The Association of Excess Body Weight with Risk of ESKD Is Mediated Through Insulin Resistance, Hypertension, and Hyperuricemia

Josef Fritz,[1] Wolfgang Brozek,[2] Hans Concin,[2] Gabriele Nagel,[2,3] Julia Kerschbaum,[4,5] Karl Lhotta,[6,7] Hanno Ulmer,[1] and Emanuel Zitt[2,6,7]

Due to the number of contributing authors, the affiliations are listed at the end of this article.

ABSTRACT

Background Insulin resistance, hypertension, hyperuricemia, and hypercholesterolemia are hypothesized to be important intermediates in the relationship between excess body weight and CKD risk. However, the magnitude of the total effect of excess body weight on ESKD mediated through these four pathways remains to be quantified.

Methods We applied a model for analysis of correlated mediators to population-based data from 100,269 Austrian individuals (mean age 46.4 years). Association of body mass index (BMI) was coalesced with ESKD risk into direct association. Indirect associations were mediated through the triglyceride-glucose (TyG) index (as an indicator of insulin resistance), mean arterial pressure (MAP), uric acid (UA), and total cholesterol (TC).

Results Mean follow-up was 23.1 years with 463 (0.5%) incident ESKD cases. An unhealthy metabolic profile (prevalence 32.4%) was associated with a markedly increased ESKD risk (multivariably adjusted hazard ratio (aHR), 3.57; 95% CI, 2.89 to 4.40), independent of BMI. A 5-kg/m^2 higher BMI was associated with a 57% increased ESKD risk ($aHR_{total\ association}$, 1.57; 1.38 to 1.77). Of this association, 99% (76% to 140%) arose from all mediators jointly; 33% (22% to 49%) through TyG index; 34% (24% to 50%) through MAP; 30% (21% to 45%) through UA; and 2% (−1% to 4%) through TC. The remaining direct association was nonsignificant ($aHR_{direct\ association}$, 1.01; 0.88 to 1.14).

Conclusions TyG index, MAP, and UA, but not TC, mediate the association of BMI with ESKD in middle-aged adults. Our findings highlight that in addition to weight reduction, the control of metabolic risk factors might be essential in mitigating the adverse effects of BMI on kidney function.

JASN 33: 1377–1389, 2022. doi: https://doi.org/10.1681/ASN.2021091263

Excess body weight is associated with an increased risk of incident CKD, kidney function decline, and development of ESKD in the general population.[1–4] Despite this evident and strong epidemiologic link, the underlying biologic mechanisms still remain unclear. Metabolic factors linked to excess body weight, such as insulin resistance, hypertension, hyperuricemia, and dyslipidemia, may act as causal intermediates in the relationship between overweight/obesity and renal risk, but their relative contributions in this relationship are unknown.[5–9]

Insulin resistance, hypertension, hyperuricemia, and hypercholesterolemia are established metabolic risk factors that have been associated with risk of various diseases, such as cardiovascular disease, CKD, and ESKD.[5,10–21] Overweight and obesity are

Received September 23, 2021. Accepted March 24, 2022.

Published online ahead of print. Publication date available at www.jasn.org.

Correspondence: Dr. Emanuel Zitt, Agency for Preventive and Social Medicine, Bregenz, Department of Internal Medicine III, Academic Teaching Hospital Feldkirch, Carinagasse 47, A-6800 Feldkirch, Austria. Email: emanuel.zitt@lkhf.at

in general associated with a worse profile in these metabolic factors. However, some overweight/obese individuals show a lower burden of metabolic abnormalities, often referred to as overweight/obese metabolically healthy individuals. In contrast, a fraction of individuals present with an unhealthy metabolic profile even among normal weight individuals. Studying how overweight/obesity in combination with the metabolic health status affects the risk of kidney disease is a first step in better understanding the complex relationships between excess body weight, metabolic factors, and kidney disease.

However, studies about the relationship between overweight and obesity, metabolic health, and the risk of ESKD are scarce and results conflicting. In the Reasons for Geographic and Racial Differences in Stroke study, a higher body mass index (BMI) was associated with a lower risk of ESKD in metabolically healthy individuals, and a twofold higher ESKD risk was found in metabolically unhealthy participants irrespective of their weight status.[22] Another US cohort study found no association between metabolically healthy obesity and ESKD either, but confirmed the increased risk in metabolically unhealthy individuals.[23]

These two studies suggest that the effect of BMI on ESKD might be mediated in part through metabolic factors. Indeed, a recent Mendelian randomization study with UK biobank data provided evidence for a largely causal association between adiposity (measured as BMI) and CKD, and showed that BP and diabetes explained about two-thirds of this causal relationship.[24] Moreover, in a previous Austrian population-based study, we have shown that the triglyceride-glucose index (TyG index; a recently proposed indicator of insulin resistance[25]) was significantly associated with incident ESKD and mediated approximately 40% of the relationship of BMI with ESKD.[13] However, it is still unclear which overweight- and obesity-related metabolic factors contribute most to the association of BMI with ESKD risk.

Using data of >100,000 participants of the Vorarlberg Health Monitoring and Promotion Program (VHM&PP), the aims of this study were (*1*) to evaluate the increase in ESKD risk of a metabolically unhealthy profile compared with a healthy metabolic profile; and (*2*) to quantify the contributions of insulin resistance, hypertension, hyperuricemia, and hypercholesterolemia as mediators in the relationship between BMI and ESKD risk, both individually and in combination.

Significance Statement

Insulin resistance, hypertension, hyperuricemia, and hypercholesterolemia are candidates for mediating the effect of BMI on ESKD. However, the independent contributions of these factors have not been quantified in prospective studies to date. Applying a model of mediation, the authors quantified the contribution of these four metabolic factors to the association of BMI with ESKD in a population-based cohort of 100,269 predominantly healthy Austrian individuals. They found that the association of BMI with ESKD was mediated through TyG index (a measure of insulin resistance), mean arterial pressure, and uric acid, but not through total cholesterol. The findings suggest that in addition to weight reduction, the control of metabolic risk factors is important in mitigating the adverse effects of BMI on kidney function.

METHODS

Data Source and Study Population

The VHM&PP, conducted by the Agency for Preventive and Social Medicine, is a large population-based risk factor surveillance program in Vorarlberg, the westernmost province of Austria. In the course of the program, which was initiated in 1985, every adult residing in Vorarlberg was invited to participate, and a screening examination was performed by local general practitioners according to a standard protocol. Between January of 1985 and June of 2005, 99,894 female and 85,473 male residents aged older than 18 years (more than half of the adult population of Vorarlberg) were enrolled in the VHM&PP. During the screening examination, height and weight (in light clothing) were measured by medical staff, smoking status was inquired, and a blood draw was taken. Occupational status (blue collar, white collar, or self-employed) was determined and used as a surrogate measure of socioeconomic status. Participants who were retired at baseline were classified according to their former occupation, and individuals not employed outside the home were classified according to their spouse's or partner's occupation. A more detailed description of the program and examination procedures is reported elsewhere.[3,26,27]

Because an overnight fast was part of the protocol only from 1988 onwards, we excluded 8073 participants (4.4%) who did not have an examination with a blood draw in fasting status. Moreover, as uric acid (UA) was routinely determined only in women above the age of 50 years at screening, but not measured in women at younger ages, we excluded women under 50 years of age. Furthermore, participants were excluded with incomplete exposure, covariate, or mediator variables; with a baseline BMI<20 kg/m^2 or a baseline age>75 years; and with a follow-up time <2 years, resulting in a final analysis population of 100,269 individuals (75,282 men and 24,987 women). Detailed numbers are provided in the flow chart in Supplemental Figure 1. Of note, the decision to apply these exclusion criteria was made *a priori* without any data exploration. In order to avoid nonlinear effects due to a J-shaped association between BMI and ESKD when including underweight individuals as shown by Herrington et al.,[28] we restricted our analysis to individuals with a BMI of 20 kg/m^2 and higher. The first 2 years of follow-up were excluded to reduce the possibility of reverse causation.

Outcome data were obtained by linking the VHM&PP database with the Austrian Dialysis and Transplant Registry (OEDTR) and the National Mortality Registry. The OEDTR collects data provided by the Austrian dialysis and transplant centers on all patients undergoing chronic RRT (hemodialysis,

peritoneal dialysis, kidney transplantation) in Austria since 1964 with an almost complete follow-up.[29]

All study procedures were performed in accordance with the Declaration of Helsinki and relevant guidelines. Institutional review board approval for the study was obtained from the Ethics Committee of the State of Vorarlberg. Written, informed consent was obtained from all VHM&PP participants, and all patients registered in the OEDTR had signed a declaration of consent to permit their data to be transferred to the registry.

STrengthening the Reporting of Observational studies in Epidemiology guidelines were followed for the preparation of this article.[30]

Definitions of Exposure, Mediators, and Outcome

BMI was calculated from height and weight records as weight (kg)/height (m)2, and categorized into normal weight (BMI 20 to <25), overweight (BMI 25 to <30), and obesity (BMI≥30) according to the World Health Organization definition. The TyG index was calculated as ln(fasting triglycerides [mg/dl] × fasting blood glucose [mg/dl]/2),[25] and mean arterial pressure (MAP) as diastolic BP+1/3×(systolic BP−diastolic BP). The outcome ESKD was defined as initiation of RRT, either dialysis or kidney transplantation. Follow-up began 2 years after the baseline health examination and ended at the diagnosis of ESKD, or at the occurrence of the censoring events death or end of the observation period (December 31, 2019), whichever occurred first.

The four metabolic factors TyG index, MAP, UA, and total cholesterol (TC) were chosen *a priori* without any data exploration. As shown previously, the TyG index is a simple and clinically useful surrogate marker for insulin resistance, superior to using glucose and triglyceride values separately.[25] Its validity is similar to the homeostatic model assessment insulin resistance (HOMA-IR) index.[31] HOMA-IR requires a direct measurement of insulin which was not available in our cohort. MAP combines information from both systolic and diastolic BP into one variable, avoiding collinearity problems that would arise when using the two variables jointly in the statistical model. Mediators were dichotomized into low/normal versus high using the 75th percentile as the cut-off value. Further, we constructed a metabolic score (MS) as the sum of the z-transformed values of these four factors. This score was then dichotomized at the value 1, resulting in a group of "metabolically healthy" individuals (*i.e.,* MS<1; 67.6% of participants), and a group of "metabolically unhealthy" individuals (*i.e.,* MS≥1; 32.4% of participants), an approach introduced previously.[32] Examples of combinations of values in metabolic factors together with the resulting MSs are shown in Supplemental Table 1.

Statistical Analyses

Only exposure, mediator, and covariate data of the first health examination were included in the analysis. ESKD incidence rates per 100,000 person-years were calculated stratified by BMI category and metabolic health status, and hazard ratios (HRs) along with 95% confidence intervals (95% CIs) were calculated from Cox proportional hazards models adjusted for baseline age, sex, smoking status, and socioeconomic status.

For quantifying mediation of the association of BMI with ESKD through the four mediators TyG index, MAP, UA, and TC, we applied the product-of-coefficients method.[33–35] Of note, because of the observational nature of our data, we prefer the term association instead of effect. In brief, two sets of regression models were fit to the data, one set of models for the mediators, and one model for the outcome. Specifically, the four mediators were regressed on the exposure (BMI) in separate linear models each, and the outcome (ESKD) was regressed on the exposure (BMI) and the four mediators (TyG index, MAP, UA, TC) in Cox proportional hazards models with time from baseline examination as the underlying time variable. Models were adjusted for age, sex, smoking status, and socioeconomic status, without inclusion of interaction terms. Both linearity and proportional hazards assumptions were assessed visually, by plotting penalized splines and scaled Schoenfeld residuals, respectively; no major deviations were detected.

From the mediator models, we obtained regression coefficients for the association of BMI with the respective mediator (pathways A_1, A_2, A_3, and A_4). From the outcome model, we obtained (*1*) regression coefficients (on the log[HR] scale) for the association of BMI with ESKD, independent of the mediators (pathway C); and (*2*) independent associations (on the log[HR] scale) between each of the mediators and ESKD (pathways B_1, B_2, B_3, and B_4). The indirect association of BMI with ESKD mediated through the *i*th mediator is defined as the product $A_i \times B_i$. The direct association of BMI with ESKD is given by the regression coefficient C. The sum of the four indirect associations (*i.e.,* joint indirect association) and the direct association gives the total association of BMI with ESKD. All of these associations were converted to the HR scale by exponentiation.

