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Waist circumference and end-stage renal disease based on glycaemic status: National Health Insurance Service data 2009–2018

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Abstract

Background Obesity is associated with an increased risk of developing type 2 diabetes mellitus (T2DM) and end-stage renal disease (ESRD). This study aimed to examine the effect of waist circumference (WC) on the risk for ESRD based on glycaemic status in a Korean population-based sample.

Methods This cohort study with a 9.2-year follow-up period used a population-based National Health Insurance Service health checkup database with approximately 10 585 852 participants who were followed up from 2009 to the time of ESRD diagnosis. WC was categorized into seven levels in 5-cm increments, with Level 4 as the reference group. Glycaemic status was categorized into the following groups: normal fasting glucose (NFG), impaired fasting glucose (IFG), newly diagnosed T2DM, T2DM treated with ≤2 oral hypoglycaemic agents (OHAs) and diabetes treated with ≥3 OHAs or insulin. We calculated hazard ratios (HRs) and 95% confidence intervals (CIs) for ESRD according to WC values and glycaemic status of the participants.

Results The study finally included 10 177 245 patients with a mean age of 47.1 (13.8) years. The study population included 5 604 446 men (55.1%) and 4 572 799 women (45.9%). In total, 8.3% (n = 877 143) of the study population had diabetes. During the mean follow-up of 9.2 (1.0) years (93 554 951 person-years of follow-up), 23 031 individuals were newly diagnosed with ESRD. The ESRD risk increased in parallel with an increase in WC in participants without T2DM, that is, the NFG and IFG groups (adjusted HRs [95% CIs] of WC Levels 4, 5 and 6: 1.17 [1.09–1.26], 1.37 [1.25–1.51] and 1.84 [1.63–2.07] in the NFG group and 1.06 [0.97–1.16], 1.23 [1.10–1.38] and 1.80 [1.57–2.06] in the IFG group, respectively). In patients with T2DM, the risk for ESRD was significantly increased in those with a low WC (adjusted HRs [95% CIs] of WC Level 1: 2.23 [1.77–2.80], 3.18 [2.70–3.74] and 10.31 [9.18–11.59] in patients with newly diagnosed diabetes, patients on ≤2 OHAs and those on ≥3 OHAs or insulin, respectively). The association between WC and ESRD thus showed a J-shaped pattern in patients with newly diagnosed T2DM and a U-shaped pattern in those on ≤2 OHAs and on ≥3 OHAs or insulin.

Conclusions Central obesity substantially increases the risk of developing ESRD regardless of glycaemic status. The harmful effects of low WC only become significant with the progression of T2DM.

Keywords diabetes mellitus; end-stage renal disease; glycaemic status; obesity; waist circumference

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Introduction

The global incidence and prevalence of obesity, type 2 diabetes mellitus (T2DM) and end-stage renal disease (ESRD) have increased in recent years, thus requiring urgent attention.[1] Obesity is associated with an increased risk of developing T2DM,[2] known as a leading cause of chronic kidney disease (CKD) that can progress to and is the leading cause of ESRD.[3] However, the independent correlation between obesity and kidney disease remains unclear. Conventional risk factors for both CKD and obesity, such as T2DM, have been speculated as playing a role.[4] Several population-based observational studies have identified obesity as a risk factor for CKD and ESRD.[5–8] However, we have previously demonstrated a positive relationship between low body mass index (BMI) and the risk of ESRD in a nationwide Korean population-based cohort study (*n* = 9 969 848) with a follow-up period of 8.2 years.[9] We found that patients with obesity and underweight patients had a high risk of ESRD and that a strong association between low BMI and the risk of ESRD according to T2DM status exists.[9]

BMI and waist circumference (WC) are the basic anthropometric measurements of obesity. BMI is the most used parameter to assess obesity in epidemiologic studies and clinical guidelines; however, WC may display stronger associations with ESRD risk than BMI.[10] This is because WC directly reflects abdominal obesity[11] and better predicts the prevalence or incidence of co-morbidities rather than BMI.[12,13] A recent meta-analysis demonstrated that increased WC is an independent risk factor for the decline in glomerular filtration rate (GFR).[14] However, no nationwide longitudinal cohort studies have compared the effect of WC on the risk of ESRD in individuals with and without T2DM.

Therefore, we aimed to evaluate the association between WC and ESRD risk according to the glycaemic status in a Korean population-based sample using the National Health Insurance Service (NHIS) health checkup data.

Methods

The National Health Insurance Service database and health checkup programme

The NHIS is a national insurer managed by the Korean government and serves approximately 97% of the Korean population. It collects medical information from approximately 50 million Koreans.[15] Any researcher can use the Korean NHIS data following approval of the study protocol by the official review committee. The NHIS database manages claims using the Korean Classification of Disease (6th edition), a modified version of the International Classification of Diseases (10th edition) (ICD-10), adapted for the Korean healthcare system.[16,17]

Study population

We used information from the NHIS health checkup database from 2002 to 2018. We selected participants older than 20 years who had undergone health checkups in 2009. They were followed up until 31 December 2018 (*n* = 10 585 852). We excluded those with missing data (*n* = 380 690), type 1 diabetes mellitus (T1DM) (*n* = 18 217) and a history of ESRD before the checkup (*n* = 9700). A total of 10 177 245 participants were included in this study. They were monitored from the baseline to the date of diagnosing ESRD because the primary endpoint was the incidence of ESRD. The mean observational time was 9.19 (1.04) years (*Figure S1*).

