Supplemental Material

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

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

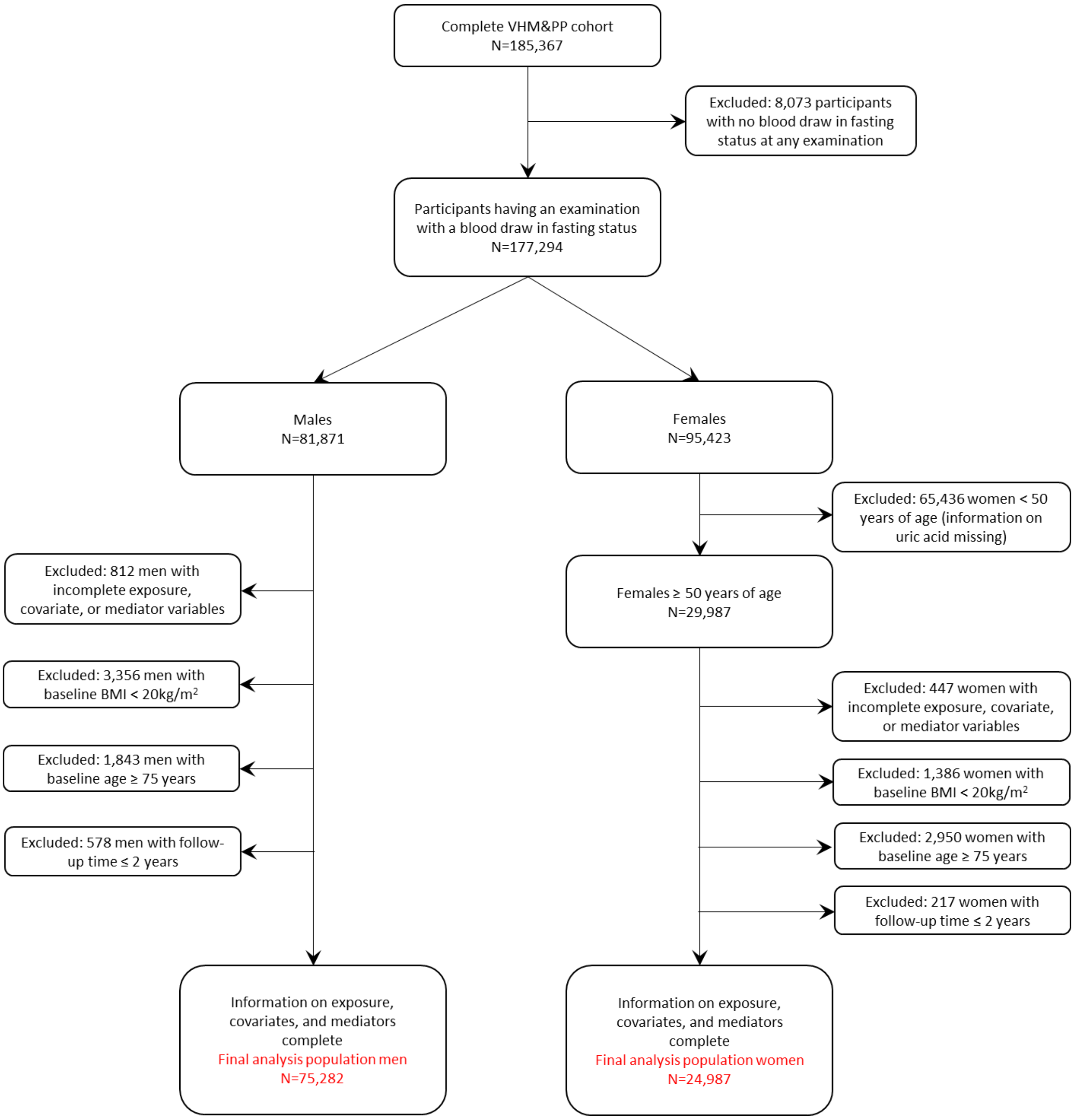

Figure S1: Flow chart of the study design of the Vorarlberg Health Monitoring and Promotion Program (VHM&PP), with details on the exclusions leading to the final analysis population of 100,269 VHM&PP participants.

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)
	≥75th 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	**<75th 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)
	≥75th 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	**<75th 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)
	≥75th 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	**<75th 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)
	≥75th 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)
	≥75th 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	**<75th 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)
	≥75th 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	**<75th 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)
	≥75th 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	**<75th 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)
	≥75th 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