## 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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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] | $\text { TyG index }{ }^{1}$ | $\begin{aligned} & \text { TyG index } \\ & \text { z-score } \end{aligned}$ | $\begin{gathered} \mathbf{M A P}^{2} \\ {[\mathbf{m m H g}]} \end{gathered}$ | MAP zscore | $\begin{gathered} \text { UA } \\ {[\mu \mathrm{mol} / \mathrm{L}]} \end{gathered}$ | UA z-score | $\begin{gathered} \mathrm{TC} \\ {[\mathrm{mmol} / \mathrm{L}]} \end{gathered}$ | TC z-score | Metabolic score | $\begin{gathered} \text { Metabolic } \\ \text { health } \\ \text { status }^{3} \\ \hline \end{gathered}$ |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 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 $(\mathrm{mg} / \mathrm{dL}) \times$ blood glucose $(\mathrm{mg} / \mathrm{dL}) / 2]$.
${ }^{2}$ Defined as diastolic blood pressure $+1 / 3 \times$ (systolic blood pressure - diastolic blood pressure) [ mmHg ].
${ }^{3} \mathrm{MH}$ is defined as a value of the metabolic score of $<1$; MUH is defined as a value of the metabolic score of $\geq 1$.
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 <br> (BMI 20 to $<\mathbf{2 5} \mathbf{~ m g} / \mathrm{kg}^{2}$ ) |  |  | Overweight(BMI 25 to $<30 \mathrm{mg} / \mathrm{kg}^{2}$ ) |  |  | Obesity(BMI $\geq 30 \mathrm{mg} / \mathrm{kg}^{2}$ ) |  |  | Total |  |  |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
|  |  | Incident ESKD cases / N | $\begin{aligned} & \hline \text { Incident } \\ & \text { ESKD } \\ & \text { cases per } \\ & \mathbf{1 0 0 , 0 0 0} \\ & \text { person- } \\ & \text { years } \\ & (\mathbf{9 5 \%} \mathrm{CI}) \end{aligned}$ | $\begin{gathered} \text { Multi- } \\ \text { variably- } \\ \text { adjusted } \\ \mathbf{H R}^{1} \\ (\mathbf{9 5 \%} \mathbf{C I}) \end{gathered}$ | Incident <br> ESKD <br> cases / <br> N | Incident ESKD cases per 100,000 personyears (95\% CI) | $\begin{aligned} & \text { Multi- } \\ & \text { variably- } \\ & \text { adjusted } \\ & \text { HR }^{1} \\ & (\mathbf{9 5 \%} \mathbf{C I}) \end{aligned}$ | Incident <br> ESKD <br> cases / <br> N | Incident ESKD cases per 100,000 personyears (95\% CI) | $\begin{gathered} \text { Multi- } \\ \text { variably- } \\ \text { adjusted } \\ \mathbf{H R}^{1} \\ \mathbf{( 9 5 \%} \mathbf{C I}) \end{gathered}$ | Incident ESKD cases / N | Incident ESKD cases per 100,000 personyears ( $95 \%$ CI) | $\begin{gathered} \text { Multi- } \\ \text { variably- } \\ \text { adjusted } \\ \mathbf{H R}^{2} \\ \mathbf{( 9 5 \% ~ C I )} \end{gathered}$ |