Definitions of chronic kidney disease and end-stage renal disease

CKD and ESRD were defined as a GFR $<$ 60 and $<$15 mL/min/1.73 m^2, respectively, and as a combination of special V codes, such as those for peritoneal dialysis (V003), haemodialysis (V001) or kidney transplantation (V005), which were all assigned to patients with CKD. The estimated GFR (eGFR) was calculated based on the Modification of Diet in Renal Disease study equation[18]:

$$\text{eGFR}\left(\text{mL/min/1.73 m}^2\right) = 186 \times \text{standardized serumcreatinine}^{-1.154} \times \text{age}^{-0.203} \times 0.742\ [\text{forwomen}].$$

Definition of abdominal obesity

WC was measured in centimetres at the middle point between the rib cage and iliac crest by trained examiners. WC was categorized into seven levels at 5-cm intervals: Level 1, $<$75 cm in men and $<$70 cm in women; Level 2, $<$80 cm in men and $<$75 cm in women; Level 3, 80 to $<$85 cm in men and 75 to $<$80 cm in women; Level 4, 85 to $<$90 cm in men and 80 to $<$85 cm in women; Level 5, 90 to $<$95 cm in men and 85 to $<$90 cm in women; Level 6, 95 to $<$100 cm in men and 90 to $<$95 cm in women; and Level 7, $\geq$100 cm in men and $\geq$95 cm in women. Abdominal obesity was defined as a WC $\geq$ 90 and $\geq$85 cm in men and women, respectively, according to the definition used by the Korean Society for the Study of Obesity.[19]

Glycaemic status and the definition of chronic diseases

All participants were categorized into five groups based on their glycaemic status, according to the early combination approach of oral hypoglycaemic agents (OHAs), normal fasting glucose (NFG), impaired fasting glucose (IFG), newly diagnosed T2DM, patients with T2DM treated with ≤2 OHAs and patients with T2DM treated with ≥3 OHAs or insulin. IFG was defined as a fasting plasma glucose (FPG) level of 100–125 mg/dL. Newly diagnosed T2DM was defined as a diagnosis of T2DM at the time of national health examinations in 2009 in patients who did not receive OHAs or insulin. T2DM was defined as having an FPG glucose level ≥ 126 mg/dL or at least one claim per year for the prescription of hypoglycaemic drugs under ICD-10 codes E11–E14.[20] Patients with type 1 diabetes who had claims under the ICD-10 code E10 were excluded from this study. We also analysed the risk of ESRD by WC levels, stratified by glycaemic status. Hypertension was defined as a blood pressure ≥ 140/90 mmHg or at least one claim per year for an anti-hypertensive medication prescription under ICD-10 codes I10–I15. Dyslipidaemia was defined by total cholesterol ≥ 240 mg/dL or at least one claim per year for a prescription of anti-dyslipidaemic agents under the ICD-10 code E78.

General health behaviours and sociodemographic variables

Smoking history was categorized as non-smokers, ex-smokers and current smokers. We classified drinking status into three categories as follows: abstinence (no alcoholic drinks consumed within the last year), moderate drinking (<30 g alcohol/day) and heavy drinking (≥30 g alcohol/day). We determined the participants' level of physical activity (PA) using a questionnaire. Participants were asked to answer as to the number of days per week they performed PA at different intensities as follows: For vigorous-intensity PA, the questions included 'In the past week, on how many days did you participate in strenuous activities that left you breathless for more than 20 min per day?' and 'In the past week, on how many days did you engage in activities that made you breathe a little harder than usual for more than 30 min per day?'. For moderate-intensity PA, the question included 'In the past week, on how many days did you walk for at least 30 min per day, including at least 10 min at a time?'. According to the guidelines of exercise testing and prescription,[21,22] those who engaged in vigorous-intensity PA for 3 days or moderate-intensity PA for 5 days a week were judged to engage in 'regular physical activity'.[21,22] The income level was divided by quartiles, namely, Q1 (lowest), Q2, Q3 and Q4 (highest).

Statistical analyses

General characteristics of the participants are expressed as the mean (standard deviation) and number (percentage) for continuous and categorical variables, respectively. We used a Student's *t*-test or χ^2 test to compare the baseline characteristics between participants with and without T2DM. Moreover, we conducted an analysis of variance or a χ^2 test to compare the baseline characteristics of participants in the different WC groups (Levels 1–7). We used multivariable Cox proportional hazard models to obtain the hazard ratios (HRs) and 95% confidence intervals (CIs) for ESRD by WC levels in those with or without T2DM, with WC Level 4 as the reference group. HRs were adjusted for age (years), sex, smoking (non-smokers, ex-smokers and current smokers), drinking (no alcoholic drinks consumed within the last year, <30 g alcohol/day and ≥30 g alcohol/day), regular exercise (yes or no), income (Quartile 1), hypertension (yes or no), dyslipidaemia (yes or no), pre-existing cardiovascular disease (CVD) (yes or no), the use of angiotensin-converting enzyme inhibitors (ACEIs)/angiotensin receptor blockers (ARBs), the use of statins and BMI (kg/m^2). Furthermore, we performed subgroup analyses using multivariable Cox proportional hazard models by classifying the participants by their age (≥65 vs. <65 years), sex (men vs. women), the presence of CKD, the history of pre-existing CVD, the use of ACEIs/ARBs and the use of statins, using Level 4 as the reference. We calculated the incidence rate (IR) per 1000 person-years, HR and 95% CI for ESRD by WC levels, according to the glycaemic status by constructing multivariable Cox proportional hazard models using WC Level 4 as a reference after adjusting for all covariates. A two-tailed *P*-value < 0.05 was considered statistically significant.