In case of a rare outcome (ESKD incidence of 0.5% in our analysis), and under the assumptions (*1*) of causal relationships as depicted in the directed acyclic graph in Figure 1, in particular that age, sex, smoking status, and socioeconomic status account for the majority of confounding; and (*2*) that the models are correctly specified, these associations have a direct causal interpretation.[35–37] We can think of the indirect association between BMI and ESKD through the *i*th mediator as the effect of BMI that is due to mediation through the *i*th mediator, and of the direct association of BMI with ESKD as the remaining effect of BMI not explained through the set of mediators. If one mediator (M_1) causally affects another mediator (M_2), the interpretation of an indirect effect has to be amended, in so far as the indirect effect through M_1 captures the exposure effect mediated through M_1 directly, but not the causal

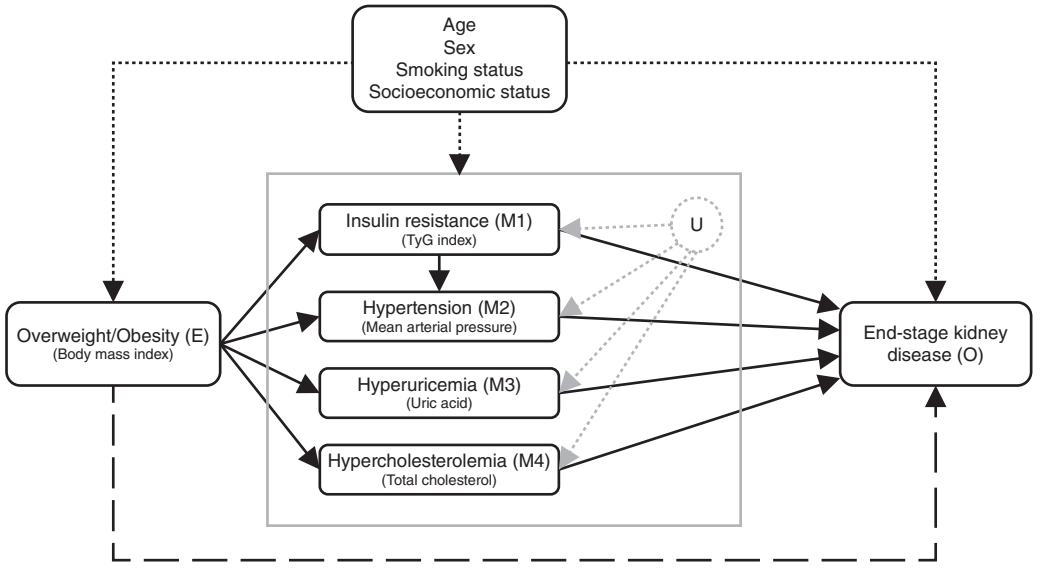

Figure 1. Underlying causal framework of the relationship between BMI and ESKD. Directed acyclic graph depicting the conceptional framework between exposure overweight/obesity (E; operationalized as BMI); mediators insulin resistance (M1), hypertension (M2), hyperuricemia (M3), and hypercholesterolemia (M4) (operationalized as TyG index, MAP, UA, and TC, respectively); outcome ESKD (O); and relevant confounders age, sex, and smoking status. Dotted arrows represent confounding pathways, whereas the other arrows (solid [indirect effects *via* mediators] and dashed [direct effect of overweight/obesity]), due to their unidirectionality, can convey exposure effects to the outcome, and are thus causal pathways. Of note, we also included an arrow from insulin resistance to hypertension because the evidence of insulin resistance causally affecting BP levels is strong.[43,59] The absence of any other arrows among the mediators themselves (apart from the insulin resistance-hypertension link) encodes our assumption that they do not relevantly causally affect one another.[40–42] Metabolic factors are correlated; however, this does not imply causation.[43,44] The correlations among the mediators could be brought about by some unmeasured common causes of the mediators (depicted as "U" in the diagram) other than the variables age, sex, or smoking status which we adjust for, such as lifestyle factors (*e.g.*, diet quality, alcohol consumption, physical activity), medication use, or genetics. All statistical models are on the basis of the causal framework depicted in this figure and are adjusted for age, sex, and smoking status.

descendant M_2, and the indirect effect through M_2 captures the exposure effect through M_2, with and without the causal antecedent M_1. This needs to be considered when interpreting the indirect associations through the TyG index and MAP, because there is evidence for insulin resistance causally affecting BP[11,38,39] (thus the arrow from insulin resistance to hypertension in Figure 1); see also the discussion part of this manuscript. Evidence for other causal relationships between the four mediators is weak (indicated by the absence of arrows in Figure 1),[40–44] and therefore the interpretation of indirect associations through UA and through TC is more straightforward. Exact definitions of direct and indirect associations in terms of counterfactuals (the full technical terms are interventional direct and interventional indirect effects) and more detailed descriptions can be found elsewhere.[35,37]

The proportions of the various derived associations relative to the total association between BMI and risk of ESKD were calculated on the log-transformed HR scale, because HRs are additive on this scale. We used bootstrapping with 5000 samples to calculate 95% CIs for all parameters of interest. Stratified analyses by sex and primary underlying kidney disease were performed as well. In addition, a sensitivity analysis without the exclusion of the first 2 years of follow-up was done.

Finally, we compared associations of BMI with ESKD risk (conditioning on the same covariates as listed above), both adjusted and unadjusted for the mediators, also known as the difference method for mediation analysis.[34,45]

Statistical analyses were conducted in R, version 3.5.1.[46] All statistical tests were two-sided at a significance level of 0.05.

RESULTS

Characteristics of the Study Population

The analyzed cohort included 100,269 participants (24.9% female, mean baseline age 46.4 years, SD 14.6) initially free of ESKD, of whom 463 (0.5%) developed ESKD over a mean follow-up of 23.1 years (Table 1). The primary underlying kidney disease was classified as diabetic kidney disease in 24.4% (n=113) of ESKD cases, vascular nephropathy in 32.2% (n=149) of cases, and other disease in 43.4% (n=201) of cases. Mean time from baseline until ESKD was 15.5 (SD 7.8) years. Mean BMI (kg/m^2) at baseline was 26.1 (SD 3.8); 41.2% of the participants were overweight, and

13.9% obese. Baseline characteristics stratified by sex and BMI categories are given in Table 1. Women were markedly older than men (mean [SD] 60.1 [6.8] versus 41.8 [13.6]) due to the exclusion of women younger than 50 years. Distribution of age, laboratory parameters, and other covariates differed across BMI categories as expected.

BMI Categories, Metabolic Health Status, and ESKD Incidence

An unhealthy metabolic profile (prevalence in the total population: 32.4%) was associated with an increased ESKD risk (multivariably adjusted HR, 3.57; 95% CI, 2.89 to 4.40), independent of BMI (Table 2). Likewise, ESKD risk across the BMI categories of normal weight, overweight, and obesity strongly depended on the metabolic health status. Overweight and obesity, paired with a metabolically healthy profile, were associated with an increase in ESKD risk compared with the reference category of metabolically healthy normal weight (adjusted $HR_{overweight,\ healthy}$, 1.11; 95% CI, 0.78 to 1.60; $HR_{obese,\ healthy}$, 1.98; 95% CI, 1.20 to 3.25); however, to a much lesser extent than when paired with a metabolically unhealthy profile ($HR_{overweight,\ unhealthy}$, 3.93; 95% CI, 2.91 to 5.29; $HR_{obese,\ unhealthy}$, 5.75; 95% CI, 4.17 to 7.93). A metabolically unhealthy profile was associated with a substantial increase in ESKD risk even in the presence of normal weight ($HR_{normal\ weight,\ unhealthy}$, 4.50; 95% CI, 3.20 to 6.31). Similar patterns were also observed for low/

Table 1. Participant characteristics of the VHM&PP cohort, overall and stratified by sex and BMI categories

Characteristic	Total (*n*=100,269)	Sex		Baseline BMI [kg/m^2]		
		Male (*n*=75,282)	Female (*n*=24,987)	≥20 to <25 (*n*=45,093)	≥25 to <30 (*n*=41,262)	≥30 (*n*=13,914)
Baseline age [years]	46.4 (14.6)	41.8 (13.6)[a]	60.1 (6.8)[a]	42.9 (15.0)	48.3 (13.8)	52.0 (12.8)
Smoking status						
Never smoker	64,056 (63.9%)	42,878 (57.0%)	21,178 (84.8%)	29,063 (64.5%)	25,745 (62.4%)	9248 (66.5%)
Current/ever smoker	36,213 (36.1%)	32,404 (43.0%)	3809 (15.2%)	16,030 (35.5%)	15,517 (37.6%)	4666 (33.5%)
Socioeconomic status						
Blue collar	36,268 (36.2%)	24,733 (32.9%)	11,535 (46.2%)	14,898 (33.0%)	15,229 (36.9%)	6141 (44.1%)
White collar	45,909 (45.8%)	34,899 (46.4%)	11,010 (44.1%)	21,704 (48.1%)	18,795 (45.6%)	5410 (38.9%)
Self-employed	8266 (8.2%)	6880 (9.1%)	1386 (5.5%)	3797 (8.4%)	3440 (8.3%)	1029 (7.4%)
Missing	9826 (9.8%)	8770 (11.6%)	1056 (4.2%)	4694 (10.4%)	3798 (9.2%)	1334 (9.6%)
BMI [kg/m^2]	26.1 (3.8)	25.8 (3.5)	27.0 (4.5)	23.0 (1.3)	27.1 (1.4)	33.0 (3.2)
Normal weight (20.0–24.9 kg/m^2)	45,093 (45.0%)	35,320 (46.9%)	9773 (39.1%)	45,093 (100%)	0 (0%)	0 (0%)
Overweight (25–29.9 kg/m^2)	41,262 (41.2%)	31,534 (41.9%)	9728 (38.9%)	0 (0%)	41,262 (100%)	0 (0%)
Obese (≥30.0 kg/m^2)	13,914 (13.9%)	8428 (11.2%)	5486 (22.0%)	0 (0%)	0 (0%)	13,914 (100%)
Fasting glucose [mmol/L]	5.0 (1.4)	5.0 (1.3)	5.2 (1.6)	4.8 (1.1)	5.1 (1.4)	5.5 (1.9)
Fasting glucose >6.9 mmol/L	4813 (4.8%)	3078 (4.1%)	1735 (6.9%)	1167 (2.6%)	2081 (5.0%)	1565 (11.2%)
Fasting triglyceride [mmol/L]	1.7 (1.3)	1.7 (1.4)	1.6 (1.0)	1.4 (1.0)	1.9 (1.4)	2.2 (1.6)
TyG index[b]	8.6 (0.6)	8.6 (0.7)	8.6 (0.6)	8.4 (0.6)	8.7 (0.6)	9.0 (0.7)
Systolic BP [mm Hg]	134.9 (20.1)	132.0 (18.5)	143.8 (22.0)	129.1 (18.0)	137.3 (19.6)	146.9 (21.5)
Diastolic BP [mm Hg]	82.9 (10.9)	82.1 (10.8)	85.5 (10.9)	79.8 (9.8)	84.3 (10.6)	89.1 (11.7)
MAP[c] [mm Hg]	100.3 (12.8)	98.7 (12.2)	105.0 (13.3)	96.2 (11.3)	101.9 (12.4)	108.3 (13.6)
Fasting TC [mmol/L]	5.8 (1.2)	5.6 (1.2)	6.3 (1.2)	5.5 (1.2)	5.9 (1.2)	6.0 (1.2)
UA [μmol/L]	324.6 (81.0)	341.3 (76.2)	274.3 (74.0)	308.9 (75.1)	333.6 (81.2)	349.1 (88.6)
Follow-up [years]	23.1 (6.9)	23.4 (6.8)	22.5 (7.3)	23.8 (6.7)	23.0 (6.9)	21.3 (7.2)
Death by any cause during F/U	27,407 (27.3%)	15,591 (20.7%)	11,816 (47.3%)	9730 (21.6%)	12,338 (29.9%)	5339 (38.4%)
ESKD during F/U	463 (0.5%)	353 (0.5%)	110 (0.4%)	138 (0.3%)	207 (0.5%)	118 (0.8%)
Primary kidney disease[d]						
Diabetic kidney disease	113 (24.4%)	81 (22.9%)	32 (29.1%)	17 (12.3%)	40 (19.3%)	56 (47.5%)
Vascular nephropathy	149 (32.2%)	117 (33.1%)	32 (29.1%)	48 (34.8%)	68 (32.9%)	33 (28.0%)
Other diseases	201 (43.4%)	155 (43.9%)	46 (41.8%)	73 (52.9%)	99 (47.8%)	29 (24.6%)
Time from baseline to ESKD[e]	15.5 (7.8)	16.0 (8.0)	14.1 (7.2)	15.5 (8.0)	15.6 (7.9)	15.4 (7.5)
Age at start of RRT [years]	68.1 (11.8)	66.5 (12.4)	74.1 (7.5)	67.5 (13.2)	69.1 (11.0)	67.2 (11.4)

Statistics are given as *n* (%) or as mean (SD). F/U, follow-up.