| Overall |  | $\begin{gathered} \hline 115 / \\ 35,320 \end{gathered}$ | $\begin{gathered} 13.6 \\ (11.2-16.3) \end{gathered}$ | $\begin{aligned} & 1.00 \\ & \text { (Ref) } \end{aligned}$ | $\begin{gathered} \hline 158 / \\ 31,534 \end{gathered}$ | $\begin{gathered} 21.6 \\ (18.4-25.3) \end{gathered}$ | $\begin{gathered} \hline 1.15 \\ (0.90-1.47) \end{gathered}$ | $\begin{gathered} \hline 80 / \\ 8,428 \end{gathered}$ | $\begin{gathered} 44.4 \\ (35.2-55.3) \end{gathered}$ | $\begin{gathered} \hline 2.23 \\ (1.67-2.98) \end{gathered}$ | $\begin{gathered} \hline 353 / \\ 75,282 \end{gathered}$ | $\begin{gathered} 20.1 \\ (18.0-22.3) \end{gathered}$ | - |
| TyG-I | $<75{ }^{\text {th }}$ pct | $\begin{gathered} 77 / \\ 30,321 \end{gathered}$ | $\begin{gathered} 10.5 \\ (8.3-13.2) \end{gathered}$ | $\begin{gathered} 1.00 \\ \text { (Ref) } \end{gathered}$ | $\begin{gathered} 84 / \\ 21,267 \end{gathered}$ | $\begin{gathered} 16.9 \\ (13.5-20.9) \end{gathered}$ | $\begin{gathered} 1.16 \\ (0.85-1.59) \end{gathered}$ | $\begin{gathered} 22 / \\ 4,208 \end{gathered}$ | $\begin{gathered} 24.1 \\ (15.1-36.4) \end{gathered}$ | $\begin{gathered} 1.57 \\ (0.97-2.53) \end{gathered}$ | $\begin{gathered} 183 / \\ 55,796 \end{gathered}$ | $\begin{gathered} 13.9 \\ (11.9-16.0) \end{gathered}$ | $\begin{gathered} 1.00 \\ \text { (Ref) } \end{gathered}$ |
|  | $\geq 75{ }^{\text {th }}$ pct | $\begin{gathered} 38 / \\ 4,999 \end{gathered}$ | $\begin{gathered} 32.8 \\ (23.2-45.0) \end{gathered}$ | $\begin{gathered} 2.43 \\ (1.65-3.59) \end{gathered}$ | $\begin{gathered} 74 / \\ 10,267 \end{gathered}$ | $\begin{gathered} 31.7 \\ (24.9-39.8) \end{gathered}$ | $\begin{gathered} 1.95 \\ (1.41-2.69) \end{gathered}$ | $\begin{gathered} 58 / \\ 4,220 \end{gathered}$ | $\begin{gathered} 65.4 \\ (49.6-84.5) \end{gathered}$ | $\begin{gathered} 3.97 \\ (2.81-5.62) \end{gathered}$ | $\begin{gathered} 170 / \\ 19,486 \end{gathered}$ | $\begin{gathered} 38.8 \\ (33.2-45.1) \end{gathered}$ | $\begin{gathered} 1.95 \\ (1.57-2.43) \end{gathered}$ |
| MAP | $<75{ }^{\text {th }}$ pet | $\begin{gathered} 63 / \\ 30,450 \end{gathered}$ | $\begin{gathered} 8.5 \\ (6.6-10.9) \end{gathered}$ | $\begin{aligned} & 1.00 \\ & \text { (Ref) } \end{aligned}$ | $\begin{gathered} 73 / \\ 22,082 \end{gathered}$ | $\begin{gathered} 14.0 \\ (11.0-17.6) \end{gathered}$ | $\begin{gathered} 1.26 \\ (0.90-1.77) \end{gathered}$ | $\begin{gathered} 26 / \\ 4,222 \end{gathered}$ | $\begin{gathered} 28.1 \\ (18.3-41.1) \end{gathered}$ | $\begin{gathered} 2.41 \\ (1.52-3.82) \end{gathered}$ | $\begin{gathered} 162 / \\ 56,754 \end{gathered}$ | $\begin{gathered} 12.0 \\ (10.2-14.0) \end{gathered}$ | $\begin{aligned} & 1.00 \\ & \text { (Ref) } \end{aligned}$ |
