4 ± 43.3 | < 0.001 |
| **eGFR (mL/min/1.73m²)** | 86.4 ± 34.7 | 85.1 ± 35.2 | 85.5 ± 35.8 | 84.9 ± 35.8 | 84.1 ± 36.0 | < 0.001 |
| **Log Triglyceride** | 148.6 (148.4-148.8) | 148.3 (148.1-148.5) | 150.5 (150.3-150.7) | 150.3 (150.0-150.5) | 149.1 (148.8-149.3) | < 0.001 |
| **Death (n, (%))** | 52,768 (10.3) | 49,731 (9.2) | 40,344 (8.1) | 37,465 (7.3) | 40,149 (7.3) | < 0.001 |

Abbreviations: BP, blood pressure; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; OHA, oral hypoglycemic agents; Q, quintile. Low income was defined as those bottoms 25% of incomes. Chronic kidney disease was defined as eGFR < 60 mL/min/1.73m². Data are expressed as the mean ± SD or n (%). *p* values for the trend were < 0.001 for all variables because of the large size of the study population.

 doi:10.20944/preprints201912.0213.v1

*3.2. Association with adult height, incidence of end-stage renal disease, and all-cause mortality in subjects with type 2 diabetes mellitus*

The relative risk of newly diagnosed ESRD and mortality was analyzed according to quintiles for adult height. Multivariable Cox regression analyses for incidence of ESRD and all-cause mortality are shown in Table 2. Overall, the incidence of ESRD and all-cause death in type 2 DM were 1.59 and 12.14 per 1,000 person-years, respectively. The incidence of ESRD was 1.66, 1.61, 1.59, 1.51, and 1.56, respectively, and incidence of all-cause death was 14.90, 13.25, 11.63, 10.49, and 10.50, respectively, per 1,000 person-years. All other groups had significantly lower incidence rates of ESRD compared with those in the lowest quintile in type 2 DM.

The lowest quintile of adult height was used as a reference category of the HRs of ESRD and all-cause mortality, as shown in Table 2. Height was negatively associated with incidence of ESRD in multivariable analysis. The HR for incident ESRD was 0.93 (95% CI, 0.9–0.97), 0.9 (95% CI, 0.87–0.94), 0.86 (95% CI, 0.83–0.89), and 0.86 (95% CI, 0.83–0.89) for the second, third, fourth, and fifth quintiles versus the first quintile of adult height, respectively, after adjusting for age, sex, smoking, alcohol intake, regular exercise, low income, BMI, hyperlipidemia, hypertension, CKD, insulin use, OHA, and DM duration > 5 years ($p$ trend < 0.001, Table 2, model 3). Adult height was an independent predictor of newly diagnosed ESRD even after full adjustment of confounding factors.

An incrementally lower risk of all-cause death was also observed for higher quintiles of adult height compared with the lowest quintile group in multivariable analysis. The tallest group had approximately 20 percent lower risk of all-cause death than the shortest group even after adjustment for age, sex, smoking, alcohol intake, regular exercise, low income, BMI, hyperlipidemia, hypertension, CKD, insulin use, OHA, and DM duration > 5 years. The HR for all-cause death was 0.88 (95% CI, 0.87–0.89), 0.84 (95% CI, 0.83–0.85), 0.81 (95% CI, 0.80–0.82), and 0.79 (95% CI, 0.78–0.81) for the second, third, fourth, and fifth quintiles versus the first quintile of adult height, respectively, even after full multivariable adjustment ($p$ trend < 0.001).