[a]The explanation for the difference in mean age between men and women is that women younger than 50 years of age were excluded because UA was not routinely determined for them in VHM&PP, whereas this exclusion was not done for men.

[b]TyG index calculated as ln(triglycerides [mg/dl]×blood glucose [mg/dl]/2).

[c]Defined as diastolic BP+1/3×(systolic BP−diastolic BP) [mm Hg].

[d]Percentages are on the basis of patients who developed ESKD only.

[e]Calculated on the basis of patients who developed ESKD only.

Table 2. Comparison of ESKD incidence rates and multivariably adjusted HRs for the sample of 100,269 VHM&PP participants across BMI groups, single mediator levels, and combined metabolic health status at the baseline examination

Variable	Normal Weight (BMI 20 to <25 mg/kg^2)			Overweight (BMI 25 to <30 mg/kg^2)			Obesity (BMI ≥30 mg/kg^2)			Total		
	Incident ESKD Cases/*N*	Incident ESKD Cases per 100,000 Person-Years (95% CI)	Multivariably Adjusted HR[a] (95% CI)	Incident ESKD Cases/*N*	Incident ESKD Cases per 100,000 Person-Years (95% CI)	Multivariably Adjusted HR[a] (95% CI)	Incident ESKD Cases/*N*	Incident ESKD Cases per 100,000 Person-Years (95% CI)	Multivariably Adjusted HR[a] (95% CI)	Incident ESKD Cases/*N*	Incident ESKD Cases per 100,000 Person-Years (95% CI)	Multivariably Adjusted HR[b] (95% CI)
Overall	138/45,093	12.9 (10.8 to 15.2)	1.00 (Ref)	207/41,262	21.8 (18.9 to 24.9)	1.32 (1.06 to 1.64)	118/13,914	39.7 (32.9 to 47.6)	2.42 (1.89 to 3.11)	463/100,269	20.0 (18.2 to 21.9)	—
TyG-I												
<75th pct	93/38,852	10.0 (8.1 to 12.2)	1.00 (Ref)	112/28,652	16.8 (13.8 to 20.2)	1.33 (1.01 to 1.75)	33/7695	19.7 (13.6 to 27.7)	1.56 (1.05 to 2.33)	238/75,199	13.5 (11.8 to 15.3)	1.00 (Ref)
≥75th pct	45/6241	31.8 (23.2 to 42.5)	2.58 (1.81 to 3.70)	95/12,610	33.5 (27.1 to 40.9)	2.37 (1.77 to 3.16)	85/6219	65.7 (52.5 to 81.2)	4.77 (3.54 to 6.43)	225/25,070	40.1 (35.44 to 46.2)	2.18 (1.80 to 2.64)
MAP												
<75th pct	77/37,137	8.6 (6.8 to 10.7)	1.00 (Ref)	86/27,256	13.4 (10.7 to 16.6)	1.26 (0.93 to 1.72)	36/6224	26.5 (18.5 to 36.6)	2.52 (1.69 to 3.75)	199/70,617	11.9 (10.3 to 13.7)	1.00 (Ref)
≥75th pct	61/7956	34.6 (26.5 to 44.4)	3.12 (2.21 to 4.40)	121/14,006	39.1 (32.4 to 46.7)	3.14 (2.34 to 4.22)	82/7690	51.0 (40.5 to 63.3)	4.53 (3.29 to 6.24)	264/29,652	40.8 (36.0 to 46.0)	2.42 (1.99 to 2.95)
UA												
<75th pct	80/36,702	9.2 (7.3 to 11.4)	1.00 (Ref)	102/28,821	15.3 (12.5 to 18.6)	1.33 (0.99 to 1.78)	54/8639	29.0 (21.8 to 37.9)	2.43 (1.71 to 3.45)	236/74,162	13.7 (12.0 to 15.5)	1.00 (Ref)
≥75th pct	58/8391	29.1 (22.1 to 37.6)	3.30 (2.34 to 4.65)	105/12,441	36.9 (30.2 to 44.7)	3.18 (2.36 to 4.29)	64/5275	57.6 (44.4 to 73.6)	4.85 (3.48 to 6.77)	227/26,107	38.2 (33.4 to 44.5)	2.46 (2.02 to 2.99)
TC												
<75th pct	94/36,375	10.8 (8.7 to 13.2)	1.00 (Ref)	113/29,291	16.7 (13.7 to 20.0)	1.18 (0.90 to 1.56)	72/9500	35.7 (27.9 to 44.9)	2.52 (1.84 to 3.44)	279/75,166	15.9 (14.1 to 17.9)	1.00 (Ref)
≥75th pct	44/8718	21.9 (15.9 to 29.4)	1.49 (1.03 to 2.14)	94/11,971	34.4 (27.8 to 42.1)	2.12 (1.58 to 2.84)	46/4414	48.4 (35.4 to 63.4)	3.22 (2.25 to 4.61)	184/25,103	32.3 (27.8 to 37.3)	1.56 (1.29 to 1.88)
Metabolically healthy	64/37,538	7.1 (5.5 to 9.0)	1.00 (Ref)	55/24,595	9.5 (7.2 to 12.4)	1.11 (0.78 to 1.60)	21 5631	17.0 (10.5 to 25.9)	1.98 (1.20 to 3.25)	140/67,764	8.7 (7.3 to 10.3)	1.00 (Ref)
Metabolically unhealthy	74/7555	43.9 (34.5 to 55.1)	4.50 (3.20 to 6.31)	152/16,667	40.7 (34.5 to 47.7)	3.93 (2.91 to 5.29)	97/8283	56.0 (45.4 to 68.3)	5.75 (4.17 to 7.93)	323/32,505	45.2 (40.4 to 50.4)	3.57 (2.89 to 4.40)

Single mediators were categorized into high (*i.e.*, ≥75th percentile) versus low/normal (*i.e.*, <75th percentile). The 75th percentiles were 8.99 for TyG index, 106.67 mm Hg for MAP, 374.72 mmol/L for UA, and 6.53 μmol/L for cholesterol, respectively. Metabolically healthy was defined as a value of <1 when summing up the four z-transformed mediators TyG index, MAP, UA, and TC, whereas metabolically unhealthy was defined as a value of ≥1. Refer to Supplemental Table 1 for examples of specific combinations of values in metabolic factors and the resulting MSs. TyG-I, TyG index; pct, percentile.

[a]HRs from a Cox proportional hazards model adjusted for baseline age, sex, smoking status, and socioeconomic status.

[b]HRs from a Cox proportional hazards model adjusted for baseline age, sex, smoking status, socioeconomic status, and additionally BMI.

normal (<75th percentile) versus high (≥75th percentile) values of the single factors TyG index, MAP, UA, and, attenuated, for TC (Table 2).

The likelihood of a metabolically unhealthy profile increased over the BMI categories (the prevalence of a metabolically unhealthy profile was 16.8% in normal weight individuals, 40.4% in overweight individuals, and 59.5% in obese individuals), and consequently ESKD incidence rates were lowest in normal weight participants, with a clear increase in overweight and obese individuals (12.9; 95% CI, 10.8 to 15.2, ESKD incident cases per 100,000 person-years; versus 21.8; 95% CI, 18.9 to 24.9; versus 39.7; 95% CI, 32.9 to 47.6; Table 2).

Despite the differences in baseline age, patterns were similar in men and in women, although the analysis of women was limited by small ESKD incidence numbers. Detailed information on sex-specific ESKD incidence rates is provided in Supplemental Tables 2 and 3.

Associations of Mediators with BMI, with ESKD Risk, and among Themselves

BMI was strongly associated with all mediators. Adjusting for age, sex, smoking status, and socioeconomic status, a BMI increase of 5 kg/m^2 was associated with an increase of 0.41 (95% CI, 0.40 to 0.42) SDs in TyG index, 0.37 (95% CI, 0.36 to 0.38) SDs in MAP, 0.32 (95% CI, 0.31 to 0.32) SDs in UA, and 0.12 (95% CI, 0.11 to 0.12) SDs in TC (Figure 2). The four mediators were mildly to moderately correlated among each other, even after adjusting for BMI, age, sex, smoking status, and socioeconomic status (partial Pearson correlation: ρ=0.088 between TyG index and MAP, ρ=0.168 between TyG index and UA, ρ=0.359 between TyG index and TC, ρ=0.099 between MAP and UA, ρ=0.076 between MAP and TC, and ρ=0.133 between UA and TC; all P<0.001). Regarding the independent contributions of the single mediators to the risk of ESKD, a 1-SD increase in TyG index was associated with an increase in the risk of ESKD by 44% (HR, 1.44; 95% CI, 1.30 to 1.59), a 1-SD increase in MAP was associated with a risk increase by 53% (HR, 1.53; 95% CI, 1.39 to 1.67), and a 1-SD increase in UA with a risk increase of 54% (HR, 1.54; 95% CI, 1.39 to 1.70); in contrast, TC was not significantly associated with ESKD risk (HR, 1.07; 95% CI, 0.96 to 1.17, per 1-SD increase) (Figure 2).

BMI and Risk of ESKD Mediated through TyG Index, MAP, UA, and TC

A 5-kg/m^2 higher BMI was associated with an increase in ESKD risk by 57% ($HR_{total\ association}$, 1.57; 95% CI, 1.38 to

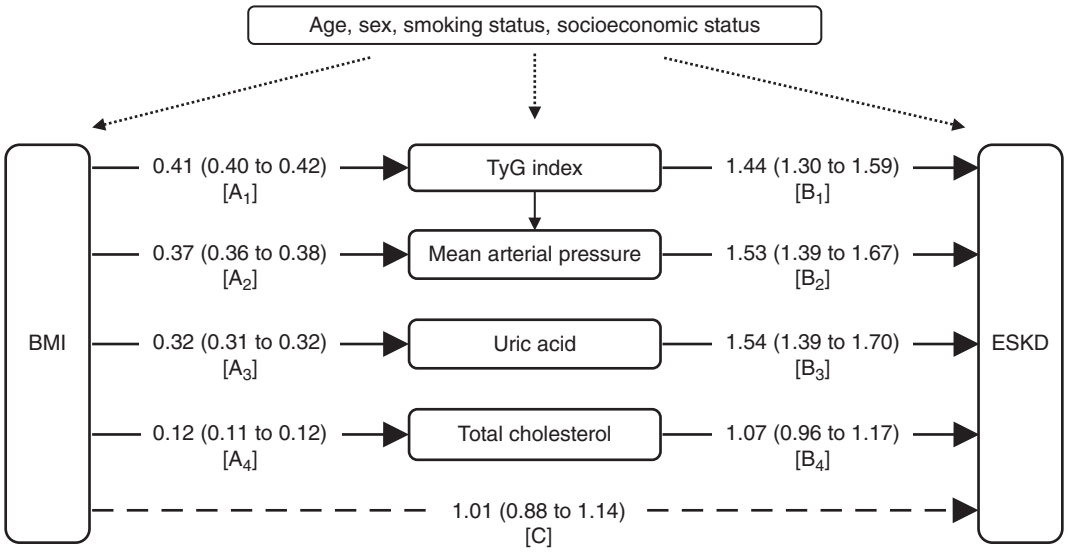

Figure 2. Path diagram with associated β estimates for the relationships between BMI, metabolic factors, and ESKD. Path diagram of the relationship between BMI; mediators TyG index, MAP, UA, and TC; and ESKD. The labels on the arrows display β estimates (and 95% CIs) of regression models using BMI values divided by 5 and mediator values adjusted for all antecedent nodes. In particular, [A1] to [A4] are β estimates from linear regression models regressing z-transformed mediator values on BMI/5, age, sex, smoking status, and socioeconomic status (thus the interpretation is SD increase in the respective mediator per 5-kg/m^2 increase in BMI); [B1] to [B4] and [C] are exponentiated β estimates (*i.e.*, HRs) from Cox proportional hazards models for outcome ESKD adjusted for BMI/5 and z-transformed mediator values, age, sex, smoking status, and socioeconomic status. Thus, the interpretation of [B1] to [B4] is risk increase of incident ESKD per SD increase in the respective mediator, and the interpretation of [C] is risk increase of incident ESKD per 5-kg/m^2 increase in BMI. Multiplication of [A1] with log([B1]), of [A2] with log([B2]), of [A3] with log([B3]), and of [A4] with log([B4]) yields the log-transformed indirect associations of the mediation model from Table 3. BMI was divided by 5 to be able to interpret β estimates as change in the outcome per 5-kg/m^2 increase in BMI, and mediator values were standardized to be able to compare regression parameter estimates across the four mediators.