|  | $\geq 75{ }^{\text {th }}$ pct | $\begin{gathered} 52 / \\ 4,870 \end{gathered}$ | $\begin{gathered} 48.0 \\ (35.9-63.0) \end{gathered}$ | $\begin{gathered} 3.77 \\ (2.59-5.49) \end{gathered}$ | $\begin{gathered} 85 / \\ 9,452 \end{gathered}$ | $\begin{gathered} 40.5 \\ (32.3-50.0) \end{gathered}$ | $\begin{gathered} 2.81 \\ (2.00-3.93) \end{gathered}$ | $\begin{gathered} 54 / \\ 4,206 \end{gathered}$ | $\begin{gathered} 61.7 \\ (46.4-80.5) \end{gathered}$ | $\begin{gathered} 4.49 \\ (3.09-6.52) \end{gathered}$ | $\begin{gathered} 191 / \\ 18,528 \end{gathered}$ | $\begin{gathered} 47.1 \\ (40.6-54.2) \end{gathered}$ | $\begin{gathered} 2.46 \\ (1.96-3.08) \end{gathered}$ |
| UA | $<75{ }^{\text {th }}$ pct | $\begin{gathered} 61 / \\ 27,383 \end{gathered}$ | $\begin{gathered} 9.3 \\ (7.1-11.9) \end{gathered}$ | $\begin{gathered} 1.00 \\ \text { (Ref) } \end{gathered}$ | $\begin{gathered} 67 / \\ 20,020 \end{gathered}$ | $\begin{gathered} 14.4 \\ (11.2-18.3) \end{gathered}$ | $\begin{gathered} 1.12 \\ (0.79-1.59) \end{gathered}$ | $\begin{gathered} 30 / \\ 4,151 \end{gathered}$ | $\begin{gathered} 33.8 \\ (22.8-48.3) \end{gathered}$ | $\begin{gathered} 2.42 \\ (1.56-3.75) \end{gathered}$ | $\begin{gathered} 158 / \\ 51,554 \end{gathered}$ | $\begin{gathered} 13.1 \\ (11.1-15.3) \end{gathered}$ | $\begin{aligned} & 1.00 \\ & \text { (Ref) } \end{aligned}$ |
|  | $\geq 75^{\text {th }}$ pet | $\begin{gathered} 54 / \\ 7,937 \end{gathered}$ | $\begin{gathered} 28.4 \\ (21.3-37.0) \end{gathered}$ | $\begin{gathered} 2.95 \\ (2.04-4.25) \end{gathered}$ | $\begin{gathered} 91 / \\ 11,514 \end{gathered}$ | $\begin{gathered} 34.2 \\ (27.5-42.0) \end{gathered}$ | $\begin{gathered} 2.61 \\ (1.88-3.62) \end{gathered}$ | $\begin{gathered} 50 / \\ 4,277 \end{gathered}$ | $\begin{gathered} 54.7 \\ (40.6-72.1) \end{gathered}$ | $\begin{gathered} 4.08 \\ (2.80-5.95) \end{gathered}$ | $\begin{gathered} 195 / \\ 23,728 \end{gathered}$ | $\begin{gathered} 35.6 \\ (30.8-41.0) \end{gathered}$ | $\begin{gathered} 2.28 \\ 1.84-2.83) \end{gathered}$ |
| TC | $<75{ }^{\text {th }}$ pet | $\begin{gathered} 81 / \\ 30,348 \end{gathered}$ | $\begin{gathered} 11.1 \\ (8.8-13.8) \end{gathered}$ | $\begin{gathered} 1.00 \\ \text { (Ref) } \end{gathered}$ | $\begin{gathered} 95 / \\ 23,493 \end{gathered}$ | $\begin{gathered} 17.4 \\ (14.1-21.3) \end{gathered}$ | $\begin{gathered} 1.12 \\ (0.83-1.51) \end{gathered}$ | $\begin{gathered} 48 / \\ 6,005 \end{gathered}$ | $\begin{gathered} 37.5 \\ (27.7-49.7) \end{gathered}$ | $\begin{gathered} 2.24 \\ (1.56-3.21) \end{gathered}$ | $\begin{gathered} 224 / \\ 59,846 \end{gathered}$ | $\begin{gathered} 15.9 \\ (13.9-18.2) \end{gathered}$ | $\begin{gathered} 1.00 \\ (\text { Ref) } \end{gathered}$ |
|  | $\geq 75{ }^{\text {th }}$ pct | $\begin{gathered} 34 / \\ 4,972 \end{gathered}$ | $\begin{gathered} 29.3 \\ (20.3-40.9) \end{gathered}$ | $\begin{gathered} 1.67 \\ (1.12-2.51) \end{gathered}$ | $\begin{gathered} 63 / \\ 8,041 \end{gathered}$ | $\begin{gathered} 34.1 \\ (26.2-43.6) \end{gathered}$ | $\begin{gathered} 1.78 \\ (1.27-2.49) \end{gathered}$ | $\begin{gathered} 32 / \\ 2,423 \end{gathered}$ | $\begin{gathered} 61.4 \\ (42.0-86.6) \end{gathered}$ | $\begin{gathered} 3.28 \\ (2.17-4.96) \end{gathered}$ | $\begin{gathered} 129 / \\ 15,436 \end{gathered}$ | $\begin{gathered} 36.5 \\ (30.5-43.4) \end{gathered}$ | $\begin{gathered} 1.55 \\ (1.25-1.94) \end{gathered}$ |


