## Supplemental Material Legends

**Supplementary Figure 1**: Flow diagram of the ROADMAP and OFU studies and illustration of participant inclusion in the current study.

**Supplementary Figure 2**: Mediation analysis of risk for microalbuminuria development with inclusion of CXCL-16, TGF-β1 and angiopoietin-2.

**A-C:** Tested mediators: changes in baseline serum TGF-β1 and angiopoietin-2. Independent variable: changes in CXCL-16.
**A:** the first step was the demonstration that higher CXCL-16 levels had a measurable impact on microalbuminuria development after accounting for baseline risk covariates.
**B1 and B2:** second, we checked if mediator changes (TGF-β1, angiopoietin-2) correlated with higher risk for microalbuminuria development, after accounting for baseline risk covariates.
**C1 and C2:** subsequently, we calculated the influence of higher CXCL-16 levels on the tested mediators (TGF-β1, angiopoietin-2). Finally, we jointly calculated the influence of the mediator on microalbuminuria development, after accounting for baseline risk covariates, and the direct effects of the independent variable (CXCL-16).

This last step shows that higher serum TGF-β1 partially mediates (20%, p=0.003 for the average causal mediation effect (ACME)) and angiopoietin-2 partially mediates (9%, p=0.007 for the ACME) the original effect of CXCL-16 on microalbuminuria development and, consequently, CXCL-16 remains directly associated with microalbuminuria development in an independent manner (characterizing incomplete mediation).

**D-F:** Tested mediators: changes in baseline serum CXCL-16 and angiopoietin-2. Independent variable: changes in TGF-β1.
**D:** the first step was the demonstration that higher TGF-β1 levels had a measurable impact on microalbuminuria development after accounting for baseline risk covariates.
**E1 and E2:** second, we checked if mediator changes (CXCL-16 and angiopoietin-2) correlated with microalbuminuria development, after accounting for baseline risk covariates.
**F1 and F2:** third, we calculated the influence of higher CXCL-16 on the tested mediators (TGF-β1, angiopoietin-2). Finally, we jointly calculated the influence of the mediator on microalbuminuria development, after accounting for baseline risk covariates, and the direct effects of the independent variable (TGF-β1).
This last step shows that higher serum CXCL-16 and angiopoietin-2 levels don't mediate the original effect of TGF-β1 on microalbuminuria development and, consequently, TGF-β1 remains directly associated with microalbuminuria development in an independent manner.

**G-I:** Tested mediators: changes in baseline serum CXCL-16 and TGF-β1. Independent variable: changes in angiopoietin-2.
**G:** the first step was the demonstration that higher angiopoietin-2 levels had a measurable impact on microalbuminuria development after accounting for baseline risk covariates.
**H1 and H2:** second, we checked if mediator changes (CXCL-16 and TGF-β1) correlated with microalbuminuria development, after accounting for baseline risk covariates.
**I1 and I2:** third, we calculated the influence of higher angiopoietin-2 on the tested mediators (CXCL-16 and TGF-β1). Subsequently, we jointly calculated the influence of the mediator on microalbuminuria development, after accounting for baseline risk covariates, and the direct effects of the independent variable (angiopoietin-2).
This last step shows that higher serum CXCL-16 partially mediates (10%, $p<0.001$ for the ACME) and TGF-β1 doesn't mediates (0%, $p<0.001$ for the ACME) the original effect of angiopoietin-2 on microalbuminuria development and, consequently, angiopoietin-2 remains directly associated with microalbuminuria development in an independent manner (characterizing incomplete mediation).

**Supplementary Figure 3**: Multilevel mediation analysis of risk for microalbuminuria development with inclusion of the combination of the three markers (CXCL-16, TGF-β1 and angiopoietin-2)

**Supplementary Table 1:** Univariable association of individual clinical risk factors (top) and measured biomarkers (bottom) with new-onset microalbuminuria.

**Supplementary Table 2a:** Spearman correlation coefficients between selected serum biomarker levels

**Supplementary Table 2b:** Spearman correlation coefficients between selected serum biomarker concentrations and clinical risk factors

**Supplementary Table 3:** Clinical characteristics of the available datasets at baseline, split by presence or absence of olmesartan in the ROADMAP trial.