**Table 2.** Multivariate Cox regression analysis for end-stage renal disease and mortality by quintiles of adult height in diabetic patients

| | Events /Observed | Follow-up duration (Person-years) | Incidence rate (per 1,000 person-years) | HR (95% CI) | | |
|---|---|---|---|---|---|---|
| | | | | Model 1 | Model 2 | Model 3 |
| **ESRD** | | | | | | |
| **Q1** | 5,856/513,054 | 3,528,708 | 1.66 | 1 (reference) | 1 (reference) | 1 (reference) |
| **Q2** | 6,022/541,528 | 3,739,612 | 1.61 | 0.97 (0.94-1.01) | 0.99 (0.95-1.02) | 0.93 (0.9-0.97) |
| **Q3** | 5,496/500,279 | 3,455,874 | 1.59 | 0.97 (0.94-1.01) | 1.00 (0.96-1.03) | 0.90 (0.87-0.94) |
| **Q4** | 5,371/514,133 | 3,558,167 | 1.51 | 0.95 (0.92-0.99) | 0.98 (0.94-1.02) | 0.86 (0.83-0.89) |
| **Q5** | 5,959/552,913 | 3,809,028 | 1.56 | 0.98 (0.94-1.01) | 1.01 (0.98-1.05) | 0.86 (0.83-0.89) |
| | ***p*-trend** | | | 0.085 | 0.691 | < 0.001 |
| **All-cause mortality** | | | | | | |
| **Q1** | 52,768/513,054 | 3,542,352 | 14.90 | 1 (reference) | 1 (reference) | 1 (reference) |
| **Q2** | 49,731/541,528 | 3,753,381 | 13.25 | 0.88 (0.87-0.89) | 0.89 (0.88-0.90) | 0.88 (0.87-0.89) |
| **Q3** | 40,344/500,279 | 3,468,864 | 11.63 | 0.84 (0.83-0.85) | 0.86 (0.84-0.87) | 0.84 (0.83-0.85) |
| **Q4** | 37,465/514,133 | 3,570,716 | 10.49 | 0.80 (0.79-0.82) | 0.83 (0.82-0.84) | 0.81 (0.80-0.82) |
| **Q5** | 40,149/552,913 | 3,822,972 | 10.50 | 0.79 (0.78-0.80) | 0.82 (0.81-0.83) | 0.79 (0.78-0.81) |
| | ***p*-trend** | | | < 0.001 | < 0.001 | < 0.001 |

Abbreviations: BMI, body mass index; CI, confidence interval; CKD, chronic kidney disease; DM, diabetes mellitus; ESRD, end-stage renal disease; HR, hazard ratio; HTN, hypertension; OHA, oral hypoglycemia agents; Q, quintile. Model 1: adjusted for age, sex, BMI, Model 2: adjusted for age, sex, BMI, smoking, alcohol intake, regular exercise, and low income, Model 3: adjusted for age, sex, BMI, smoking, alcohol intake, regular exercise, low income, hyperlipidemia, hypertension, CKD, insulin use, OHA, and DM duration > 5 years.

 doi:10.20944/preprints201912.0213.v1

*3.3. Association with adult height stratified by sex and incidence of end-stage renal disease and all-cause mortality in subjects with type 2 diabetes mellitus*

The HR for adult height was stratified by sex in multivariable-adjusted models (Table 3). A similar pattern was found in the association between heights, risk of ERSD, and death in subjects classified according to sex. Diabetic patients with tall stature had lower incidences of ESRD and all-cause death after adjusting for age, sex, smoking, alcohol intake, regular exercise, low income, BMI, hyperlipidemia, hypertension, CKD, insulin use, OHA, and DM duration > 5 years in both males and females. The HRs of ESRD for the second, third, fourth, and fifth quintiles versus the first quintile of adult height decreased to 0.95 (95% CI, 0.91–1.00), 0.91 (95% CI, 0.87–0.95), 0.89 (95% CI, 0.85–0.93), and 0.86 (95% CI, 0.83–0.90), respectively, for males ($p$ trend < 0.001) and to 0.90 (95% CI, 0.84–0.95), 0.88 (95% CI, 0.82–0.94), 0.82 (95% CI, 0.77–0.88), and 0.84 (95% CI, 0.79–0.90), respectively, for females ($p$ trend < 0.001). The HRs of all-cause death for the second, third, fourth, and fifth quintiles versus the first quintile of adult height decreased to 0.90 (95% CI, 0.88–0.91), 0.85 (95% CI, 0.84–0.87), 0.83 (95% CI, 0.82–0.85), and 0.81 (95% CI, 0.79–0.82) for males ($p$ trend < 0.001), respectively, and to 0.86 (95% CI, 0.84–0.88), 0.83 (95% CI, 0.81–0.85), 0.78 (95% CI, 0.77–0.80), and 0.80 (95% CI, 0.78–0.82) for females, respectively, even after full multivariable adjustment ($p$ trend < 0.001, Table 3, model 3). To further investigate the association between height and ESRD risk according to sex, subjects were divided into deciles according to adult height for sex, and the HR of ERSD was evaluated. All other groups had a significantly lower risk of ESRD than the lowest decile group in both males and females with type 2 DM (Figure S1).