Results

Characteristics of the study population

The study included 10 177 245 patients. Overall, the mean age was 47.1 (13.8) years and 55.1% of the study population were men (*n* = 542 205). In total, 8.3% (*n* = 877 143) of the study population had diabetes. During the mean follow-up of 9.2 (1.0) years (93 554 951 person-years of follow-up), 23 031 individuals were newly diagnosed with ESRD. *Table 1* summarizes the baseline characteristics of the participants according to the seven WC levels. BMI, blood pressure, fasting glucose, total cholesterol, triglyceride, low-density lipoprotein cholesterol and the prevalence of hypertension, dyslipidaemia, T2DM and CVD increased with higher WC levels (all $P < 0.001$). Higher WC was also associated with more use of ACEIs/ARBs and statins (all $P < 0.001$). The group with an increased WC had lower high-density lipoprotein

Table 1 Baseline characteristics of participants according to baseline waist circumference (in seven levels)

	Waist circumference levels[a]						
	1 (n = 1 764 153)	2 (n = 1 979 781)	3 (n = 2 420 080)	4 (n = 2 016 523)	5 (n = 1 181 186)	6 (n = 526 537)	7 (n = 288 985)
Age (years)	40.0 (13.6)	44.6 (13.3)	47.6 (13.3)	50.2 (13.4)	51.8 (13.7)	52.8 (14.2)	52.0 (15.3)
Sex (female, %)	671 962 (38.1)	987 887 (50.0)	1 500 627 (62.0)	1 254 322 (62.2)	737 563 (62.4)	301 580 (57.3)	150 505 (52.1)
WC (cm)	67.5 (4.3)	74.5 (2.9)	80.0 (2.8)	84.9 (2.8)	89.8 (2.8)	94.5 (2.8)	101.8 (14.9)
BMI (kg/m^2)	20.1 (1.8)	22.0 (1.8)	23.5 (1.9)	25.0 (2.6)	26.5 (2.2)	28.0 (4.7)	30.7 (3.3)
SBP (mmHg)	115.1 (13.5)	119.3 (14.0)	122.8 (14.3)	125.4 (14.6)	127.6 (14.8)	129.5 (15.1)	131.8 (15.7)
DBP (mmHg)	72.1 (9.2)	74.5 (9.5)	76.5 (9.7)	78.1 (9.8)	79.3 (10.0)	80.3 (10.2)	81.7 (10.7)
Glycaemic status, n (%)							
Normal	1 465 761 (83.1)	1 508 227 (76.2)	1 668 243 (68.9)	1 260 855 (62.5)	671 981 (56.9)	275 797 (52.4)	137 844 (47.7)
IFG	254 509 (14.4)	379 485 (19.2)	566 560 (23.4)	533 299 (26.5)	337 011 (28.5)	155 150 (29.5)	85 380 (29.5)
T2DM							
New onset	20 290 (1.2)	36 477 (1.8)	67 938 (2.8)	74 749 (3.7)	54 462 (4.6)	28 314 (5.4)	18 724 (6.5)
≤2 OHAs	14 099 (0.8)	35 591 (1.8)	77 203 (3.2)	98 318 (4.9)	78 248 (6.6)	44 590 (8.5)	30 583 (10.6)
≥3 OHAs or insulin	9494 (0.5)	20 001 (1.0)	40 136 (1.7)	49 302 (2.4)	39 484 (3.3)	22 686 (4.3)	16 454 (5.7)
Glucose (mg/dL)	90.6 (16.9)	93.7 (19.6)	97.0 (22.8)	99.9 (25.2)	102.4 (27.2)	104.7 (29.5)	107.7 (32.7)
TC (mg/dL)	182.2 (36.3)	190.5 (39.0)	196.6 (40.7)	201.0 (43.0)	203.2 (43.3)	204.9 (44.4)	206.1 (45.8)
HDL-C (mg/dL)	62.6 (33.2)	58.8 (33.2)	55.7 (32.1)	53.8 (33.9)	52.6 (32.5)	52.2 (32.1)	52.1 (31.2)
LDL-C (mg/dL)	103.56 (36.9)	111.02 (37.6)	115.21 (38.2)	117.65 (39.2)	118.23 (40.1)	118.83 (40.7)	119.19 (41.6)
TG (mg/dL)[b]	78.2 [78.2–78.3]	96.3 [96.3–96.4]	116.3 [116.3–116.4]	132.6 [132.5–132.7]	144.7 [144.6–144.9]	151.9 [151.7–152.1]	157.1 [156.7–157.3]
eGFR (mL/min/1.73 m^2)	91.5 (45.5)	88.8 (44.1)	87.0 (44.5)	86.0 (45.5)	85.3 (45.0)	84.8 (43.8)	85.4 (44.0)
Smoking							
Never	957 646 (54.3)	1 036 299 (52.3)	1 180 110 (48.8)	1 009 478 (50.1)	602 262 (51.0)	285 647 (54.3)	165 271 (57.2)
Former	723 836 (41.0)	814 540 (41.1)	1 033 981 (42.7)	819 112 (40.6)	457 307 (38.7)	186 739 (35.5)	94 130 (32.67)
Current	82 671 (4.7)	128 942 (6.5)	205 989 (8.5)	187 933 (9.3)	121 617 (10.3)	54 151 (10.3)	29 584 (10.2)
Drinking							
Never	957 646 (54.3)	1 036 299 (52.3)	1 180 110 (48.8)	1 009 478 (50.1)	602 262 (51.0)	285 647 (54.3)	165 271 (57.2)
Mild	723 836 (41.0)	814 540 (41.1)	1 033 981 (42.7)	819 112 (40.6)	457 307 (38.7)	186 739 (35.5)	94 130 (32.6)
Heavy	82 671 (4.7)	128 942 (6.5)	205 989 (8.5)	187 933 (9.3)	121 617 (10.3)	54 151 (10.3)	29 584 (10.2)
Physical activity	254 846 (14.5)	360 878 (18.2)	474 589 (19.6)	393 103 (19.5)	222 372 (18.8)	93 047 (17.7)	46 220 (16.0)
Income (low, %)	422 893 (24.0)	444 966 (22.5)	495 606 (20.5)	404 425 (20.1)	238 718 (20.2)	108 884 (20.7)	61 779 (21.4)
Co-morbidities and medications							
Hypertension	155 250 (8.8)	312 155 (15.8)	577 604 (23.9)	663 649 (32.9)	488 979 (41.4)	257 895 (49.0)	164 493 (56.9)
Dyslipidaemia	116 331 (6.6)	238 340 (12.0)	423 986 (17.5)	467 017 (23.2)	324 722 (27.5)	165 019 (31.3)	99 570 (34.5)
Diabetes	43 883 (2.5)	92 069 (4.7)	185 277 (7.7)	222 369 (11.0)	172 194 (14.6)	95 590 (18.2)	65 761 (22.8)
CVD	13 002 (0.7)	22 820 (1.2)	41 166 (1.7)	47 507 (2.4)	35 135 (3.0)	18 893 (3.6)	11 203 (3.9)
ACEIs/ARBs	49 730 (2.8)	111 232 (5.6)	223 963 (9.3)	279 674 (13.9)	218 289 (18.5)	120 867 (23.0)	79 721 (27.6)
Statins	13 002 (0.7)	22 820 (1.2)	41 166 (1.7)	47 507 (2.4)	35 135 (3.0)	18 893 (3.6)	11 203 (3.9)