| Metabolically healthy | $\begin{gathered} 52 / \\ 29,652 \end{gathered}$ | $\begin{gathered} 7.2 \\ (5.4-9.5) \end{gathered}$ | $\begin{gathered} 1.00 \\ \text { (Ref) } \end{gathered}$ | $\begin{gathered} 42 / \\ 18,420 \end{gathered}$ | $\begin{gathered} 9.7 \\ (7.0-13.1) \end{gathered}$ | $\begin{gathered} 1.03 \\ (0.69-1.55) \end{gathered}$ | $\begin{gathered} 12 / \\ 3,113 \end{gathered}$ | $\begin{gathered} 17.7 \\ (9.2-31.0) \end{gathered}$ | $\begin{gathered} 1.79 \\ (0.95-3.36) \end{gathered}$ | $\begin{gathered} 106 / \\ 51,185 \end{gathered}$ | $\begin{gathered} 8.7 \\ (7.1-10.5) \end{gathered}$ | $\begin{gathered} 1.00 \\ \text { (Ref) } \end{gathered}$ |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| Metabolically unhealthy | $\begin{gathered} 63 / \\ 5,668 \end{gathered}$ | $\begin{gathered} 48.9 \\ (37.6-62.6) \end{gathered}$ | $\begin{gathered} 4.47 \\ (3.08-6.49) \end{gathered}$ | $\begin{gathered} 116 / \\ 13,114 \end{gathered}$ | $\begin{gathered} 39.0 \\ (32.2-46.7) \end{gathered}$ | $\begin{gathered} 3.29 \\ (2.35-4.60) \end{gathered}$ | $\begin{gathered} 681 \\ 5,315 \end{gathered}$ | $\begin{gathered} 60.5 \\ (47.0-76.7) \end{gathered}$ | $\begin{gathered} 5.26 \\ (3.64-7.61) \end{gathered}$ | $\begin{gathered} 247 / \\ 24,097 \end{gathered}$ | $\begin{gathered} 45.8 \\ (40.3-51.9) \end{gathered}$ | $\begin{gathered} 3.39 \\ (2.66-4.32) \end{gathered}$ |

${ }^{1}$ 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 $75^{\text {th }}$ percentile) vs. low/normal (i.e. below the $75^{\text {th }}$ percentile). The $75^{\text {th }}$ percentiles were 8.99 for TyG index, 106.67 mmHg for mean arterial pressure, $374.72 \mathrm{mmol} / \mathrm{L}$ for uric acid, and $6.53 \mu \mathrm{~mol} / \mathrm{L}$ 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 $\geq 1$. Refer to Table $\mathbf{S 1}$ 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 $\mathbf{2 4 , 9 8 7}$
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 $<25 \mathrm{mg} / \mathrm{kg}^{2}$ ) |  |  | Overweight(BMI 25 to $<30 \mathrm{mg} / \mathrm{kg}^{2}$ ) |  |  | Obesity$\left(\mathrm{BMI} \geq \mathbf{3 0} \mathrm{mg} / \mathrm{kg}^{2}\right)$ |  |  | Total |  |  |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