Table 3. Decomposition of the total association of BMI, both continuously and as categories, with risk of ESKD into indirect associations mediated through the TyG index, MAP, UA, and TC, and the remaining direct association, for the full sample of 100,269 VHM&PP participants

Variable	HR (95% CI)	Proportion of Total Association (95% CI)
BMI continuous[a]		
Total association	1.57 (1.38 to 1.77)	—
Direct association	1.01 (0.88 to 1.14)	1% (−40% to 24%)
Joint IA	1.56 (1.49 to 1.64)	99% (76% to 140%)
IA through TyG index	1.16 (1.11 to 1.21)	33% (22% to 49%)
IA through MAP	1.17 (1.13 to 1.21)	34% (24% to 50%)
IA through UA	1.15 (1.11 to 1.18)	30% (21% to 45%)
IA through TC	1.01 (0.995 to 1.02)	2% (−1% to 4%)
Overweight versus normal weight		
Total association	1.25 (0.99 to 1.56)	—
Direct association	0.80 (0.63 to 1.005)	—[b]
Joint IA	1.57 (1.47 to 1.66)	—[b]
IA through TyG index	1.13 (1.07 to 1.19)	—[b]
IA through MAP	1.16 (1.12 to 1.20)	—[b]
IA through UA	1.17 (1.12 to 1.21)	—[b]
IA through TC	1.02 (0.997 to 1.05)	—[b]
Obesity versus normal weight		
Total association	2.35 (1.81 to 3.01)	—
Direct association	0.89 (0.66 to 1.18)	−14% (−67% to 16%)
Joint IA	2.65 (2.31 to 3.00)	114% (84% to 167%)
IA through TyG index	1.48 (1.31 to 1.64)	46% (30% to 69%)
IA through MAP	1.38 (1.25 to 1.51)	38% (24% to 61%)
IA through UA	1.30 (1.20 to 1.42)	31% (19% to 50%)
IA through TC	0.998 (0.97 to 1.02)	0% (−3% to 3%)

Decomposition of the total association into the direct association and the joint indirect association (and splitting the joint indirect association further up into indirect associations through single mediators) was done according to the product-of-coefficients methods proposed by Vansteelandt & Daniel.[35] 95% CIs were calculated using bootstrapping with 5000 bootstrap resamples. All models were adjusted for baseline age, sex, smoking status, and socioeconomic status as depicted in the directed acyclic graph in Figure 1. Proportions of the total association can potentially be >100% or <0% for direct/indirect associations, which can occur if the direct and indirect associations operate in different directions. IA, indirect association.
[a]HRs given per 5-kg/m^2 increase.
[b]Proportions of the total association not given because the nonsignificance of the total association would lead to numerically instable numbers.

1.77) (Table 3). This association could be explained by the joint contribution of the four mediators TyG index, MAP, UA, and TC (proportion jointly mediated, 99%; 95% CI, 76% to 140%; $HR_{joint\ indirect\ association}$, 1.56; 95% CI, 1.49 to 1.64), and the remaining direct association was not statistically significant ($HR_{direct\ association}$, 1.01; 95% CI, 0.88 to 1.14). Regarding the contributions of the single mediators, the pathways *via* TyG index (proportion mediated, 33%; 95% CI, 22% to 49%), MAP (34%; 95% CI, 24% to 50%), and UA (30%; 95% CI, 21% to 45%) contributed to the total association of BMI with ESKD risk in comparable amounts, whereas the pathway *via* TC (2%; 95% CI, −1% to 4%) did not significantly contribute (Table 3). The negligible contribution of TC was due to the combination of both a weaker association of BMI with TC and a much weaker, nonsignificant independent contribution of TC to risk of ESKD, compared with the other mediators (Figure 2). Subgroup analyses revealed similar patterns across men and women (Table 4). Stratified analyses revealed distinct patterns of mediation depending on the underlying kidney disease (Supplemental Table 4).

Investigating BMI categories, the total association of BMI with ESKD risk (expressed as HRs) was 1.25 (95% CI, 0.99 to 1.56) for overweight versus normal weight, and increased to 2.35 (95% CI, 1.81 to 3.01) for the obesity group. For both groups, the total association was fully (*i.e.*, nonsignificant direct association) mediated through MAP, TyG index, and UA, but not TC ($HR_{direct\ association}$, 0.80; 95% CI, 0.63 to 1.00, for overweight; and 0.89; 95% CI, 0.66 to 1.18, for obesity, respectively) (Table 3).

The finding of this mediation model, namely full mediation of the association of BMI with ESKD by the metabolic factors under consideration, was confirmed in separate analyses using the traditional difference method for mediation analysis (Supplemental Table 5). The difference method does not allow a further decomposition into single components, though. The inclusion of the first 2 years of follow-up did not substantially alter the results (Supplemental Table 6).

DISCUSSION

In this large, observational, population-based cohort study we aimed to quantify the contributions of several different overweight- and obesity-related metabolic factors to the association of BMI with ESKD risk. In a first step, we showed that a metabolically unhealthy profile was associated with a markedly increased ESKD risk, not only in overweight and obese, but also in normal weight individuals. This means that ESKD risk is not only associated with BMI, but, importantly, also with the metabolic health status, and suggests that metabolic factors might be important mediators in the relationship between BMI and ESKD. In a second step, we quantified the independent contributions of each of the four metabolic factors TyG index, MAP, UA, and TC as mediators to the BMI-ESKD relationship. We found that the three mediators TyG index, MAP, and UA were each significantly and independently associated with the risk of ESKD. Each of them independently mediated around one-third of the total association of BMI with ESKD risk, and thus TyG index, MAP, and UA mediate the BMI-ESKD relationship to a high degree. In contrast, the mediating role of TC was negligible. No sex differences were detected, and thus these findings apply equally to men and women.

The association between excess body weight and the development of CKD and ESKD is well supported by global data in millions of individuals of variable baseline risk and

Table 4. Decomposition of the total association of BMI with risk of ESKD into indirect associations mediated through the TyG index, MAP, UA, and TC, and the remaining direct association; separately for the 75,282 male and the 24,987 female VHM&PP participants

Variable	Men		Women	
	HR (95% CI)[a]	Proportion of Total Association (95% CI)	HR (95% CI)[a]	Proportion of Total Association (95% CI)
BMI continuous				
Total association	1.56 (1.31 to 1.83)	—	1.56 (1.29 to 1.86)	—
Direct association	0.97 (0.80 to 1.16)	−6% (−80% to 25%)	1.002 (0.81 to 1.21)	0% (−77% to 33%)
Joint IA	1.60 (1.50 to 1.71)	106% (75% to 180%)	1.56 (1.42 to 1.70)	100% (67% to 177%)
IA through TyG index	1.16 (1.10 to 1.22)	33% (20% to 60%)	1.18 (1.11 to 1.25)	37% (22% to 67%)
IA through MAP	1.18 (1.13 to 1.23)	38% (24% to 67%)	1.14 (1.07 to 1.21)	29% (14% to 56%)
IA through UA	1.15 (1.10 to 1.20)	31% (19% to 56%)	1.16 (1.10 to 1.23)	33% (18% to 66%)
IA through TC	1.02 (0.99 to 1.04)	4% (−2% to 10%)	0.9997 (0.99 to 1.01)	0% (−1% to 1%)

Decomposition of the total association into the direct association and the joint indirect association (and splitting the joint indirect association further up into indirect associations through single mediators) was done according to the product-of-coefficients methods proposed in Vansteelandt & Daniel.[35] The 95% CIs were calculated using bootstrapping with 5000 bootstrap resamples. All models were adjusted for baseline age, smoking status, and socioeconomic status as depicted in the directed acyclic graph in Figure 1. IA, indirect association.

[a]HRs given per 5-kg/m^2 increase.

age including adolescents.[2,4,47] Our finding of a 57% higher risk of ESKD with each 5-kg/m^2 higher BMI in a middle-aged low-risk general population confirms the relevance of this preventable risk factor. This observed risk increase is consistent with the strength of association between BMI and ESKD as observed in UK data on >1.4 million people with similar baseline characteristics as in our study.[28] This fact becomes even more important considering the growing number of obese individuals worldwide, with the prevalence of obesity having more than doubled since 1980 in >70 countries as reported by the Global Burden of Disease study.[48]

Far less is known about the causal pathways connecting excess body weight and ESKD. Using data of 281,228 genotyped UK Biobank participants in a Mendelian randomization study, Zhu *et al.* found that the mediators diabetes mellitus and BP in combination explained about two-thirds of the association between BMI and CKD, a portion underestimated using conventional epidemiologic analysis.[24] In our study, the two factors TyG index and MAP mediated 67% of the total association of BMI with ESKD, a similar number to the one reported by Zhu *et al.* despite several important differences in study design and analysis (prospective versus cross-sectional design, differences in baseline age, use of TyG index versus diabetes mellitus, ESKD as the outcome versus a broader CKD definition). Despite these differences, findings of the two studies are similar, indicating robustness and generalizability of the results. A further strength of our study is the addition of the potential mediators UA and TC which were not investigated by Zhu *et al.*

Hypercholesterolemia did not contribute as a relevant mediator to the BMI-ESKD association due to a weaker association of BMI with TC and a much weaker independent contribution of TC to the risk of ESKD, compared with the other three studied mediators. In line with this finding, Hsu *et al.* and Kastarinen *et al.* did not observe an association between TC levels and long-term risk for ESKD over a 25-year period[18,49]; and also in a randomized, controlled trial simvastatin plus ezetimibe, although lowering cholesterol levels, did not lead to a reduction in ESKD incidence compared with the placebo group.[50] A time-window analysis exploring the association between metabolic factors and ESKD showed that the effect of hypercholesterolemia was highest in the first 5 years, diminishing thereafter and lacking after ≥15 years of follow-up.[51] Hypercholesterolemia in the years before ESKD may be caused by progressive CKD and nephrotic proteinuria, for example, in diabetic kidney disease, and may therefore be considered a consequence rather than a cause of progressive kidney disease. This view is supported by a report from the Chronic Renal Insufficiency Cohort study showing that TC levels are not associated with CKD progression over a period of 4 years.[52]

Insulin resistance has been found to be associated with CKD independently of diabetes.[53,54] Mechanistically, insulin resistance is assumed to cause glomerular hyperfiltration, increased sodium retention, tubular dysfunction, and renal tissue inflammation and fibrosis.[6,8,55] As an indicator for insulin resistance, we used the TyG index, which has been proven to correlate well with the euglycemic-hyperinsulinemic clamp test and HOMA-IR index,[31] and was recently found to be significantly associated with the risk of ESKD.[13]

Hypertension is another established and important risk factor of ESKD.[19,56] The relationship between body weight and BP and the development of hypertension with excess body weight is firmly supported by epidemiologic and preclinical human and animal experimental evidence.[9,57,58] Among the several different biologic mechanisms between obesity and hypertension, insulin resistance itself is a contributing mediator.[43,59] This has to be considered when interpreting the indirect associations mediated through the TyG index and MAP in our study. Specifically, the

component of the association of BMI with ESKD risk that is mediated *via* the "double-mediator" pathway BMI→TyG index→MAP→ESKD is part of the indirect association mediated through MAP, but not the indirect association through the TyG index. If anything, the implicit involvement of the TyG index in part of the indirect association through MAP renders the role of the TyG index in the relationship between BMI and ESKD even more prominent. Indeed, we previously demonstrated that the TyG index as a single mediator mediated 42% of the BMI-ESKD relationship,[13] whereas the contribution independent of the other metabolic factors was 33% in this study.