**Supplementary Table 4:** Odds ratio (OR) for developing microalbuminuria before and after bootstrapped multivariate regression analysis

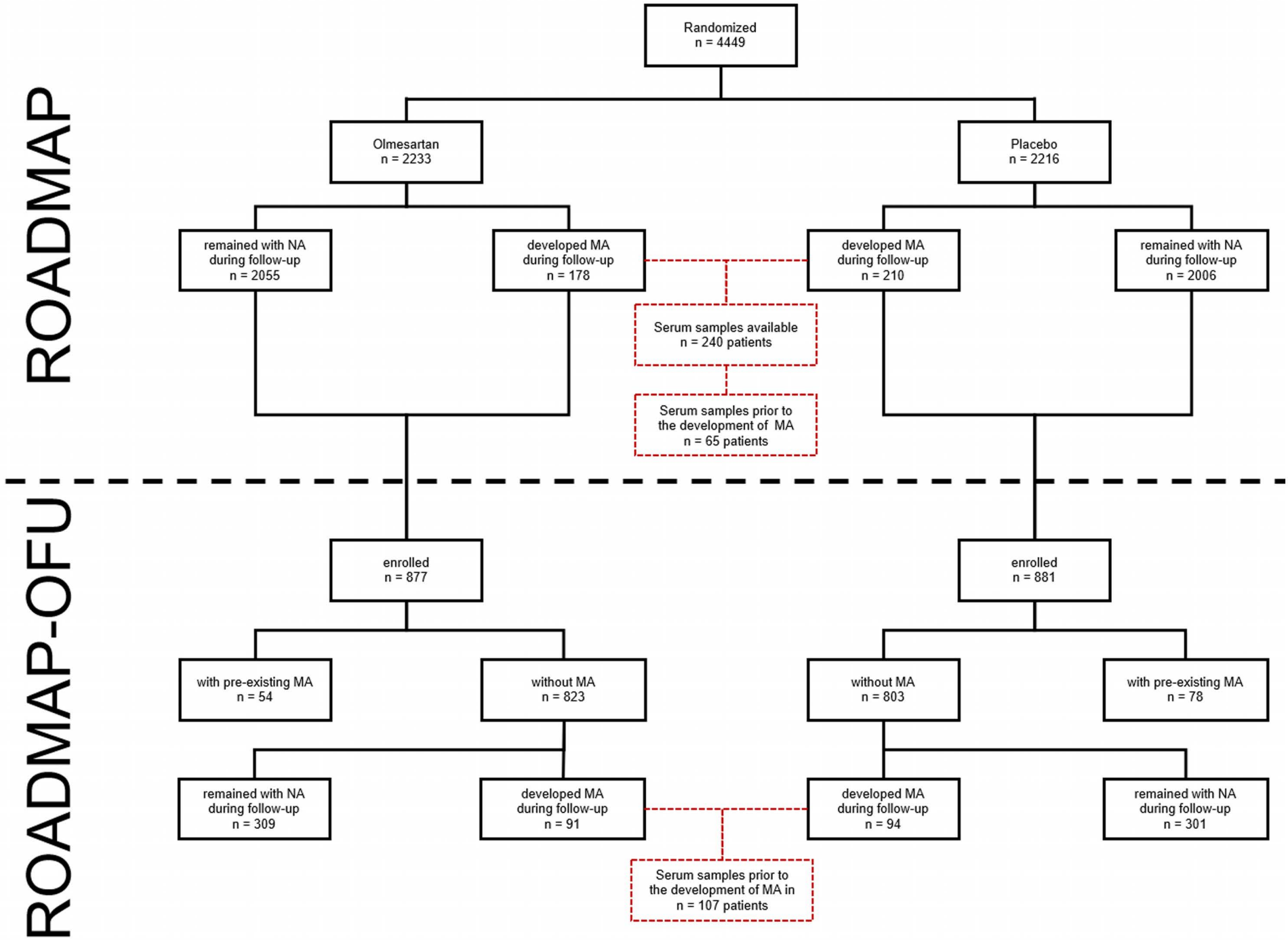
**Supplementary Table 5:** Log-rank test of comparing the different quartiles of all 3 biomarkers associated with an increasing incidence of the composite outcome (de novo microalbuminuria).