|  |  | Incident ESKD cases / N | Incident ESKD cases per 100,000 personyears (95\% CI) | Multi-variablyadjusted $\mathbf{H R}^{1}$ ( $95 \% \mathrm{CI}$ ) | Incident ESKD cases / N | Incident ESKD cases per 100,000 personyears (95\% CI) | $\begin{aligned} & \text { Multi- } \\ & \text { variably- } \\ & \text { adjusted } \\ & \text { HR }^{1} \\ & (\mathbf{9 5 \%} \mathbf{C I}) \end{aligned}$ | Incident ESKD cases / N | Incident ESKD cases per 100,000 personyears (95\% CI) | $\begin{aligned} & \text { Multi- } \\ & \text { variably- } \\ & \text { adjusted } \\ & \text { HR }^{1} \\ & (\mathbf{9 5 \%} \mathbf{C I}) \end{aligned}$ | Incident ESKD cases / N | Incident ESKD cases per 100,000 personyears (95\% CI) | $\begin{aligned} & \text { Multi- } \\ & \text { variably- } \\ & \text { adjusted } \\ & \mathbf{H R}^{2} \\ & \mathbf{( 9 5 \%} \mathbf{C I}) \end{aligned}$ |
| Overall |  | $\begin{gathered} 23 / \\ 9,773 \end{gathered}$ | $\begin{gathered} \hline 10.2 \\ (6.5-15.3) \end{gathered}$ | $\begin{aligned} & \hline 1.00 \\ & \text { (Ref) } \end{aligned}$ | $\begin{gathered} 49 / \\ 9,728 \end{gathered}$ | $\begin{gathered} 22.2 \\ (16.4-29.4) \end{gathered}$ | $\begin{gathered} 2.17 \\ (1.32-3.57) \end{gathered}$ | $\begin{gathered} 38 / \\ 5,486 \end{gathered}$ | $\begin{gathered} 32.5 \\ (23.0-44.6) \end{gathered}$ | $\begin{gathered} \hline 3.23 \\ (1.92-5.43) \end{gathered}$ | $\begin{gathered} \hline 110 / \\ 24,987 \end{gathered}$ | $\begin{gathered} 19.5 \\ (16.1-23.6) \end{gathered}$ | - |
| TyG-I | $<75{ }^{\text {th }}$ pct | $\begin{gathered} 16 / \\ 8,531 \end{gathered}$ | $\begin{gathered} 8.0 \\ (4.6-13.0) \end{gathered}$ | 1.00 <br> (Ref) | $\begin{gathered} 28 / \\ 7,385 \end{gathered}$ | $\begin{gathered} 16.4 \\ (10.9-23.7) \end{gathered}$ | $\begin{gathered} 2.06 \\ (1.11-3.81) \end{gathered}$ | $\begin{gathered} 11 / \\ 3,487 \end{gathered}$ | $\begin{gathered} 14.4 \\ (7.2-25.8) \end{gathered}$ | $\begin{gathered} 1.84 \\ (0.85-3.98) \end{gathered}$ | $\begin{gathered} 55 / \\ 19,403 \end{gathered}$ | $\begin{gathered} 12.3 \\ (9.3-16.0) \end{gathered}$ | $\begin{gathered} 1.00 \\ (\text { Ref) } \end{gathered}$ |
|  | $\geq 75{ }^{\text {th }}$ pct | $\begin{gathered} 7 / \\ 1,242 \end{gathered}$ | $\begin{gathered} 27.1 \\ (10.9-55.9) \end{gathered}$ | $\begin{gathered} 3.27 \\ (1.34-7.99) \end{gathered}$ | $\begin{gathered} 21 / \\ 2,343 \end{gathered}$ | $\begin{gathered} 42.0 \\ (26.0-64.2) \end{gathered}$ | $\begin{gathered} 5.11 \\ (2.66-9.84) \end{gathered}$ | $\begin{gathered} 27 / \\ 1,999 \end{gathered}$ | $\begin{gathered} 66.4 \\ (43.7-96.6) \end{gathered}$ | $\begin{gathered} 8.28 \\ (4.44-15.43) \end{gathered}$ | $\begin{gathered} 55 / \\ 5,584 \end{gathered}$ | $\begin{gathered} 47.2 \\ (35.6-61.5) \end{gathered}$ | $\begin{gathered} 3.23 \\ (2.19-4.77) \end{gathered}$ |