Note: Values are presented as number (percentage) or mean (standard deviation). Abbreviations: ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; BMI, body mass index; CVD, cardiovascular disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; IFG, impaired fasting glucose; LDL-C, low-density lipoprotein cholesterol; OHAs, oral hypoglycaemic agents; SBP, systolic blood pressure; T2DM, type 2 diabetes mellitus; TC, total cholesterol; TG, triglyceride; WC, waist circumference.

[a]WC levels (in centimetres): Level 1 (<75 in men and <70 in women), Level 2 (75 to <80 in men and 70 to <75 in women), Level 3 (80 to <85 in men and 75 to <80 in women), Level 4 (85 to <90 in men and 80 to <85 in women), Level 5 (90 to <95 in men and 85 to <90 in women), Level 6 (95 to <100 in men and 90 to <95 in women) and Level 7 (≥100 in men and ≥95 in women).

[b]Geometric mean [95% confidence interval].

cholesterol and decreased eGFR (all $P < 0.001$). A total of 877 143 (8.6%) patients were diagnosed with T2DM: 300 954, 378 632 and 197 557 as newly diagnosed, treated with ≤2 OHAs and treated with ≥3 OHAs or insulin, respectively (*Table S1*).

End-stage renal disease for each waist circumference level according to the presence of type 2 diabetes mellitus

Participants with an increased WC displayed a higher risk for ESRD than those with WC Level 4 (85 to <90 cm in men and 80 to <85 cm in women) as the reference level. Moreover, the HR of ESRD increased in parallel with the WC (HR = 1.14, 1.30 and 1.78 and 1.12, 1.34 and 1.96 in those without and with T2DM, respectively), after adjusting for other covariates (age, sex, smoking, drinking, regular exercise, income [Quartile 1], hypertension, dyslipidaemia, pre-existing CVD, the use of ACEIs/ARBs, the use of statins and BMI) (*Figure 1* and *Table* S2). The maximum HRs were evident in the groups with the highest WC (Level 7 ≥ 100 and ≥95 cm in men and women, respectively) and with T2DM (HR = 1.96, 95% CI [1.80–2.14], $P < 0.001$). The risk for ESRD also increased as WC decreased. This was lowest in the group with WC Level 3 (WC 80–84.9 cm in men and 75–79.9 cm in women) and evident for participants with T2DM (HR = 0.98, 95% CI [0.93–1.04]) as well as those without T2DM (HR = 0.99, 95% CI [0.94–1.05]). However, participants in the Level 1 group with the lowest WC (<75 cm in men and <70 cm in women) displayed a similar increase in the HR, compared with the reference group regardless of the presence of T2DM, after adjusting for all covariates including the BMI (HR = 1.08, 95% CI [1.00–1.17] and HR = 1.19, 95% CI [1.08–1.31], with and without T2DM, respectively).

Effect of waist circumference on end-stage renal disease risk according to glycaemic status

We analysed the IRs per 1000 person-years and HRs of ESRD by WC level, which were stratified based on glycaemic status, after adjusting for all baseline covariates, including the BMI (*Figure 2* and *Table* S3). In groups without T2DM, IRs (per 1000 person-years) were highest in the Level 7 group with the highest WC (≥100 cm in men and ≥95 cm in women) (IR = 0.28 in NFG; HR = 0.33 in IFG). In groups with newly diagnosed T2DM, IRs per 1000 person-years were similar between the Level 1 group with the lowest WC (<75 cm in men and <70 cm in women) and the Level 7 group (IR = 0.43 and 0.52 in Levels 1 and 7, respectively). However, in groups with progression of diabetes (≤2 OHAs and ≥3 OHAs or insulin), IRs were highest in the Level 1 group and increased with worsening glycaemic status (1.34 for ≤2 OHAs and 4.95 for ≥3 OHAs or insulin). In groups with newly diagnosed T2DM, on ≤2 OHAs and on ≥3 OHAs or insulin, HRs in the WC Level 1 group increased with worsening glycaemic status (HR = 2.23 for newly diagnosed T2DM, 3.18 for diabetes ≤2 OHAs and 10.31 for diabetes using ≥3 OHAs), using the normal WC Level 4 as the reference.