**Supplementary Table 6:** Calibration and sensitivity analysis of the risk prediction models.

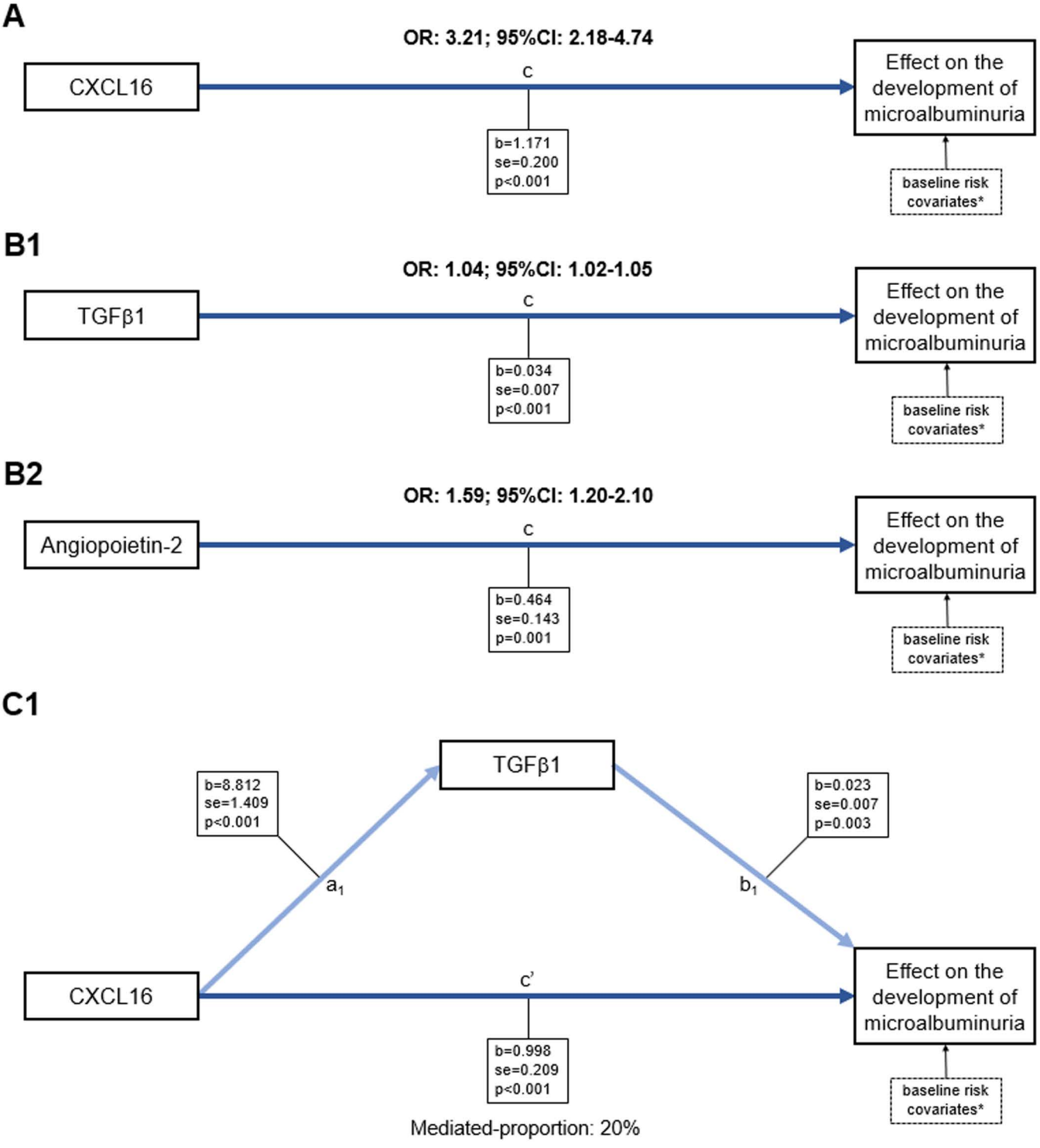
**Supplementary Table 7:** Prediction performance analysis for individual and combined biomarkers

**Supplementary Table 8:** Biomarkers of interest. Relevant clinical studies in patients with early stage cardiovascular disease or cardiovascular risk factors. Supposed pathways and underlying molecular mechanisms.