| MAP | $<75{ }^{\text {th }}$ pct | $\begin{gathered} 14 / \\ 6,687 \end{gathered}$ | $\begin{gathered} 8.9 \\ (4.9-14.9) \end{gathered}$ | $\begin{gathered} 1.00 \\ \text { (Ref) } \end{gathered}$ | $\begin{gathered} 13 / \\ 5,174 \end{gathered}$ | $\begin{gathered} 10.8 \\ (5.7-18.4) \end{gathered}$ | $\begin{gathered} 1.21 \\ (0.57-2.58) \end{gathered}$ | $\begin{gathered} 10 / \\ 2,002 \end{gathered}$ | $\begin{gathered} 23.0 \\ (11.0-42.3) \end{gathered}$ | $\begin{gathered} 2.63 \\ (1.17-5.94) \end{gathered}$ | $\begin{gathered} 37 / \\ 13,863 \end{gathered}$ | $\begin{gathered} 11.5 \\ (8.1-15.9) \end{gathered}$ | $\begin{gathered} 1.00 \\ (\text { Ref }) \end{gathered}$ |
|  | $\geq 75^{\text {th }}$ pct | $\begin{gathered} 9 / \\ 3,086 \end{gathered}$ | $\begin{gathered} 13.2 \\ (6.0-25.1) \end{gathered}$ | $\begin{gathered} 1.55 \\ (0.67-3.60) \end{gathered}$ | $\begin{gathered} 36 / \\ 4,554 \end{gathered}$ | $\begin{gathered} 36.1 \\ (25.3-50.0) \end{gathered}$ | $\begin{gathered} 4.19 \\ (2.25-7.81) \end{gathered}$ | $\begin{gathered} 28 / \\ 3,484 \end{gathered}$ | $\begin{gathered} 38.2 \\ (25.4-55.2) \end{gathered}$ | $\begin{gathered} 4.46 \\ (2.34-8.51) \end{gathered}$ | $\begin{gathered} 73 / \\ 11,124 \end{gathered}$ | $\begin{gathered} 30.3 \\ (23.7-38.1) \end{gathered}$ | $\begin{gathered} 2.32 \\ (1.53-3.50) \end{gathered}$ |
| UA | $<75{ }^{\text {th }}$ pct | $\begin{gathered} 19 / \\ 9,319 \end{gathered}$ | $\begin{gathered} 8.8 \\ (5.3-13.7) \end{gathered}$ | $\begin{gathered} 1.00 \\ \text { (Ref) } \end{gathered}$ | $\begin{gathered} 35 / \\ 8,801 \end{gathered}$ | $\begin{gathered} 17.3 \\ (12.1-24.1) \end{gathered}$ | $\begin{gathered} 1.98 \\ (1.13-3.46) \end{gathered}$ | $\begin{gathered} 24 / \\ 4,488 \end{gathered}$ | $\begin{gathered} 24.7 \\ (15.8-36.7) \end{gathered}$ | $\begin{gathered} 2.87 \\ (1.57-5.26) \end{gathered}$ | $\begin{gathered} 78 / \\ 22,608 \end{gathered}$ | $\begin{gathered} 15.1 \\ (12.0-18.9) \end{gathered}$ | $\begin{gathered} 1.00 \\ \text { (Ref) } \end{gathered}$ |
|  | $\geq 75^{\text {th }}$ pct | $\begin{gathered} 4 / \\ 454 \end{gathered}$ | $\begin{gathered} 44.3 \\ (12.1-113.4) \end{gathered}$ | $\begin{gathered} 4.95 \\ (1.68-14.61) \end{gathered}$ | $\begin{aligned} & 14 / \\ & 927 \end{aligned}$ | $\begin{gathered} 76.3 \\ (41.7-128.1) \end{gathered}$ | $\begin{gathered} 8.87 \\ (4.42-17.84) \end{gathered}$ | $\begin{aligned} & 14 / \\ & 998 \end{aligned}$ | $\begin{gathered} 71.3 \\ (39.0-119.6) \end{gathered}$ | $\begin{gathered} 8.20 \\ (4.09-16.42) \end{gathered}$ | $\begin{gathered} 32 / \\ 2,379 \end{gathered}$ | $\begin{gathered} 68.1 \\ (46.6-96.1) \end{gathered}$ | $\begin{gathered} 3.71 \\ (2.41-5.73) \end{gathered}$ |
| TC | $<75{ }^{\text {th }}$ pct | $\begin{gathered} 13 / \\ 6,027 \end{gathered}$ | $\begin{gathered} 9.2 \\ (4.9-15.8) \end{gathered}$ | $\begin{gathered} 1.00 \\ \text { (Ref) } \end{gathered}$ | $\begin{gathered} 18 / \\ 5,798 \end{gathered}$ | $\begin{gathered} 13.6 \\ (8.1-21.5) \end{gathered}$ | $\begin{gathered} 1.48 \\ (0.72-3.02) \end{gathered}$ | $\begin{gathered} 24 / \\ 3,495 \end{gathered}$ | $\begin{gathered} 32.5 \\ (20.8-48.3) \end{gathered}$ | $\begin{gathered} 3.56 \\ (1.81-7.01) \end{gathered}$ | $\begin{gathered} 55 / \\ 15,320 \end{gathered}$ | $\begin{gathered} 15.9 \\ (12.0-20.7) \end{gathered}$ | $\begin{gathered} 1.00 \\ \text { (Ref) } \end{gathered}$ |