A new finding, which to our knowledge has not been described previously, is the significant mediating contribution of UA on the association of BMI with ESKD. Hyperuricemia is independently associated with new-onset CKD as shown in a large meta-analysis of 13 individual studies, with an increasing effect estimate with longer follow-up.[5] In contrast, the effect of UA on the progression of CKD remains controversial.[60–64] Randomized, controlled trials showed no beneficial effect of UA-lowering therapy on the progression of CKD in patients with type 1 diabetes and diabetic kidney disease[65] or advanced CKD stages 3 and 4.[66] However, these studies did not address UA-lowering therapy in obese patients with hyperuricemia and normal kidney function or early stages of CKD. Therefore, UA could play a role as a causal risk factor for kidney disease onset rather than disease progression. Regarding ESKD, Hsu *et al.* reported increased serum UA levels to be an independent risk factor for ESKD.[18] However, far less is known about the role of UA in the association between excess body weight and ESKD. Our finding of a roughly equal amount of mediation through UA as compared with the TyG index and MAP emphasizes that besides the established mediators hypertension and insulin resistance (or diabetes), hyperuricemia should be in the focus of future studies investigating the effect of overweight and obesity on kidney function as well.

Our study suggests that in individuals with overweight and obesity focused interventions, either pharmaceutic or behavioral, on the risk factors insulin resistance, hypertension, and hyperuricemia might carry the potential to strongly decrease the renal risk. In this regard, sodium-glucose cotransporter 2 inhibitors, which have recently been shown to significantly slow the progression of CKD,[67] may be a promising therapeutic option, because they lower BP and serum UA, improve insulin sensitivity, and decrease body weight and obesity-related glomerular hyperfiltration.[68,69]

The outstanding importance of maintaining a healthy metabolic profile, not only in overweight and obese but also in normal weight individuals, is supported by our analysis comparing the association of metabolic health with ESKD risk, both within BMI categories and overall. Within all categories, including normal weight, a metabolically unhealthy profile increased ESKD risk markedly (by a factor of 3 or more), whereas the risk increase across BMI categories within categories of metabolic health, in particular in metabolically unhealthy individuals, was comparatively moderate (2.0- and 1.3-times higher risk for obese versus normal weight individuals in the metabolically healthy and unhealthy groups, respectively). In a recent US cohort study, metabolically unhealthy obesity, but not metabolically healthy obesity, was associated with an increased risk of ESKD over a median follow-up of 5 years compared with healthy normal weight.[23] This is similar to our finding, and although in our study also metabolically healthy obesity was associated (albeit to a lesser degree) with ESKD, the null finding in the US cohort study is probably due to insufficient statistical power (only six ESKD cases in metabolically healthy obese individuals). Further, the two studies differ regarding study population characteristics, length of follow-up, and definition of metabolic health. In the absence of metabolic abnormalities, a long follow-up time might be necessary to adequately capture associations between metabolically healthy overweight/obesity and ESKD. However, metabolically healthy overweight and obesity may represent a temporary intermediate low-risk state and may later be burdened by a worsening metabolic risk factor profile, which eliminates the primary lower risk.

Some limitations of our study warrant mention. First, although the sample size is large, the statistical power and the precision of the estimates is limited by the number of outcomes (n=463). ESKD is a rare event; however, our observed cumulative ESKD incidence of about 0.5% in a middle-aged low-risk general population is in line with the estimated age-related risk of RRT in Europe and the 0.4% ESKD incidence in a large meta-analysis including 39 general population cohorts.[4,70] Second, excess body weight was determined by BMI only. Information on waist circumference or waist-to-hip ratio, which allow a better characterization of body fat distribution,[71,72] was not available in the VHM&PP cohort. Third, the TyG index is only an indicator of insulin resistance; however, no direct measurement of insulin was available. Fourth, data on baseline kidney function, physical activity, other lifestyle factors, pharmacologic therapy, and other potential confounders were not available, which might introduce confounding bias to our results. However, the long time period of 15.5 years between baseline and ESKD and the exclusion of the first 2 years of follow-up in our analysis make it unlikely that a significant number of participants already had a relevant kidney disease at baseline. Lastly, our results are on the basis of a middle-aged, low-risk, population-based White cohort, and therefore it is uncertain how far findings can be generalized to other ages and ethnic groups or to patients with higher comorbidity burden.

Strengths of our study include the length of follow-up, the accurate assessment of the outcome ESKD using the OEDTR, and the application of a state-of-the-art mediation analysis tool, allowing a mathematically consistent decomposition of

the total association of BMI with ESKD risk not only into a direct and indirect association, but also further splitting up the joint indirect association into independent contributions of the single mediators. This is not possible with traditional methods for mediation analysis, such as the difference method.[34,45]

In conclusion, we found that the total association of excess body weight with the risk of ESKD is to a high degree mediated through insulin resistance, hypertension, and hyperuricemia, with a similar contribution of around one-third for each of these three factors. In contrast, hypercholesterolemia was not a relevant mediator. Apart from promoting body weight reduction to reach normal weight, focused intervention on the three targets insulin resistance, hypertension, and hyperuricemia not only in overweight and obese but also in normal weight individuals might lower renal risk. This should ideally be tested in controlled trials in the future.

DISCLOSURES

K. Lhotta reports Honoraria: Amgen, AstraZeneca, Baxter, Bayer, Boehringer-Ingelheim, Vifor. E. Zitt reports Honoraria: Boehringer-Ingelheim, Otsuka Pharmaceutical GmbH, Vifor Pharma; Advisory or Leadership Role: AMGEN, AstraZeneca; and Other Interests or Relationships: Board Member of the Austrian Society of Nephrology, Member of the European Renal Association, Member of the European Renal Association Chronic Kidney Disease-Mineral and Bone Disorder Working Group, and Medical Research Director Agency for Preventive and Social Medicine. All remaining authors have nothing to disclose.

FUNDING

None.

ACKNOWLEDGMENTS

We are indebted to the study participants of the VHM&PP cohort for providing data, to the general practitioners who collected the data, and to the patients and staff of all dialysis units in Vorarlberg who provided the data for the OEDTR. We would like to thank Elmar Stimpfl for excellent technical support and Georg Posch from the Agency for Preventive and Social Medicine as well as Markus Wallner, Martina Rüscher, Wolfgang Grabher, and Gabriela Dür from the Vorarlberg State Government. There was no financial compensation for these services.

AUTHOR CONTRIBUTIONS

Josef Fritz and Wolfgang Brozek were responsible for data curation. Josef Fritz and Hanno Ulmer were responsible for formal analysis. Josef Fritz, Wolfgang Brozek, Hans Concin, Julia Kerschbaum, Karl Lhotta, Hanno Ulmer, and Emanuel Zitt were responsible for investigation. Josef Fritz, Wolfgang Brozek, and Julia Kerschbaum were responsible for the methodology. Josef Fritz, Hanno Ulmer, and Emanuel Zitt wrote the original draft. Josef Fritz, Wolfgang Brozek, Hans Concin, Gabriele Nagel, Julia Kerschbaum, Karl Lhotta, Hanno Ulmer, and Emanuel Zitt reviewed and edited the manuscript. Wolfgang Brozek was responsible for validation. Hans Concin, Gabriele Nagel, Karl Lhotta, Hanno Ulmer, and Emanuel Zitt supervised the study. Gabriele Nagel, Hanno Ulmer, and Emanuel Zitt conceptualized the study.

SUPPLEMENTAL MATERIAL

This article contains the following supplemental material online at http://jasn.asnjournals.org/lookup/suppl/doi:10.1681/ASN.2021091263/-/DCSupplemental.

Supplemental Figure 1. Flow chart of the study design of the Vorarlberg Health Monitoring and Promotion Program (VHM&PP), with details on the exclusions leading to the final analysis population of 100,269 VHM&PP participants.

Supplemental Table 1. Representative examples of combinations of values in metabolic factors together with the resulting z-scores, metabolic scores, and metabolic health status.

Supplemental Table 2. Comparison of ESKD incidence rates and multivariably adjusted hazard ratios for the sample of 75,282 male VHM&PP participants across body mass index (BMI) groups, single mediator levels, and combined metabolic health status at the baseline examination.

Supplemental Table 3. Comparison of ESKD incidence rates and multivariably adjusted hazard ratios for the sample of 24,987 female VHM&PP participants across body mass index (BMI) groups, single mediator levels, and combined metabolic health status at the baseline examination.

Supplemental Table 4. Decomposition of the total association of body mass index (BMI) with risk of ESKD into indirect associations mediated through the TyG index, mean arterial pressure (MAP), uric acid, and total cholesterol (TC), and the remaining direct association; stratified by the primary underlying kidney disease.

Supplemental Table 5. Difference method for mediation analysis: Associations of body mass index (BMI) with ESKD risk, with and without adjusting for the four metabolic factors TyG index, mean arterial pressure (MAP), uric acid, and total cholesterol (TC), in the VHM&PP analysis population.

Supplemental Table 6. Decomposition of the total association of body mass index (BMI) with risk of ESKD into indirect associations mediated through the TyG index, mean arterial pressure (MAP), uric acid, and total cholesterol (TC), and the remaining direct association, for the full sample of VHM&PP participants, including also those with <2 years of follow-up (N=101,064).

REFERENCES

1. Hsu CY, McCulloch CE, Iribarren C, Darbinian J, Go AS: Body mass index and risk for end-stage renal disease. *Ann Intern Med* 144: 21–28, 2006
2. Garofalo C, Borrelli S, Minutolo R, Chiodini P, De Nicola L, Conte G: A systematic review and meta-analysis suggests obesity predicts onset of chronic kidney disease in the general population. *Kidney Int* 91: 1224–1235, 2017
3. Zitt E, Pscheidt C, Concin H, Kramar R, Peter RS, Beyersmann J, et al: Long-term risk for end-stage kidney disease and death in a large population-based cohort. *Sci Rep* 8: 7729, 2018
4. Chang AR, Grams ME, Ballew SH, Bilo H, Correa A, Evans M, et al; CKD Prognosis Consortium (CKD-PC): Adiposity and risk of decline in glomerular filtration rate: meta-analysis of individual participant data in a global consortium. *BMJ* 364: k5301, 2019
5. Li L, Yang C, Zhao Y, Zeng X, Liu F, Fu P: Is hyperuricemia an independent risk factor for new-onset chronic kidney disease?: A