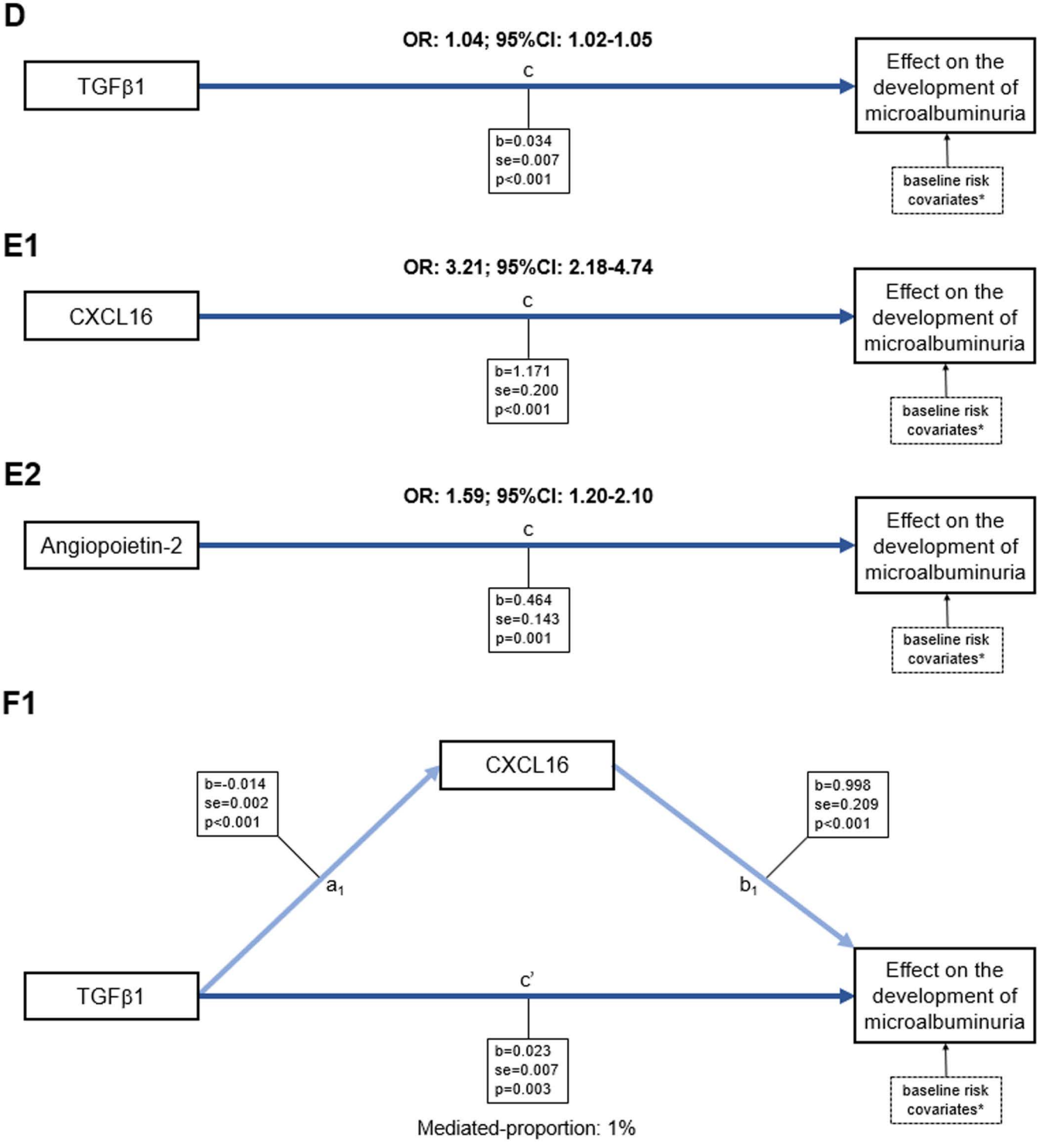
**Modified SROBE statement**




Supplementary Figure 1