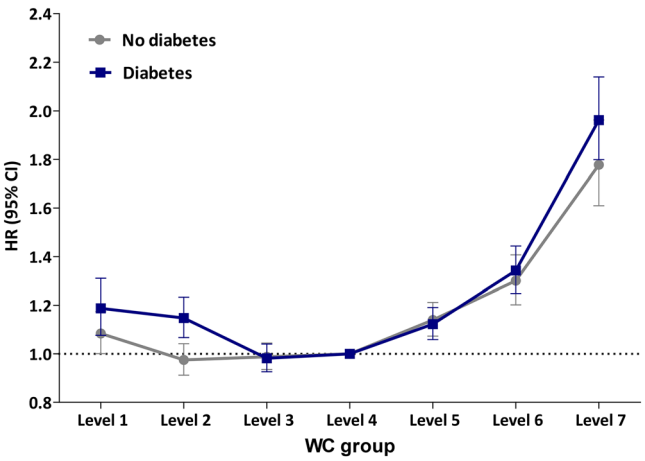

Figure 1 Adjusted hazard ratio for end-stage renal disease according to waist circumference and presence of diabetes. The hazard ratios are adjusted for age (years), sex, smoking (non-smokers, ex-smokers and current smokers), drinking (no alcoholic drinks consumed within the last year, <30 g alcohol/day and ≥30 g alcohol/day), regular exercise (yes or no), income (Quartile 1), hypertension (yes or no), dyslipidaemia (yes or no), pre-existing cardiovascular disease (yes or no), the use of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, the use of statins and body mass index (kg/m^2), corresponding to Model 4 in *Table* S2. CI, confidence interval; HR, hazard ratio; WC, waist circumference

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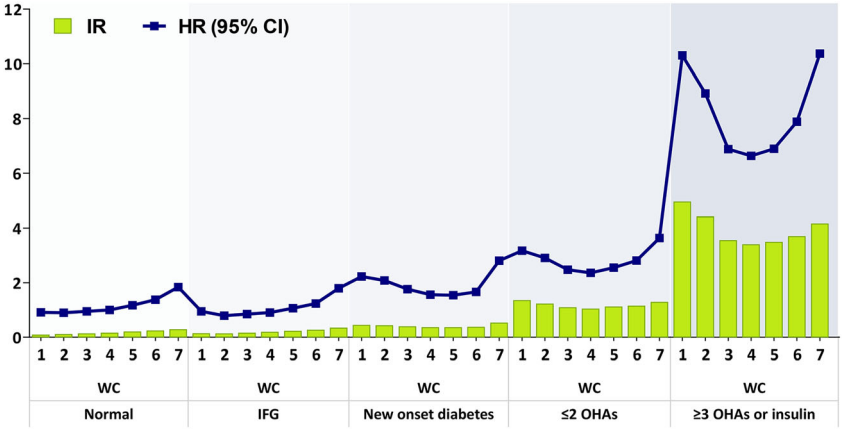

Figure 2 End-stage renal disease incidence and the adjusted hazard ratio for each waist circumference category according to glycaemic status. The hazard ratios are adjusted for age (years), sex, smoking (non-smokers, ex-smokers and current smokers), drinking (no alcoholic drinks consumed within the last year, <30 g alcohol/day and ≥30 g alcohol/day), regular exercise (yes or no), income (Quartile 1), hypertension (yes or no), dyslipidaemia (yes or no), pre-existing cardiovascular disease (yes or no), the use of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, the use of statins and body mass index (kg/m^2), corresponding to Model 4 in *Table* S3. CI, confidence interval; HR, hazard ratio; IFG, impaired fasting glucose; IR, incidence rate; OHAs, oral hypoglycaemic agents; WC, waist circumference

Subgroup analysis of end-stage renal disease risk for each waist circumference level according to the presence of type 2 diabetes mellitus

We examined the incidence of ESRD for each WC level in the subgroups by their age, sex, the presence of CKD, the history of pre-existing CVD, the use of ACEIs/ARBs and the use of statins (*Figure 3* and *Table* S4). The HR of ESRD in WC Levels 1 and 7 was significantly higher than that in the referent WC group in young participants (HR in Level 1 = 1.10 and 1.28 in young participants without and with T2DM; HR in Level 7 = 1.91 and 2.22 in young participants without and with T2DM, respectively), whereas the impact of WC on ESRD risk was less evident in older participants (HR in Level 1 = 0.86 and 0.89 in older participants without and with T2DM; HR in Level 7 = 1.48 and 1.62 in older participants without and with T2DM, respectively) (*Figure 3A* and *Table* S4A). In subgroup with pre-existing CVD and no diabetes, the association between WC and ESRD risk was not statistically significant (*Figure 3D* and *Table* S4D). The risk pattern did not vary by sex, the presence of CKD, the use of ACEIs/ARBs and the use of statins (*Figure 3B,C,E,F* and Table S4).