**Table 3.** Multivariate Cox regression analysis for end-stage renal disease and mortality stratified by sex and height in diabetic patients

| | | Events /Observed | Follow-up duration (Person-years) | Incidence rate (per 1,000 person-years) | HR (95% CI) | | |
|---|---|---|---|---|---|---|---|
| | | | | | Model 1 | Model 2 | Model 3 |
| **ESRD** | | | | | | | |
| **Male** | **Q1** | 3,803/310,139 | 2,119,982 | 1.79 | 1 (reference) | 1 (reference) | 1 (reference) |
| | **Q2** | 3,734/303,613 | 2,077,320 | 1.80 | 0.98 (0.93-1.02) | 0.99 (0.95-1.04) | 0.95 (0.91-1.00) |
| | **Q3** | 3,922/329,224 | 2,260,378 | 1.74 | 0.98 (0.93-1.02) | 1.00 (0.96-1.05) | 0.91 (0.87-0.95) |
| | **Q4** | 3,465/307,942 | 2,115,946 | 1.64 | 0.96 (0.92-1.01) | 1.00 (0.95-1.05) | 0.89 (0.85-0.93) |
| | **Q5** | 3,699/324,353 | 2,218,533 | 1.67 | 0.96 (0.92-1.00) | 1.00 (0.95-1.05) | 0.86 (0.83-0.90) |
| | | ***p*-trend** | | | 0.05 | 0.965 | < 0.001 |
| **Female** | **Q1** | 2,053/202,915 | 1,408,726 | 1.46 | 1 (reference) | 1 (reference) | 1 (reference) |
| | **Q2** | 2,288/237,915 | 1,662,292 | 1.38 | 0.95 (0.90-1.01) | 0.96 (0.90-1.02) | 0.90 (0.84-0.95) |
| | **Q3** | 1,574/171,055 | 1,195,496 | 1.32 | 0.94 (0.88-1.01) | 0.96 (0.90-1.02) | 0.88 (0.82-0.94) |
| | **Q4** | 1,906/206,191 | 1,442,222 | 1.32 | 0.93 (0.87-0.99) | 0.94 (0.89-1.00) | 0.82 (0.77-0.88) |
| | **Q5** | 2,260/228,560 | 1,590,496 | 1.42 | 1.00 (0.94-1.06) | 1.02 (0.96-1.09) | 0.84 (0.79-0.90) |
| | | ***p*-trend** | | | < 0.001 | < 0.001 | < 0.001 |
| **All-cause mortality** | | | | | | | |
| **Male** | **Q1** | 33,117/310,139 | 2,128,817 | 15.56 | 1 (reference) | 1 (reference) | 1 (reference) |
| | **Q2** | 30,950/303,613 | 2,085,784 | 14.84 | 0.89 (0.88-0.90) | 0.90 (0.89-0.92) | 0.90 (0.88-0.91) |
| | **Q3** | 28,993/329,224 | 2,269,592 | 12.77 | 0.85 (0.83-0.86) | 0.87 (0.85-0.88) | 0.85 (0.84-0.87) |
| | **Q4** | 24,238/307,942 | 2,124,047 | 11.41 | 0.82 (0.81-0.84) | 0.85 (0.83-0.86) | 0.83(0.82-0.85) |
| | **Q5** | 25,497/324,353 | 2,227,228 | 11.45 | 0.79 (0.78-0.81) | 0.83 (0.81-0.84) | 0.81 (0.79-0.82) |
| | | ***p*-trend** | | | < 0.001 | < 0.001 | < 0.001 |