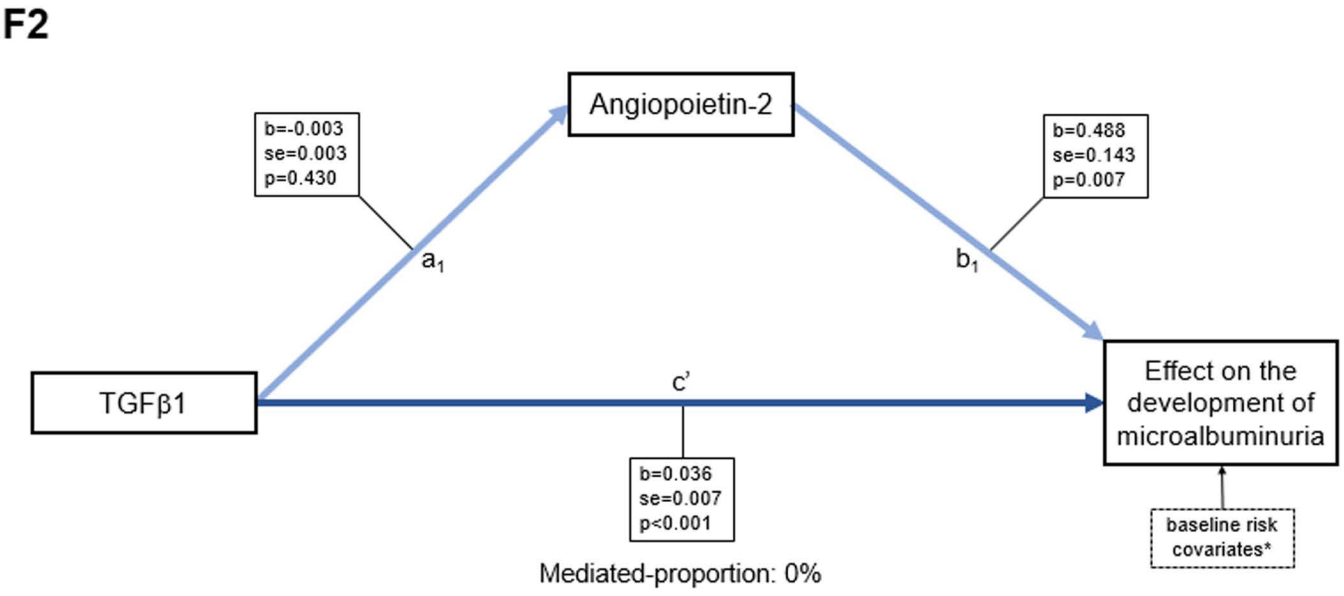



Supplementary Figure 2A-C

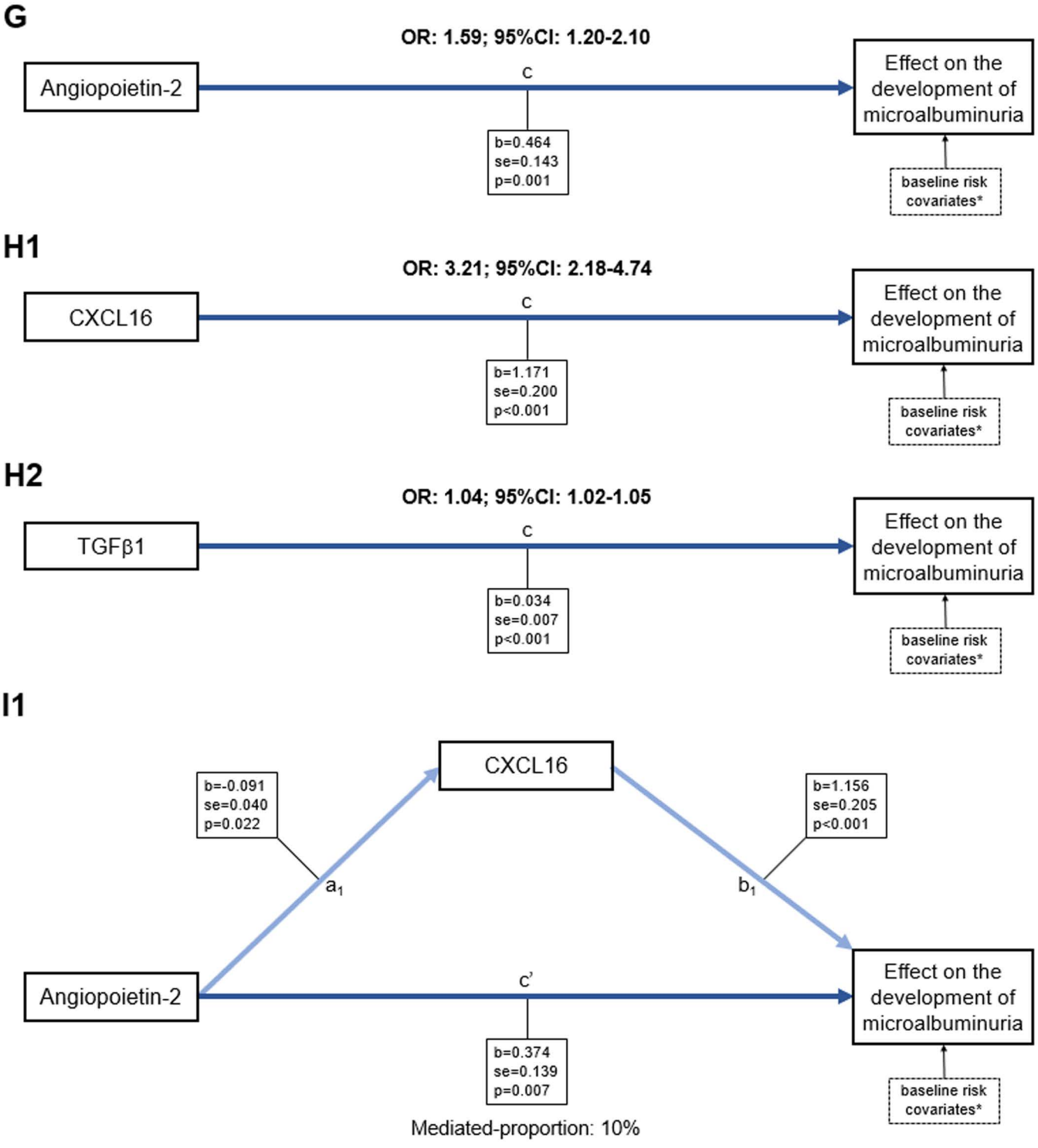