systematic review and meta-analysis based on observational cohort studies. *BMC Nephrol* 15: 122, 2014
6. Artunc F, Schleicher E, Weigert C, Fritsche A, Stefan N, Häring HU: The impact of insulin resistance on the kidney and vasculature. *Nat Rev Nephrol* 12: 721–737, 2016
7. Mount PF, Juncos LA: Obesity-related CKD: when kidneys get the munchies. *J Am Soc Nephrol* 28: 3429–3432, 2017
8. Câmara NOS, Iseki K, Kramer H, Liu ZH, Sharma K: Kidney disease and obesity: epidemiology, mechanisms and treatment. *Nat Rev Nephrol* 13: 181–190, 2017
9. Hall JE, do Carmo JM, da Silva AA, Wang Z, Hall ME: Obesity, kidney dysfunction and hypertension: mechanistic links. *Nat Rev Nephrol* 15: 367–385, 2019
10. Stamler J, Wentworth D, Neaton JD: Is relationship between serum cholesterol and risk of premature death from coronary heart disease continuous and graded? Findings in 356,222 primary screenees of the Multiple Risk Factor Intervention Trial (MRFIT). *JAMA* 256: 2823–2828, 1986
11. Reaven GM: Banting lecture 1988. Role of insulin resistance in human disease. *Diabetes* 37: 1595–1607, 1988
12. Moller DE, Flier JS: Insulin resistance–mechanisms, syndromes, and implications. *N Engl J Med* 325: 938–948, 1991
13. Fritz J, Brozek W, Concin H, Nagel G, Kerschbaum J, Lhotta K, et al: The triglyceride-glucose index and obesity-related risk of end-stage kidney disease in Austrian adults. *JAMA Netw Open* 4: e212612, 2021
14. Schaeffner ES, Kurth T, Curhan GC, Glynn RJ, Rexrode KM, Baigent C, et al: Cholesterol and the risk of renal dysfunction in apparently healthy men. *J Am Soc Nephrol* 14: 2084–2091, 2003
15. Yamagata K, Ishida K, Sairenchi T, Takahashi H, Ohba S, Shiigai T, et al: Risk factors for chronic kidney disease in a community-based population: a 10-year follow-up study. *Kidney Int* 71: 159–166, 2007
16. Lewington S, Whitlock G, Clarke R, Sherliker P, Emberson J, Halsey J, et al; Prospective Studies Collaboration: Blood cholesterol and vascular mortality by age, sex, and blood pressure: a meta-analysis of individual data from 61 prospective studies with 55,000 vascular deaths. *Lancet* 370: 1829–1839, 2007
17. Borghi C, Rosei EA, Bardin T, Dawson J, Dominiczak A, Kielstein JT, et al: Serum uric acid and the risk of cardiovascular and renal disease. *J Hypertens* 33: 1729–1741, discussion 1741, 2015
18. Hsu CY, Iribarren C, McCulloch CE, Darbinian J, Go AS: Risk factors for end-stage renal disease: 25-year follow-up. *Arch Intern Med* 169: 342–350, 2009
19. Hsu CY, McCulloch CE, Darbinian J, Go AS, Iribarren C: Elevated blood pressure and risk of end-stage renal disease in subjects without baseline kidney disease. *Arch Intern Med* 165: 923–928, 2005
20. Wilson PWF: Established risk factors and coronary artery disease: the Framingham Study. *Am J Hypertens* 7: 7S–12S, 1994
21. Flint AC, Conell C, Ren X, Banki NM, Chan SL, Rao VA, et al: Effect of systolic and diastolic blood pressure on cardiovascular outcomes. *N Engl J Med* 381: 243–251, 2019
22. Panwar B, Hanks LJ, Tanner RM, Muntner P, Kramer H, McClellan WM, et al: Obesity, metabolic health, and the risk of end-stage renal disease. *Kidney Int* 87: 1216–1222, 2015
23. Chang AR, Surapaneni A, Kirchner HL, Young A, Kramer HJ, Carey DJ, et al: Metabolically healthy obesity and risk of kidney function decline. *Obesity (Silver Spring)* 26: 762–768, 2018
24. Zhu P, Herrington WG, Haynes R, Emberson J, Landray MJ, Sudlow CLM, et al: Conventional and genetic evidence on the association between adiposity and CKD. *J Am Soc Nephrol* 32: 127–137, 2021
25. Simental-Mendía LE, Rodríguez-Morán M, Guerrero-Romero F: The product of fasting glucose and triglycerides as surrogate for identifying insulin resistance in apparently healthy subjects. *Metab Syndr Relat Disord* 6: 299–304, 2008
26. Ulmer H, Kelleher C, Diem G, Concin H: Long-term tracking of cardiovascular risk factors among men and women in a large population-based health system: the Vorarlberg Health Monitoring & Promotion Programme. *Eur Heart J* 24: 1004–1013, 2003
27. Strasak AM, Goebel G, Concin H, Pfeiffer RM, Brant LJ, Nagel G, et al; VHM&PP Study Group: Prospective study of the association of serum gamma-glutamyltransferase with cervical intraepithelial neoplasia III and invasive cervical cancer. *Cancer Res* 70: 3586–3593, 2010
28. Herrington WG, Smith M, Bankhead C, Matsushita K, Stevens S, Holt T, et al: Body-mass index and risk of advanced chronic kidney disease: prospective analyses from a primary care cohort of 1.4 million adults in England. *PLoS One* 12: e0173515, 2017
29. Wimmer F, Oberaigner W, Kramar R, Mayer G: Regional variability in the incidence of end-stage renal disease: an epidemiological approach. *Nephrol Dial Transplant* 18: 1562–1567, 2003
30. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP; STROBE Initiative: The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. *Int J Surg* 12: 1495–1499, 2014
31. Guerrero-Romero F, Simental-Mendía LE, González-Ortiz M, Martínez-Abundis E, Ramos-Zavala MG, Hernández-González SO, et al: The product of triglycerides and glucose, a simple measure of insulin sensitivity. Comparison with the euglycemic-hyperinsulinemic clamp. *J Clin Endocrinol Metab* 95: 3347–3351, 2010
32. Häggström C, Stocks T, Nagel G, Manjer J, Bjørge T, Hallmans G, et al: Prostate cancer, prostate cancer death, and death from other causes, among men with metabolic aberrations. *Epidemiology* 25: 823–828, 2014
33. Baron RM, Kenny DA: The moderator-mediator variable distinction in social psychological research: conceptual, strategic, and statistical considerations. *J Pers Soc Psychol* 51: 1173–1182, 1986
34. VanderWeele TJ: Mediation analysis: a practitioner's guide. *Annu Rev Public Health* 37: 17–32, 2016
35. Vansteelandt S, Daniel RM: Interventional effects for mediation analysis with multiple mediators. *Epidemiology* 28: 258–265, 2017
36. VanderWeele TJ: Causal mediation analysis with survival data. *Epidemiology* 22: 582–585, 2011
37. VanderWeele TJ, Vansteelandt S: Mediation analysis with multiple mediators. *Epidemiol Methods* 2: 95–115, 2014
38. Sarafidis PA, Bakris GL: Insulin resistance, hyperinsulinemia, and hypertension: an epidemiologic approach. *J Cardiometab Syndr* 1: 334–342, quiz 343, 2006
39. Wang F, Han L, Hu D: Fasting insulin, insulin resistance and risk of hypertension in the general population: a meta-analysis. *Clin Chim Acta* 464: 57–63, 2017
40. Pihlajamäki J, Gylling H, Miettinen TA, Laakso M: Insulin resistance is associated with increased cholesterol synthesis and decreased cholesterol absorption in normoglycemic men. *J Lipid Res* 45: 507–512, 2004
41. Stewart DJ, Langlois V, Noone D: Hyperuricemia and hypertension: links and risks. *Integr Blood Press Control* 12: 43–62, 2019
42. McMullan CJ, Borgi L, Fisher N, Curhan G, Forman J: Effect of uric acid lowering on renin-angiotensin-system activation and ambulatory BP: a randomized controlled trial. *Clin J Am Soc Nephrol* 12: 807–816, 2017
43. Reaven GM: Pathophysiology of insulin resistance in human disease. *Physiol Rev* 75: 473–486, 1995
44. Yoo TW, Sung KC, Shin HS, Kim BJ, Kim BS, Kang JH, et al: Relationship between serum uric acid concentration and insulin resistance and metabolic syndrome. *Circ J* 69: 928–933, 2005
45. Judd CM, Kenny DA: Process analysis: estimating mediation in treatment evaluations. *Eval Rev* 5: 602–619, 1981
46. R Core Team: *R: A language and environment for statistical computing*, Vienna, Austria, R Foundation for Statistical Computing, 2020
47. Vivante A, Golan E, Tzur D, Leiba A, Tirosh A, Skorecki K, et al: Body mass index in 1.2 million adolescents and risk for end-stage renal disease. *Arch Intern Med* 172: 1644–1650, 2012

48. Afshin A, Forouzanfar MH, Reitsma MB, Sur P, Estep K, Lee A, et al; GBD 2015 Obesity Collaborators: Health effects of overweight and obesity in 195 countries over 25 years. *N Engl J Med* 377: 13–27, 2017
49. Kastarinen M, Juutilainen A, Kastarinen H, Salomaa V, Karhapää P, Tuomilehto J, et al: Risk factors for end-stage renal disease in a community-based population: 26-year follow-up of 25,821 men and women in eastern Finland. *J Intern Med* 267: 612–620, 2010
50. Haynes R, Lewis D, Emberson J, Reith C, Agodoa L, Cass A, et al; SHARP Collaborative Group; SHARP Collaborative Group: Effects of lowering LDL cholesterol on progression of kidney disease. *J Am Soc Nephrol* 25: 1825–1833, 2014
51. Pscheidt C, Nagel G, Zitt E, Kramar R, Concin H, Lhotta K: Sex- and time-dependent patterns in risk factors of end-stage renal disease: a large Austrian cohort with up to 20 years of follow-up. *PLoS One* 10: e0135052, 2015
52. Rahman M, Yang W, Akkina S, Alper A, Anderson AH, Appel LJ, et al; CRIC Study Investigators: Relation of serum lipids and lipoproteins with progression of CKD: the CRIC study. *Clin J Am Soc Nephrol* 9: 1190–1198, 2014
53. Mykkänen L, Zaccaro DJ, Wagenknecht LE, Robbins DC, Gabriel M, Haffner SM: Microalbuminuria is associated with insulin resistance in nondiabetic subjects: the insulin resistance atherosclerosis study. *Diabetes* 47: 793–800, 1998
54. Chen J, Muntner P, Hamm LL, Jones DW, Batuman V, Fonseca V, et al: The metabolic syndrome and chronic kidney disease in U.S. adults. *Ann Intern Med* 140: 167–174, 2004
55. Whaley-Connell A, Sowers JR: Insulin resistance in kidney disease: is there a distinct role separate from that of diabetes or obesity? *Cardiorenal Med* 8: 41–49, 2017
56. Tozawa M, Iseki K, Iseki C, Kinjo K, Ikemiya Y, Takishita S: Blood pressure predicts risk of developing end-stage renal disease in men and women. *Hypertension* 41: 1341–1345, 2003
57. Garrison RJ, Kannel WB, Stokes J 3rd, Castelli WP: Incidence and precursors of hypertension in young adults: the Framingham Offspring Study. *Prev Med* 16: 235–251, 1987
58. Van Hemelrijck M, Ulmer H, Nagel G, Peter RS, Fritz J, Myte R, et al: Longitudinal study of body mass index, dyslipidemia, hyperglycemia, and hypertension in 60,000 men and women in Sweden and Austria. *PLoS One* 13: e0197830, 2018
59. Hall JE, do Carmo JM, da Silva AA, Wang Z, Hall ME: Obesity-induced hypertension: interaction of neurohumoral and renal mechanisms. *Circ Res* 116: 991–1006, 2015
60. Chonchol M, Shlipak MG, Katz R, Sarnak MJ, Newman AB, Siscovick DS, et al: Relationship of uric acid with progression of kidney disease. *Am J Kidney Dis* 50: 239–247, 2007
61. Tsai C-W, Lin S-Y, Kuo C-C, Huang C-C: Serum uric acid and progression of kidney disease: a longitudinal analysis and mini-review. *PLoS One* 12: e0170393, 2017
62. Sturm G, Kollerits B, Neyer U, Ritz E, Kronenberg F; MMKD Study Group: Uric acid as a risk factor for progression of non-diabetic chronic kidney disease? The Mild to Moderate Kidney Disease (MMKD) Study. *Exp Gerontol* 43: 347–352, 2008
63. Nacak H, van Diepen M, Qureshi AR, Carrero JJ, Stijnen T, Dekker FW, et al: Uric acid is not associated with decline in renal function or time to renal replacement therapy initiation in a referred cohort of patients with Stage III, IV and V chronic kidney disease. *Nephrol Dial Transplant* 30: 2039–2045, 2015
64. Madero M, Sarnak MJ, Wang X, Greene T, Beck GJ, Kusek JW, et al: Uric acid and long-term outcomes in CKD. *Am J Kidney Dis* 53: 796–803, 2009
65. Doria A, Galecki AT, Spino C, Pop-Busui R, Cherney DZ, Lingvay I, et al; PERL Study Group: Serum urate lowering with allopurinol and kidney function in type 1 diabetes. *N Engl J Med* 382: 2493–2503, 2020
66. Badve SV, Pascoe EM, Tiku A, Boudville N, Brown FG, Cass A, et al; CKD-FIX Study Investigators: Effects of allopurinol on the progression of chronic kidney disease. *N Engl J Med* 382: 2504–2513, 2020
67. Heerspink HJL, Stefánsson BV, Correa-Rotter R, Chertow GM, Greene T, Hou F-F, et al; DAPA-CKD Trial Committees and Investigators: Dapagliflozin in patients with chronic kidney disease. *N Engl J Med* 383: 1436–1446, 2020
68. Vallon V, Thomson SC: Targeting renal glucose reabsorption to treat hyperglycaemia: the pleiotropic effects of SGLT2 inhibition. *Diabetologia* 60: 215–225, 2017
69. Bailey CJ: Uric acid and the cardio-renal effects of SGLT2 inhibitors. *Diabetes Obes Metab* 21: 1291–1298, 2019
70. van den Brand JAJG, Pippias M, Stel VS, Caskey FJ, Collart F, Finne P, et al: Lifetime risk of renal replacement therapy in Europe: a population-based study using data from the ERA-EDTA Registry. *Nephrol Dial Transplant* 32: 348–355, 2017
71. Elsayed EF, Sarnak MJ, Tighiouart H, Griffith JL, Kurth T, Salem DN, et al: Waist-to-hip ratio, body mass index, and subsequent kidney disease and death. *Am J Kidney Dis* 52: 29–38, 2008
72. Kramer H, Gutiérrez OM, Judd SE, Muntner P, Warnock DG, Tanner RM, et al: Waist circumference, body mass index, and ESRD in the REGARDS (Reasons for Geographic and Racial Differences in Stroke) study. *Am J Kidney Dis* 67: 62–69, 2016

AFFILIATIONS

[1]Department of Medical Statistics, Informatics and Health Economics, Medical University of Innsbruck, Innsbruck, Austria
[2]Agency for Preventive and Social Medicine, Bregenz, Austria
[3]Institute of Epidemiology and Medical Biometry, Ulm University, Ulm, Germany
[4]Department of Internal Medicine IV (Nephrology and Hypertension), Medical University of Innsbruck, Innsbruck, Austria
[5]Austrian Dialysis and Transplant Registry (OEDTR), Medical University of Innsbruck, Innsbruck, Austria
[6]Department of Internal Medicine III (Nephrology and Dialysis), Academic Teaching Hospital Feldkirch, Feldkirch, Austria
[7]Vorarlberg Institute for Vascular Investigation and Treatment (VIVIT), Academic Teaching Hospital Feldkirch, Feldkirch, Austria

Supplemental Material

The association of excess body weight with risk of end-stage kidney disease is mediated through hypertension, insulin resistance and hyperuricemia

Josef Fritz, Wolfgang Brozek, Hans Concin, Gabriele Nagel, Julia Kerschbaum, Karl Lhotta, Hanno Ulmer, and Emanuel Zitt

Supplemental Table of Contents

direct association, for the full sample of VHM&PP participants, including also those with less than two years of follow up (N=101,064).