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**Table 3.** Cont.

| | | Events /Observed | Follow-up duration (Person-years) | Incidence rate (per 1,000 person-years) | HR (95% CI) | | |
|---|---|---|---|---|---|---|---|
| | | | | | Model 1 | Model 2 | Model 3 |
| Female | Q1 | 19,651/202,915 | 1,413,535 | 13.90 | 1 (reference) | 1 (reference) | 1 (reference) |
| | Q2 | 18,781/237,915 | 1,667,596 | 11.26 | 0.88 (0.86-0.90) | 0.88 (0.87-0.90) | 0.86 (0.84-0.88) |
| | Q3 | 11,351/171,055 | 1,199,272 | 9.46 | 0.85 (0.83-0.87) | 0.86 (0.84-0.88) | 0.83 (0.81-0.85) |
| | Q4 | 13,227/206,191 | 1,446,669 | 9.14 | 0.80 (0.78-0.82) | 0.81 (0.80-0.83) | 0.78 (0.77-0.80) |
| | Q5 | 14,652/228,560 | 1,595,744 | 9.18 | 0.82 (0.81-0.84) | 0.84 (0.82-0.86) | 0.80 (0.78-0.82) |
| | *p*-trend | | | | < 0.001 | < 0.001 | < 0.001 |

Abbreviations: BMI, body mass index; CI, confidence interval; CKD, chronic kidney disease; DM, diabetes mellitus; ESRD, end-stage renal disease; HR, hazard ratio; HTN, hypertension; OHA, oral hypoglycemia agents; Q, quintile. Model 1: adjusted for age, sex, BMI, Model 2: adjusted for age, sex, BMI, smoking, alcohol intake, regular exercise, and low income, Model 3: adjusted for age, sex, BMI, smoking, alcohol intake, regular exercise, low income, hyperlipidemia, hypertension, CKD, insulin use, OHA, and DM duration > 5 years.

*3.4 Subgroup analyses*

Figure 2 shows the relationship between adult height and ESRD when stratified by age, sex, social factors, and comorbidities. Subgroup analyses were performed after adjustments for age, sex, BMI, smoking, alcohol intake, regular exercise, income, hyperlipidemia, hypertension, CKD, oral hypoglycemic agent use, insulin use, and DM duration > 5 years. The association between adult height and risk of ESRD was weaker in the 30- to 39-year-old age group than in the 40- to 64-year-old age group and ≥ 65-year-old age group. In addition, the association between adult height and ESRD was also weaker in heavy drinkers and underweight (BMI < 18.5 kg/m$^2$) and obese patients (BMI > 30 kg/m$^2$) compared to non-drinkers and the normal to overweight group (18.5 ≤ BMI ≤ 30 kg/m$^2$). In contrast, there were no significant differences in the risk of developing ESRD of diabetic patients with short height between the subgroups of sex, regular exercise, smoking, abdominal obesity, and comorbidities. The lowest quintile of adult height remained higher risk for ESRD in type 2 DM compared with other quintiles regardless of which subgroup the patients belonged to sex, regular exercise, smoking, abdominal obesity, presence of hyperlipidemia, hypertension, and CKD.