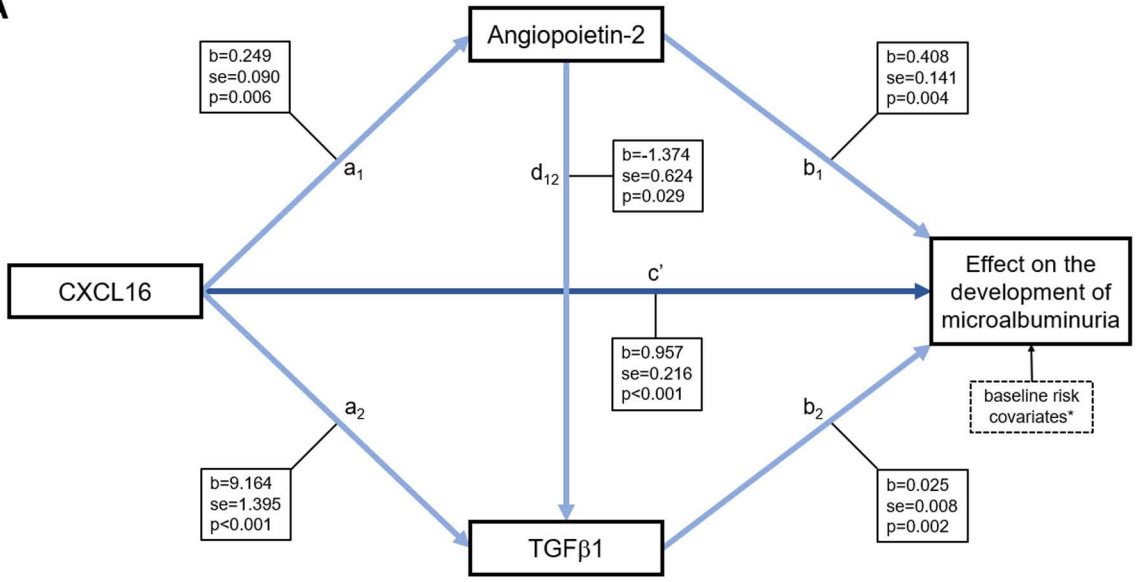



Supplementary Figure 2D-F



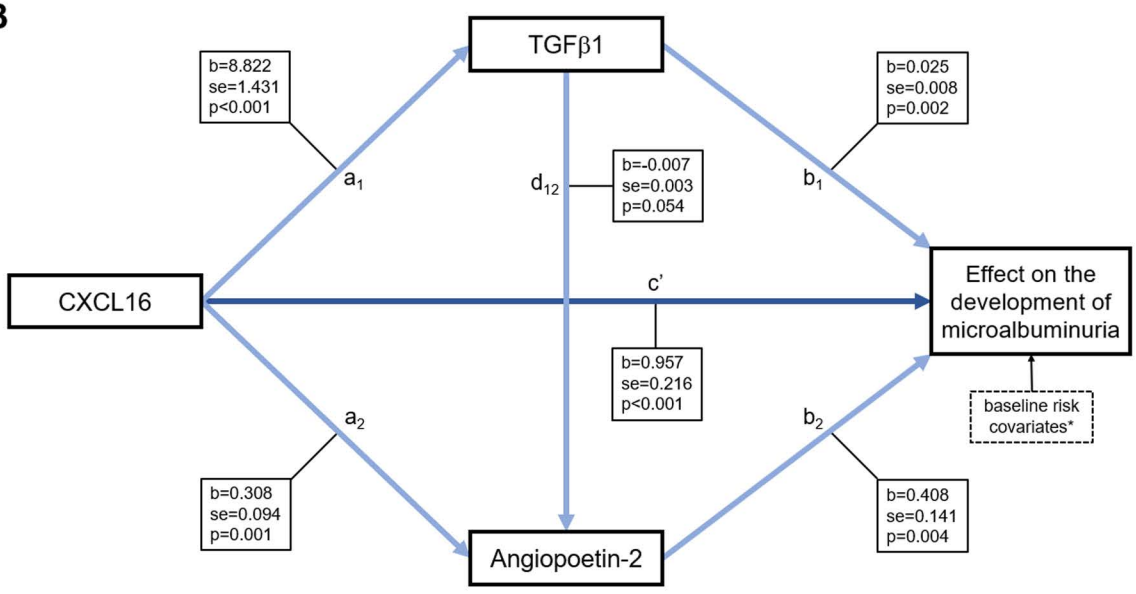

Supplementary Figure 2G-I