Discussion

In this nationwide population-based cohort study, an increased WC was associated with greater risk for ESRD. Low WC was also associated with ESRD risk; in particular, the risk of developing ESRD increased in parallel with increasing WC in participants without T2DM. Glycaemic status thus moderated the effect of WC on ESRD risk. The association between WC and ESRD revealed a J-shaped pattern in patients with newly diagnosed T2DM and a U-shaped pattern in patients with progression of T2DM. The association between WC and ESRD risk was more pronounced in those participants with newly diagnosed T2DM, those using ≤2 OHAs and those using ≥3 OHAs or insulin, after multivariate adjustment for the covariates (i.e., age, sex, smoking, drinking, regular exercise, income [Quartile 1], hypertension, dyslipidaemia, pre-existing CVD, the use of ACEIs/ARBs, the use of statins and BMI).

Abdominal adiposity, T2DM and hypertension are major risk factors for ESRD. Measuring WC is a simple method to assess abdominal adiposity that can be easily standardized and clinically applied.[23] Several studies have examined the association between BMI and ESRD risk.[5,6,9,24,25] However, only a few studies have reported an association between WC and the risk of ESRD.[10,14,26] Therefore, longitudinal studies are needed to explore the causal relationship between WC and ESRD risk. Our findings revealed some differences and similarities compared with previous studies.[10,14,26] The meaningful similarity was that central obesity substantially increased the risk of developing ESRD in the general population. However, our study has some notable differences from previous studies in terms of study design, population and research implications.

The selection and examination of our reference group were the primary difference compared with previous studies. Previously, researchers determined the reference group using participants with the lowest WC (approximately <93 cm in men and <82 cm in women) and did not separately classify the group with low WC; thus, it was impossible to derive new findings regarding low WC. In contrast, we used the WC Level 4 (85 to <90 cm in men and 80 to <85 cm in

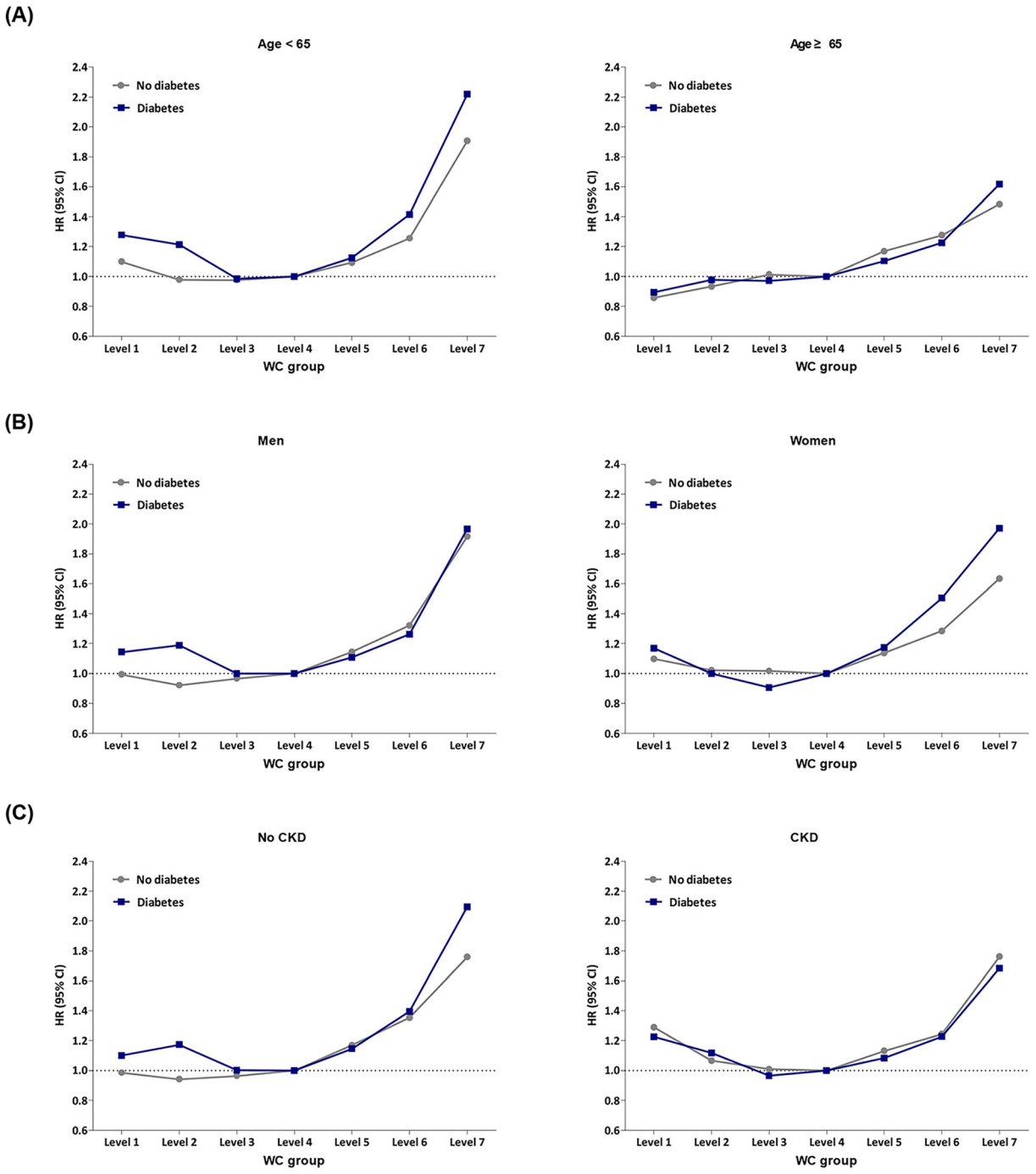

Figure 3 Subgroup analysis of the risk of end-stage renal disease in each waist circumference category. Subgroup analyses were performed according to (A) age, (B) sex, (C) the presence of chronic kidney disease, (D) the history of pre-existing cardiovascular disease, (E) the use of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers and (F) the use of statins. CI, confidence interval; CKD, chronic kidney disease; CVD, cardiovascular disease; HR, hazard ratio; WC, waist circumference