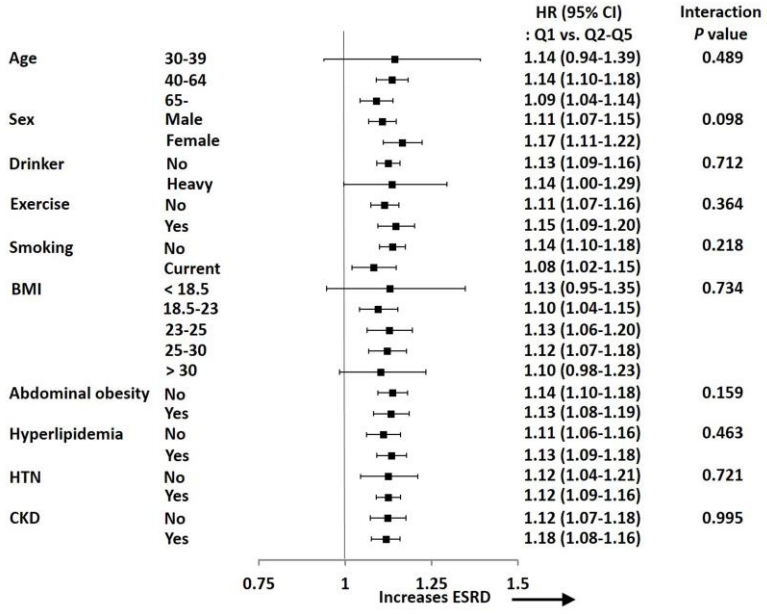


**Figure 2.** Hazard ratios and 95% confidence intervals of end-stage renal disease in the lowest quintile versus higher four quintiles of adult height in subgroups of diabetic patients. Adjusted for age, sex, body mass index, smoking, alcohol intake, regular exercise, income, hyperlipidemia, hypertension, CKD, insulin use, oral hypoglycemic agent, DM duration > 5 years.

 doi:10.20944/preprints201912.0213.v1

## 4. Discussion

This study demonstrated for the first time an inverse relationship between adult height and incidence of ESRD in diabetic patients in a large prospective cohort. Although baseline eGFR was relatively low in taller diabetic patients compared to shorter patients, taller adults showed lower incidences of ESRD and all-cause death compared with shorter adults even after adjustment for confounding factors. There was a significant difference in the relationship between incidences of ESRD, all-cause death, and adult height in both males and females. These findings suggest that short stature in adults was a significant predictor of the incidence of ESRD and all-cause mortality in diabetic patients.

Adult height represents a balance between nutritional intake and losses, particularly during growth periods. Socioeconomic status is closely correlated with both adult height and health outcomes [12]. Short stature is likely to result in low socioeconomic background, which was hypothesized to mediate the relationship between adult height and various chronic diseases. Our results showed significant associations between height and some socioeconomic indicators, such as income level and regular exercise. Unexpectedly, shorter diabetic patients had lower comorbidity of underlying disorders, such as hypertension, hyperlipidemia and CKD, had shorter duration of DM, and used less insulin and OHA. Furthermore, shorter diabetic patients were smoking and drinking less than taller diabetic patients. Nevertheless, shorter diabetic patients had significantly increased incidence of ESRD and all-cause mortality after adjustment for income level, smoking, alcohol consumption, and pre-existing medical conditions. These findings suggest that inappropriate nutritional environments in the newborn period and early childhood determine short stature in adulthood, and short stature may be a more important risk factor for ESRD and mortality than alcohol and smoking behaviors or pre-existing medical conditions in adulthood.

Adult height has an independent relationship with diabetic microvascular complications in diabetic patients. Rossing et al. demonstrated that the risk of developing diabetic nephropathy decreased 3.3% per 1-centimeter increase in height in male patients with type 1 DM [13]. Another previous study also showed that patients with macroproteinuria were significantly shorter than patients without proteinuria in both males and females patients with type 2 DM [8]. In the large cross-sectional Finnish Diabetic Nephropathy (FinnDiane) study and longitudinal study from the Diabetes Control and Complications Trial (DCCT), patients in the lowest quartile of adult height had increased risks of diabetic nephropathy and proliferative diabetic retinopathy compared with other quartiles of patients with type 1 DM [14]. Insulin resistance also contributes to the microvascular complications of DM independent of metabolic control and hypertension [15]. Previous studies reported that short stature is associated with increased risk of glucose intolerance, impaired β-cell function, and insulin resistance in diabetic patients and the general population [16-19]. These consistent relationships between short stature and insulin resistance may be implicated in the pathogenesis of diabetic nephropathy and may explain that short stature is an independent risk factor for the incidence of ESRD caused by diabetic nephropathy.