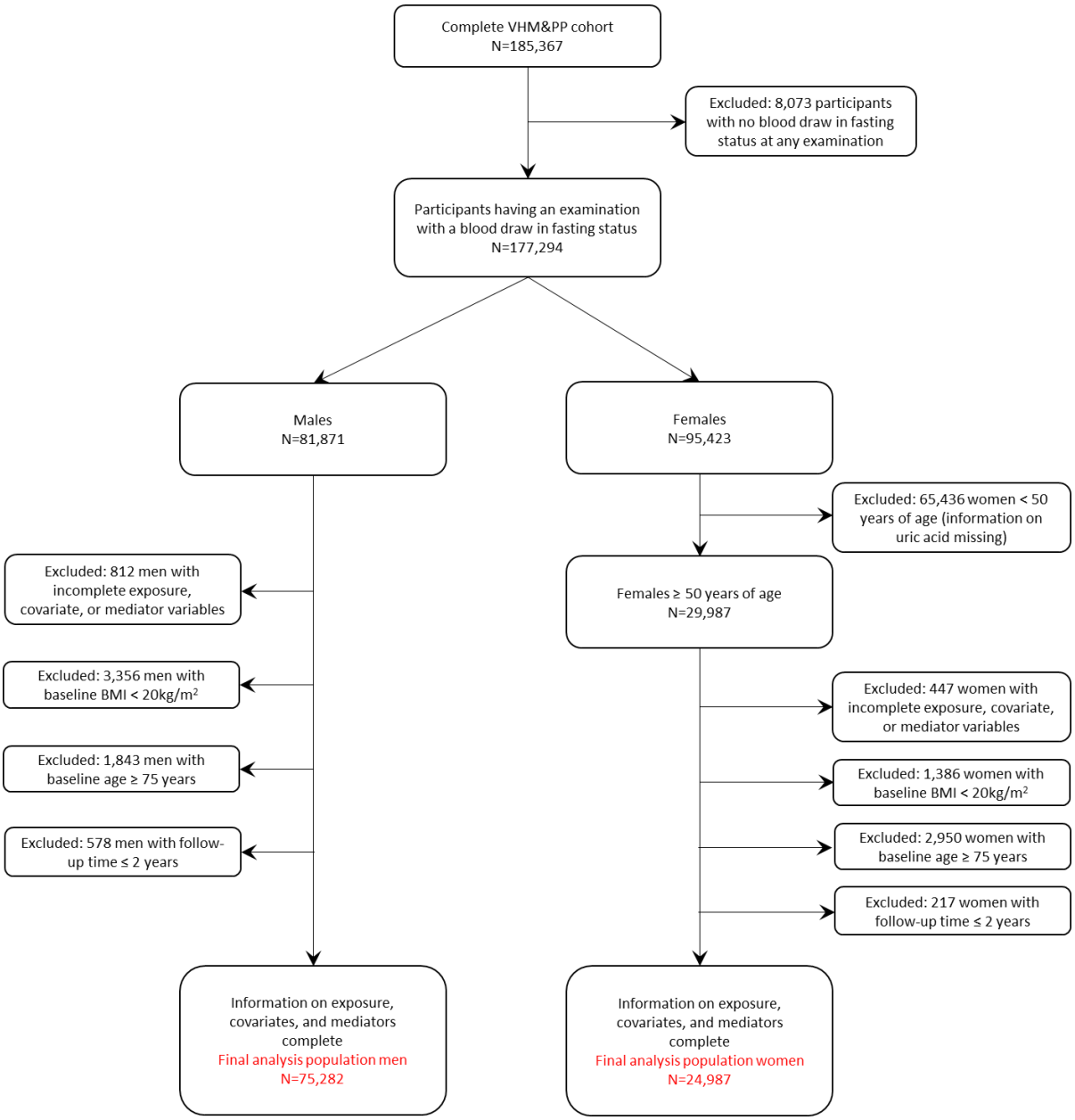

Figure S1: Flow chart of the study design of the Vorarlberg Health Monitoring and Promotion Program (VHM&PP), with details on the exclusions leading to the final analysis population of 100,269 VHM&PP participants.

Table S1: Representative examples of combinations of values in metabolic factors together with the resulting z-scores, metabolic scores, and metabolic health status.

	Glucose [mmol/L]	Triglycerides [mmol/L]	TyG index[1]	TyG index z-score	MAP[2] [mmHg]	MAP z-score	UA [µmol/L]	UA z-score	TC [mmol/L]	TC z-score	Metabolic score	Metabolic health status[3]
Case 1 (male, 35y)	5.00	1.50	8.70	0.13	80	-1.58	200	-1.54	5.00	-0.62	-3.62	MH
Case 2 (female, 52y)	6.00	2.00	9.17	0.86	100	-0.02	350	0.31	6.00	0.19	1.35	MUH
Case 3 (female, 60y)	7.00	2.50	9.54	1.46	120	1.54	500	2.16	7.00	1.01	6.17	MUH
Case 4 (male, 23y)	5.27	1.10	8.44	-0.28	98.33	-0.15	327.14	0.03	3.81	-1.60	-2.00	MH
Case 5 (male, 33y)	3.39	1.32	8.18	-0.69	113.33	1.02	291.45	-0.41	5.85	0.07	0.00	MH
Case 6 (male, 54y)	4.66	1.59	8.69	0.11	113.33	1.02	404.46	0.99	5.62	-0.12	2.00	MUH
Case 7 (female, 68y)	4.22	2.87	9.17	0.88	106.67	0.50	279.56	-0.56	9.66	3.18	4.00	MUH

[1]TyG index calculated as ln[triglycerides (mg/dL) × blood glucose (mg/dL)/2].
[2]Defined as diastolic blood pressure+1/3×(systolic blood pressure - diastolic blood pressure) [mmHg].
[3]MH is defined as a value of the metabolic score of <1; MUH is defined as a value of the metabolic score of ≥1.

Abbreviations: MAP, mean arterial pressure; MH, metabolically healthy; MUH, metabolically unhealthy; TC, total cholesterol; UA, uric acid.

Table S2: Comparison of end-stage kidney disease (ESKD) incidence rates and multivariably-adjusted hazard ratios for the sample of 75,282 male VHM&PP participants across body mass index (BMI) groups, single mediator levels, and combined metabolic health status at the baseline examination.

		Normal weight (BMI 20 to <25 mg/kg^2)			Overweight (BMI 25 to <30 mg/kg^2)			Obesity (BMI ≥30 mg/kg^2)			Total		
		Incident ESKD cases / N	Incident ESKD cases per 100,000 person-years (95% CI)	Multi-variably-adjusted HR[1] (95% CI)	Incident ESKD cases / N	Incident ESKD cases per 100,000 person-years (95% CI)	Multi-variably-adjusted HR[1] (95% CI)	Incident ESKD cases / N	Incident ESKD cases per 100,000 person-years (95% CI)	Multi-variably-adjusted HR[1] (95% CI)	Incident ESKD cases / N	Incident ESKD cases per 100,000 person-years (95% CI)	Multi-variably-adjusted HR[2] (95% CI)
Overall		115 / 35,320	13.6 (11.2-16.3)	1.00 (Ref)	158 / 31,534	21.6 (18.4-25.3)	1.15 (0.90-1.47)	80 / 8,428	44.4 (35.2-55.3)	2.23 (1.67-2.98)	353 / 75,282	20.1 (18.0-22.3)	-
TyG-I	**<75th pct**	77 / 30,321	10.5 (8.3-13.2)	1.00 (Ref)	84 / 21,267	16.9 (13.5-20.9)	1.16 (0.85-1.59)	22 / 4,208	24.1 (15.1-36.4)	1.57 (0.97-2.53)	183 / 55,796	13.9 (11.9-16.0)	1.00 (Ref)
	≥75 th pct	38 / 4,999	32.8 (23.2-45.0)	2.43 (1.65-3.59)	74 / 10,267	31.7 (24.9-39.8)	1.95 (1.41-2.69)	58 / 4,220	65.4 (49.6-84.5)	3.97 (2.81-5.62)	170 / 19,486	38.8 (33.2-45.1)	1.95 (1.57-2.43)
MAP	**<75 th pct**	63 / 30,450	8.5 (6.6-10.9)	1.00 (Ref)	73 / 22,082	14.0 (11.0-17.6)	1.26 (0.90-1.77)	26 / 4,222	28.1 (18.3-41.1)	2.41 (1.52-3.82)	162 / 56,754	12.0 (10.2-14.0)	1.00 (Ref)
	≥75 th pct	52 / 4,870	48.0 (35.9-63.0)	3.77 (2.59-5.49)	85 / 9,452	40.5 (32.3-50.0)	2.81 (2.00-3.93)	54 / 4,206	61.7 (46.4-80.5)	4.49 (3.09-6.52)	191 / 18,528	47.1 (40.6-54.2)	2.46 (1.96-3.08)
UA	**<75 th pct**	61 / 27,383	9.3 (7.1-11.9)	1.00 (Ref)	67 / 20,020	14.4 (11.2-18.3)	1.12 (0.79-1.59)	30 / 4,151	33.8 (22.8-48.3)	2.42 (1.56-3.75)	158 / 51,554	13.1 (11.1-15.3)	1.00 (Ref)
	≥75 th pct	54 / 7,937	28.4 (21.3-37.0)	2.95 (2.04-4.25)	91 / 11,514	34.2 (27.5-42.0)	2.61 (1.88-3.62)	50 / 4,277	54.7 (40.6-72.1)	4.08 (2.80-5.95)	195 / 23,728	35.6 (30.8-41.0)	2.28 1.84-2.83)
TC	**<75 th pct**	81 / 30,348	11.1 (8.8-13.8)	1.00 (Ref)	95 / 23,493	17.4 (14.1-21.3)	1.12 (0.83-1.51)	48 / 6,005	37.5 (27.7-49.7)	2.24 (1.56-3.21)	224 / 59,846	15.9 (13.9-18.2)	1.00 (Ref)
	≥75 th pct	34 / 4,972	29.3 (20.3-40.9)	1.67 (1.12-2.51)	63 / 8,041	34.1 (26.2-43.6)	1.78 (1.27-2.49)	32 / 2,423	61.4 (42.0-86.6)	3.28 (2.17-4.96)	129 / 15,436	36.5 (30.5-43.4)	1.55 (1.25-1.94)

Metabolically healthy	52 / 29,652	7.2 (5.4- 9.5)	1.00 (Ref)	42 / 18,420	9.7 (7.0-13.1)	1.03 (0.69-1.55)	12 / 3,113	17.7 (9.2-31.0)	1.79 (0.95-3.36)	106 / 51,185	8.7 (7.1-10.5)	1.00 (Ref)
Metabolically unhealthy	63 / 5,668	48.9 (37.6-62.6)	4.47 (3.08-6.49)	116 / 13,114	39.0 (32.2-46.7)	3.29 (2.35-4.60)	68 / 5,315	60.5 (47.0-76.7)	5.26 (3.64-7.61)	247 / 24,097	45.8 (40.3-51.9)	3.39 (2.66-4.32)

[1]HRs from a Cox proportional hazards model adjusted for baseline age, smoking status, and socioeconomic status.
[2]HRs from a Cox proportional hazards model adjusted for baseline age, smoking status, socioeconomic status, and additionally BMI.