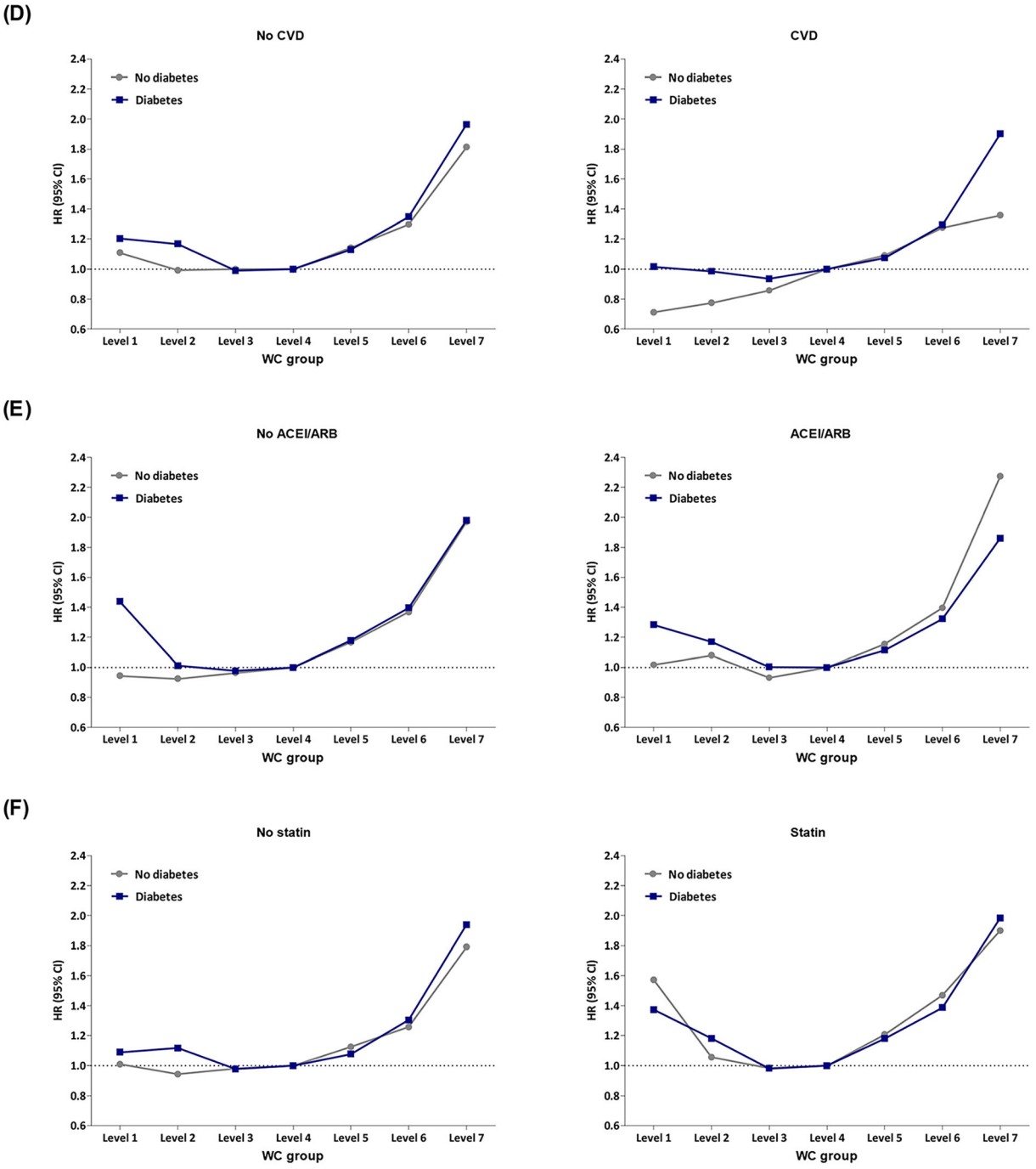

Figure 3 Continued

women) as the reference, which revealed the implications of low WC on the risk of ESRD. The second difference included baseline characteristics of the study populations. Two large prospective cohort studies of older adults enrolled participants with a mean age of 64 years.[10,26] However, we selected participants >20 years of age (*Figure 1*). Therefore, our participants were more similar and thus comparable with the general population than those in previous studies. Furthermore, the impact of WC on renal outcomes could be different among different age groups; in fact, our analyses showed that the impact of WC on ESRD risk was more prominent in younger participants. A possible explanation for this finding is that other pre-existing risk factors could have diminished the effect of increased WC as a predictor of ESRD risk (*Figure 3* and *Table* S4). Regarding sex, a study from a sub-cohort of the Women's Health Initiative including 20 117 post-menopausal women reported that central obesity was associated with an increased risk for ESRD in post-menopausal women.[26] We determined similar J-shaped patterns in both men and women regardless of T2DM, although we did not separately analyse the menopausal group (*Figure 3B*). Furthermore, we considered T2DM in the analyses, which was the major difference; previous studies did not consider the status of T2DM and low WC. T2DM is an important risk factor for ESRD, and patients with both conditions have an increased risk of cardiovascular events.[27–29] This necessitates identifying a novel risk factor for ESRD in patients with T2DM. Low WC increased the risk of developing ESRD in individuals with newly diagnosed T2DM, after adjusting for BMI (*Figure 2* and *Table* S3). To the best of our knowledge, this is the first nationwide cohort study to examine the relationship between low WC and the risk of ESRD according to the status of T2DM.