Fewer nephrons in the kidneys is a possible explanation for the association between height and risk of ESRD. Short stature is a long-term consequence of intrauterine growth retardation and catch-up failure in early childhood [20]. Adult height is directly associated with birth weight [21], and low birth weight is associated with increased risk of hypertension and glucose intolerance along with decreased renal function [20,22]. Indeed, a previous study demonstrated that nephron number increases by 257,426 per kg increased birth weight [23]. Nephron number is also independently correlated with adult height, and male adults have an increase of 28,000 glomeruli per centimeter increase in height [24,25]. The presence of fewer nephrons results in reduced glomerular filtration surface area, leading to systemic and glomerular capillary hypertension [26]. Therefore, short stature may increase the likelihood of decreasing renal function, which may lead to increased risk of ESRD.

Other possible explanations for the association between adult height and risk of ESRD is the growth hormone–insulin-like growth factor-1 (GH/IGF-1) system. IGF-1 levels were reported to be

 doi:10.20944/preprints201912.0213.v1

positively associated with height [27,28]. The kidney is a significant source of IGF-I synthesis, some of which is released into circulation. In addition, the kidney is a target organ of IGF action. IGF directly and indirectly affects renal hemodynamics by interacting with the renin-angiotensin system, promoting nephron hypertrophy, and stimulating tubular phosphate transport [29-31]. GH and IGF-1 resistance plays an additional role in decreased growth of children with CKD and the pathogenesis of diabetic kidney disease [32,33]. In addition, low IGF-1 levels are associated with increased risk of all-cause mortality and cardiovascular disease mortality in elderly people and patients with type 2 diabetes [34,35]. Short diabetic patients may have low IGF-1 levels, and therefore higher risk of ESRD and all-cause mortality than taller patients.

The major limitations of the study include its observational design of a prospective cohort with possible unmeasured confounding factors. It may be hard to explain biological mechanism for the relationship between adult height and the incidence of ESRD. Second, the diagnosis of ESRD was assessed based on ICD codes, leading to the possibility of misclassification. Finally, we did not confirm environmental factors in childhood that could affect adult height. Despite the adjustment for smoking and drinking behaviors, physical exercise, and income levels in multivariate analysis, nutritional and socioeconomic status during childhood might be more associated with height than those factors in adulthood. However, our study has several significant strengths. We analyzed an entire nationwide cohort including both males and females, as well as young and elderly people of type 2 DM. The follow-up period was enough long to confirm significant discrepancies in each ESRD event and death. We analyzed not only the incidence rates of newly diagnosed ESRD, but also demonstrated a significant difference in all-cause mortality rates.

## 5. Conclusions

This study was a large nationwide cohort study in Korea that shorter adult height is independently related to an increased risk of ESRD and all-cause death in diabetic patients. Although adult height is mainly determined by genetic influences, nutritional environment in early life may determine adult height and consequently decrease the risk of ESRD and all-cause mortality. This study provides strong justification to continue to implement and expand the effort for nutritional improvement in childhood to restrain the poor renal outcomes and death in type 2 DM. Further investigation into the possible role of epigenetic modifications in the association between short height and ESRD in type 2 DM is needed.

**Supplementary Materials:** The following are available online at www.mdpi.com/xxx/s1, Figure S1. The differences of sex of hazard ratios for the incidence of end-stage renal disease according to adult height, D = height deciles from 1st to 10$^{th}$, Table S1. Reference value of height quintiles based on age and sex groups.

**Author Contributions:** All authors have read and agree to the published version of the manuscript. Conceptualization, S.C. and S-H.K.; formal analysis and visualization, K-D.H. investigation and data curation, J-S.Y. and E.S.K.; methodology, writing—original draft preparation, Y.A.H.; writing—review and editing, supervision, S.C.; funding acquisition, S-H.K.

**Funding:** This research was supported by a grant of the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health & Welfare, Republic of Korea, grant number HI18C0275.

**Conflicts of Interest:** The authors declare no conflict of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results.

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