**A**




total Mediated-proportion: 33%

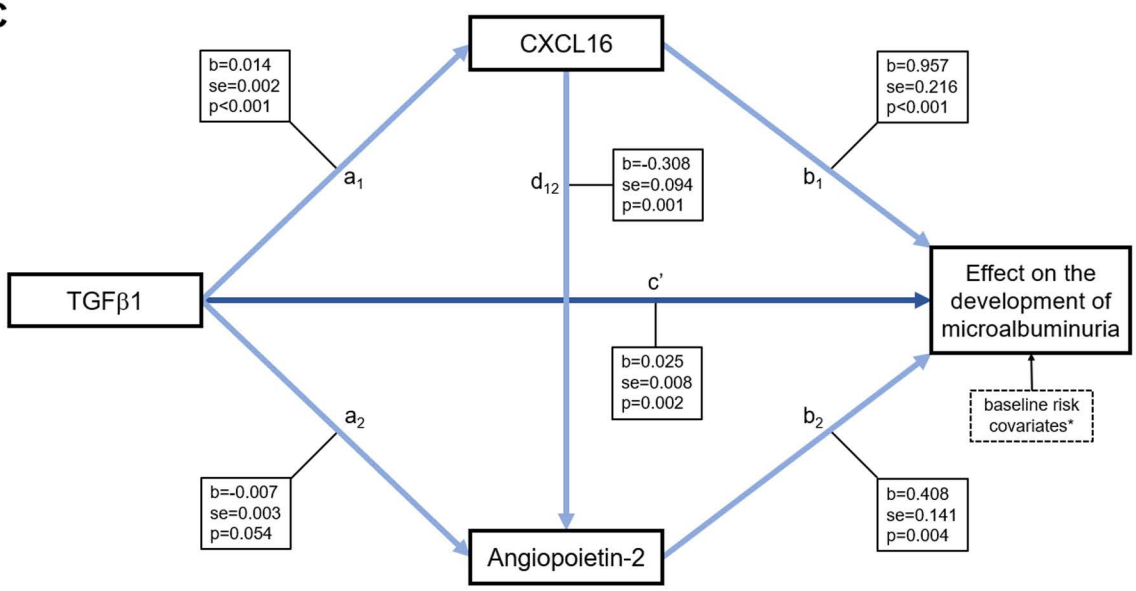
**B**




total Mediated-proportion: 33%