Recently, a global, collaborative meta-analysis of more than 5 million individuals enrolled across 63 cohorts determined the relationship between measures of adiposity and the risk of GFR decline and death.[14] GFR decline was the pre-specified primary outcome, which included 40% eGFR decline, eGFR < 10 mL/min/1.73 m^2 or ESRD. According to this meta-analysis, WC and GFR decline displayed an almost linear association, and ESRD risk did not increase in individuals with low WC, which contrary to our findings. Disparities in findings between the meta-analysis and our study could be attributed to several factors, including differences in the study population and consideration of the glycaemic status, as described above. ESRD was our study outcome, whereas the meta-analysis assessed the composite renal outcome. Low WC may play different roles in varying stages of renal dysfunction; that is, the hazardous effect of low WC could be more pronounced in patients with severe renal outcomes. Ethnic differences could be another factor. Individuals of Asian descent typically have a higher proportion of body fat than those of Caucasian descent, despite similar BMI and WC, which might contribute to a higher predisposition to insulin resistance despite less obesity than that described for self-reported Caucasians.[30] Thus, despite a low WC indicating metabolic fitness in those of Caucasian descent, this does not necessarily imply a healthy status in the Asian population, including samples such as our own.

This study focused on the association between central obesity, as measured by WC, and the risk of ESRD. Compared with BMI, anthropometric measures of abdominal obesity (such as WC, waist-to-hip ratio and sagittal abdominal diameter) appear to be more strongly associated with metabolic risk factors, incident CVD events and mortality.[31–33] Visceral adipose tissue, which causes insulin resistance, dyslipidaemia and hypertension, is responsible for the cardio-metabolic risk associated with abdominal obesity.[31,34–36] By demonstrating the increased risk of ESRD in patients with central obesity, this study provides additional evidence of the deleterious effect of central adiposity on kidney function. One limitation of the current analysis is that only WC was utilized as an indicator of obesity. Recent research has revealed that the waist-to-hip ratio is an excellent predictor of cardiovascular risk,[31] because the development of cardio-metabolic risk factors and CVD is inversely related to hip circumference.[37,38] However, as the hip circumference is not taken during the NHIS health examinations, we were unable to utilize this parameter in our analyses. Regarding BMI, the most widely used measurement for obesity, our study group has previously reported the association of BMI with ESRD risk.[9] We reported that the HR of ESRD increased as BMI decreased; the HR was the highest in the underweight group and the lowest in the overweight and obese groups. According to the present study, low WC significantly increased the risk of developing ESRD particularly in individuals with diabetes, whereas the deleterious effects of abdominal obesity on ESRD risk were consistently detected across all glycaemic categories. This connection between WC and ESRD risk was distinct from the previously documented association between BMI and ESRD risk. Thus, the main strength of this study is that this is the first to explore the specific association between WC and the risk of developing ESRD according to T2DM status.

The mechanisms responsible for the relationship between low WC and ESRD risk in patients with T2DM are unclear. One explanation for this finding is that lean patients with T2DM may be more susceptible to insulin resistance.[12,39] The hypothesis was initially proposed by Xu et al., who demonstrated the inverse relationship between BMI and mortality and functional outcome following an ischaemic stroke in patients with insulin resistance.[39] However, this paradoxical phenomenon was absent in their insulin-sensitive counterparts.[39] A similar explanation might be applied to the renal outcome. Another previous study demonstrated that patients with obesity were more likely to adhere to guideline-recommended medical treatment.[39] In other words, a patient with both diabetes and obesity is more likely to commit to a reduction in possible diabetic complications,

for example, by lifestyle modification and/or taking statins and anti-hypertensive medication.

This study had some limitations. First, generalizability to other ethnic groups was limited, as most of our study population was Korean. Second, we were unable to account for changes in the WC and glucose levels over the follow-up. Third, this research may lack the power to completely analyse interactions because of the short follow-up period. ESRD can develop following prolonged exposure to multiple risk factors, thus warranting long-term follow-up studies to determine the long-standing effects of WC on the risk of developing ESRD. Fourth, the renal outcomes may have substantially influenced the albumin/creatinine ratio.[10] However, we could not consider the albumin/creatinine ratio, as it was not routinely determined during NHIS health screening examinations. Fifth, owing to the observational nature of this study, it was not possible to establish direct cause-and-effect risk associations. Sixth, because glycated haemoglobin is not commonly measured in Korea's national health examination, we defined and categorized glycaemic status based on FPG level, which may have led to imprecise diagnoses in certain participants. To limit the likelihood of inaccurate diagnosis, we defined and categorized diabetes status using a documented diagnosis of diabetes mellitus and the prescription of antidiabetic drugs, in addition to fasting glucose level.

In conclusion, our results suggest that central obesity is a risk factor for ESRD regardless of glycaemic status. Low WC was also associated with increased risk for ESRD, but this was dependent on glycaemic status. Longer term studies with larger cohorts are required to determine if lower WC is a risk factor for ESRD, according to the presence or progression of diabetes and the presence of ethnic differences in this association.

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Conflict of interest

The authors declare that they have no competing interests.

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Online supplementary material

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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