Single mediators were categorized into high (i.e. above the 75th percentile) vs. low/normal (i.e. below the 75th percentile). The 75th percentiles were 8.99 for TyG index, 106.67 mmHg for mean arterial pressure, 374.72 mmol/L for uric acid, and 6.53 µmol/L for cholesterol, respectively. Metabolically healthy was defined as a value of <1 when summing up the four z-transformed mediators TyG index, MAP, uric acid, and total cholesterol, while metabolically unhealthy was defined as a value of ≥1. Refer to **Table S1** for examples of specific combinations of values in metabolic factors and the resulting metabolic score.

Abbreviations: CI, confidence interval; VHM&PP, Vorarlberg Health Monitoring and Prevention Programme; MAP, mean arterial pressure; HR, hazard ratio; pct, percentile; TC, total cholesterol; TyG-I, TyG index; UA, uric acid.

Table S3: Comparison of end-stage kidney disease (ESKD) incidence rates and multivariably-adjusted hazard ratios for the sample of 24,987 female VHM&PP participants across body mass index (BMI) groups, single mediator levels, and combined metabolic health status at the baseline examination.

		Normal weight (BMI 20 to <25 mg/kg^2)			Overweight (BMI 25 to <30 mg/kg^2)			Obesity (BMI ≥30 mg/kg^2)			Total		
		Incident ESKD cases / N	Incident ESKD cases per 100,000 person-years (95% CI)	Multi-variably-adjusted HR[1] (95% CI)	Incident ESKD cases / N	Incident ESKD cases per 100,000 person-years (95% CI)	Multi-variably-adjusted HR[1] (95% CI)	Incident ESKD cases / N	Incident ESKD cases per 100,000 person-years (95% CI)	Multi-variably-adjusted HR[1] (95% CI)	Incident ESKD cases / N	Incident ESKD cases per 100,000 person-years (95% CI)	Multi-variably-adjusted HR[2] (95% CI)
Overall		23 / 9,773	10.2 (6.5-15.3)	1.00 (Ref)	49 / 9,728	22.2 (16.4-29.4)	2.17 (1.32-3.57)	38 / 5,486	32.5 (23.0-44.6)	3.23 (1.92-5.43)	110 / 24,987	19.5 (16.1-23.6)	-
TyG-I	**<75th pct**	16 / 8,531	8.0 (4.6-13.0)	1.00 (Ref)	28 / 7,385	16.4 (10.9-23.7)	2.06 (1.11-3.81)	11 / 3,487	14.4 (7.2-25.8)	1.84 (0.85-3.98)	55 / 19,403	12.3 (9.3-16.0)	1.00 (Ref)
	≥75 th pct	7 / 1,242	27.1 (10.9-55.9)	3.27 (1.34-7.99)	21 / 2,343	42.0 (26.0-64.2)	5.11 (2.66-9.84)	27 / 1,999	66.4 (43.7-96.6)	8.28 (4.44-15.43)	55 / 5,584	47.2 (35.6-61.5)	3.23 (2.19-4.77)
MAP	**<75 th pct**	14 / 6,687	8.9 (4.9-14.9)	1.00 (Ref)	13 / 5,174	10.8 (5.7-18.4)	1.21 (0.57-2.58)	10 / 2,002	23.0 (11.0-42.3)	2.63 (1.17-5.94)	37 / 13,863	11.5 (8.1-15.9)	1.00 (Ref)
	≥75 th pct	9 / 3,086	13.2 (6.0-25.1)	1.55 (0.67-3.60)	36 / 4,554	36.1 (25.3-50.0)	4.19 (2.25-7.81)	28 / 3,484	38.2 (25.4-55.2)	4.46 (2.34-8.51)	73 / 11,124	30.3 (23.7-38.1)	2.32 (1.53-3.50)
UA	**<75 th pct**	19 / 9,319	8.8 (5.3-13.7)	1.00 (Ref)	35 / 8,801	17.3 (12.1- 24.1)	1.98 (1.13-3.46)	24 / 4,488	24.7 (15.8- 36.7)	2.87 (1.57-5.26)	78 / 22,608	15.1 (12.0- 18.9)	1.00 (Ref)
	≥75 th pct	4 / 454	44.3 (12.1-113.4)	4.95 (1.68-14.61)	14 / 927	76.3 (41.7-128.1)	8.87 (4.42-17.84)	14 / 998	71.3 (39.0-119.6)	8.20 (4.09-16.42)	32 / 2,379	68.1 (46.6- 96.1)	3.71 (2.41-5.73)
TC	**<75 th pct**	13 / 6,027	9.2 (4.9-15.8)	1.00 (Ref)	18 / 5,798	13.6 (8.1-21.5)	1.48 (0.72-3.02)	24 / 3,495	32.5 (20.8-48.3)	3.56 (1.81-7.01)	55 / 15,320	15.9 (12.0-20.7)	1.00 (Ref)
	≥75 th pct	10 / 3,746	11.8 (5.7-21.7)	1.26 (0.55-2.87)	31 / 3,930	35.1 (23.8-49.8)	3.71 (1.93-7.11)	14 / 1,991	32.6 (17.8-54.7)	3.53 (1.65-7.52)	55 / 9,667	25.4 (19.2-33.1)	1.61 (1.10-2.35)

Metabolically healthy	12 / 7,886	6.5 (3.3-11.3)	1.00 (Ref)	13 / 6,175	9.0 (4.8-15.4)	1.41 (0.64-3.08)	9 / 2,518	16.1 (7.3-30.5)	2.54 (1.07-6.03)	34 / 16,579	8.8 (6.1-12.3)	1.00 (Ref)
Metabolically unhealthy	11 / 1,887	27.8 (13.9-49.7)	4.47 (1.96-10.19)	36 / 3,553	4.7 (33.2-65.6)	7.57 (3.91-14.63)	29 / 2,968	47.7 (31.9-68.5)	7.67 (3.90-15.10)	76 / 8,408	43.1 (34.0-53.9)	4.44 (2.89-6.80)

[1]HRs from a Cox proportional hazards model adjusted for baseline age, smoking status, and socioeconomic status.
[2]HRs from a Cox proportional hazards model adjusted for baseline age, smoking status, socioeconomic status, and additionally BMI.

Single mediators were categorized into high (i.e. above the 75th percentile) vs. low/normal (i.e. below the 75th percentile). The 75th percentiles were 8.99 for TyG index, 106.67 mmHg for mean arterial pressure, 374.72 mmol/L for uric acid, and 6.53 µmol/L for cholesterol, respectively. Metabolically healthy was defined as a value of <1 when summing up the four z-transformed mediators TyG index, MAP, uric acid, and total cholesterol, while metabolically unhealthy was defined as a value of ≥1. Refer to **Table S1** for examples of specific combinations of values in metabolic factors and the resulting metabolic score.

Abbreviations: CI, confidence interval; VHM&PP, Vorarlberg Health Monitoring and Prevention Programme; MAP, mean arterial pressure; HR, hazard ratio; pct, percentile; TC, total cholesterol; TyG-I, TyG index; UA, uric acid.

Table S4: Decomposition of the total association of body mass index (BMI) with risk of end-stage kidney disease into indirect associations mediated through the TyG index, mean arterial pressure (MAP), uric acid, and total cholesterol (TC), and the remaining direct association; stratified by the primary underlying renal disease, for the full sample of 100,269 VHM&PP participant.

	Diabetic kidney disease (N=113)	Vascular nephropathy (N=149)	Other disease (N=201)	Overall (N=463)
	HR (95% CI)[1]	HR (95% CI)[1]	HR (95% CI)[1]	HR (95% CI)[1]
BMI continuous				
Total association	2.71 (2.24 to 3.17)	1.30 (1.00 to 1.64)	1.14 (0.94 to 1.37)	1.57 (1.38 to 1.77)
Direct association	1.53 (1.24 to 1.81)	0.85 (0.65 to 1.09)	0.80 (0.64 to 0.98)	1.01 (0.88 to 1.14)
Joint indirect association	1.77 (1.61 to 1.95)	1.54 (1.42 to 1.65)	1.43 (1.30 to 1.54)	1.56 (1.49 to 1.64)
Indirect association through TyG index	1.51 (1.44 to 1.60)	1.09 (1.01 to 1.17)	0.96 (0.91 to 1.02)	1.16 (1.11 to 1.21)
Indirect association through MAP	1.16 (1.08 to 1.25)	1.17 (1.10 to 1.24)	1.18 (1.12 to 1.23)	1.17 (1.13 to 1.21)
Indirect association through uric acid	1.02 (0.96 to 1.08)	1.19 (1.13 to 1.26)	1.23 (1.17 to 1.28)	1.15 (1.11 to 1.18)
Indirect association through TC	0.99 (0.96 to 1.01)	1.01 (0.99 to 1.03)	1.02 (1.00 to 1.04)	1.01 (1.00 to 1.02)

Decomposition of the total association into the direct association and the joint indirect association (and splitting the joint indirect association further up into indirect associations through single mediators) was done according to the product-of-coefficients methods proposed in Vansteelandt & Daniel[*]. Confidence intervals were calculated using bootstrapping with 5,000 bootstrap resamples. All models were adjusted for baseline age, smoking status, and socioeconomic status as depicted in the DAG in **Figure 1**.

[1]HRs given per 5 kg/m² increase.
Abbreviations: CI, confidence interval; HR, hazard ratio.

*Vansteelandt S, Daniel RM: Interventional Effects for Mediation Analysis with Multiple Mediators. *Epidemiology* 28: 258–265, 2017

Table S5: Difference method for mediation analysis: Associations of body mass index (BMI) with end-stage kidney disease risk, with and without adjusting for the four metabolic factors TyG index, mean arterial pressure (MAP), uric acid, and total cholesterol (TC), in the VHM&PP analysis population.

	HR (95% CI) from model not adjusted for metabolic factors (Model 1)	HR (95% CI) from model adjusted for metabolic factors (Model 2)
	Total (N=100,269)	
BMI continuous[1]	1.52 (1.38 to 1.68)	1.005 (0.89 to 1.14)
Overweight vs. normal weight	1.28 (1.03 to 1.60)	0.80 (0.64 to 0.997)
Obesity vs. normal weight	2.44 (1.90 to 3.14)	0.89 (0.67 to 1.18)
	Males only (N=75,282)	
BMI continuous[1]	1.52 (1.34 to 1.73)	0.97 (0.83 to 1.14)
	Females only (N=24,987)	
BMI continuous[1]	1.50 (1.27 to 1.77)	1.002 (0.82 to 1.23)

Results from Cox proportional hazards models, adjusted for baseline age, sex, smoking status, and socioeconomic status (Model 1), and additionally adjusted for TyG index, MAP, uric acid, and TC (Model 2).

[1]HRs given per 5 kg/m² increase.
Abbreviations: CI, confidence interval; HR, hazard ratio.

Table S6: Decomposition of the total association of body mass index (BMI) with risk of end-stage kidney disease (ESKD) into indirect associations mediated through the TyG index, mean arterial pressure (MAP), uric acid, and total cholesterol (TC), and the remaining direct association, for the full sample of VHM&PP participants, including also those with less than two years of follow up (N=101,064).

	HR (95% CI)	Proportion of total association (95% CI)
BMI continuous[1]		
Total association	1.56 (1.37 to 1.75)	-
Direct association	0.99 (0.86 to 1.13)	-2% (-46% to 22%)
Joint indirect association (IA)	1.57 (1.50 to 1.65)	102% (78% to 146%)
IA through TyG index	1.16 (1.11 to 1.20)	33% (23% to 49%)
IA through MAP	1.17 (1.13 to 1.21)	36% (25% to 54%)
IA through uric acid	1.15 (1.11 to 1.18)	31% (21% to 46%)
IA through TC	1.01 (0.997 to 1.02)	2% (-1% to 5%)

Decomposition of the total association into the direct association and the joint indirect association (and splitting the joint indirect association further up into indirect associations through single mediators) was done according to the product-of-coefficients methods proposed in Vansteelandt & Daniel*. Confidence intervals were calculated using bootstrapping with 5,000 bootstrap resamples. All models were adjusted for baseline age, sex, smoking status, and socioeconomic status as depicted in the DAG in **Figure 1**. Proportions of the total association can potentially be beyond 100% or below 0% for direct/indirect associations, which can occur if the direct and indirect associations operate in different directions.

[1]HRs given per 5 kg/m² increase.
Abbreviations: CI, confidence interval; HR, hazard ratio; IA, indirect association.

*Vansteelandt S, Daniel RM: Interventional Effects for Mediation Analysis with Multiple Mediators. *Epidemiology* 28: 258–265, 2017