|  | $\geq 75^{\text {th }}$ pct | $\begin{gathered} 10 / \\ 3,746 \end{gathered}$ | $\begin{gathered} 11.8 \\ (5.7-21.7) \end{gathered}$ | $\begin{gathered} 1.26 \\ (0.55-2.87) \end{gathered}$ | $\begin{gathered} 31 / \\ 3,930 \end{gathered}$ | $\begin{gathered} 35.1 \\ (23.8-49.8) \end{gathered}$ | $\begin{gathered} 3.71 \\ (1.93-7.11) \end{gathered}$ | $\begin{gathered} 14 / \\ 1,991 \end{gathered}$ | $\begin{gathered} 32.6 \\ (17.8-54.7) \end{gathered}$ | $\begin{gathered} 3.53 \\ (1.65-7.52) \end{gathered}$ | $\begin{gathered} 55 / \\ 9,667 \end{gathered}$ | $\begin{gathered} 25.4 \\ (19.2-33.1) \end{gathered}$ | $\begin{gathered} 1.61 \\ (1.10-2.35) \end{gathered}$ |


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

${ }^{1}$ 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 $75^{\text {th }}$ percentile) vs. low/normal (i.e. below the $75^{\text {th }}$ percentile). The $75^{\text {th }}$ percentiles were 8.99 for TyG index, 106.67 mmHg for mean arterial pressure, $374.72 \mathrm{mmol} / \mathrm{L}$ for uric acid, and $6.53 \mu \mathrm{~mol} / \mathrm{L}$ 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 $\geq 1$. Refer to Table $\mathbf{S 1}$ 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 $\mathbf{1 0 0 , 2 6 9}$ VHM\&PP participant.

|  | Diabetic kidney disease $(\mathrm{N}=113)$ | Vascular nephropathy ( $\mathrm{N}=149$ ) | Other disease $(\mathrm{N}=201)$ | $\begin{gathered} \hline \text { Overall } \\ (\mathrm{N}=463) \\ \hline \end{gathered}$ |
| :---: | :---: | :---: | :---: | :---: |
|  | 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.
${ }^{1} \mathrm{HRs}$ given per $5 \mathrm{~kg} / \mathrm{m}^{2}$ 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 ( $\mathbf{N}=100,269$ ) |  |  |
| 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 ( $\mathbf{N}=\mathbf{7 5 , 2 8 2 \text { ) }}$ |  |  |
| BMI continuous ${ }^{1}$ | 1.52 (1.34 to 1.73) | 0.97 (0.83 to 1.14) |
| Females only ( $\mathbf{N}=\mathbf{2 4 , 9 8 7 \text { ) }}$ |  |  |
| 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).
${ }^{1} \mathrm{HRs}$ given per $5 \mathrm{~kg} / \mathrm{m}^{2}$ 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 $(\mathrm{N}=101,064)$.

|  | HR (95\% CI) | Proportion of total <br> association (95\% CI) |
| :--- | :---: | :---: |
| BMI continuous ${ }^{\mathbf{1}}$ |  |  |
| 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.
${ }^{1} \mathrm{HRs}$ given per $5 \mathrm{~kg} / \mathrm{m}^{2}$ 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