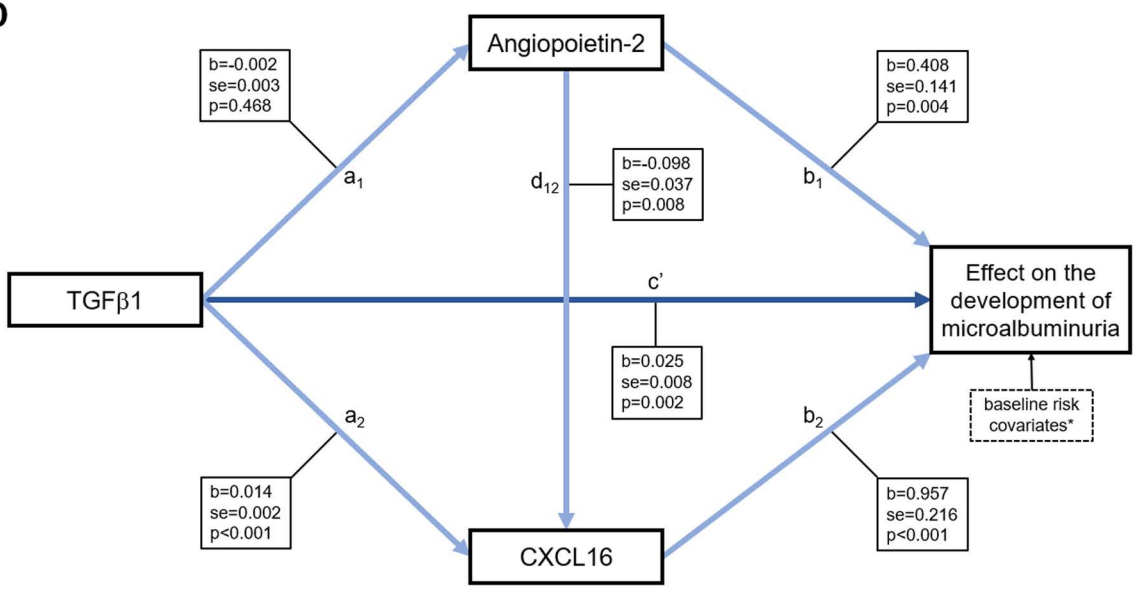
Supplementary Figure 3

**C**




total Mediated-proportion: 1%

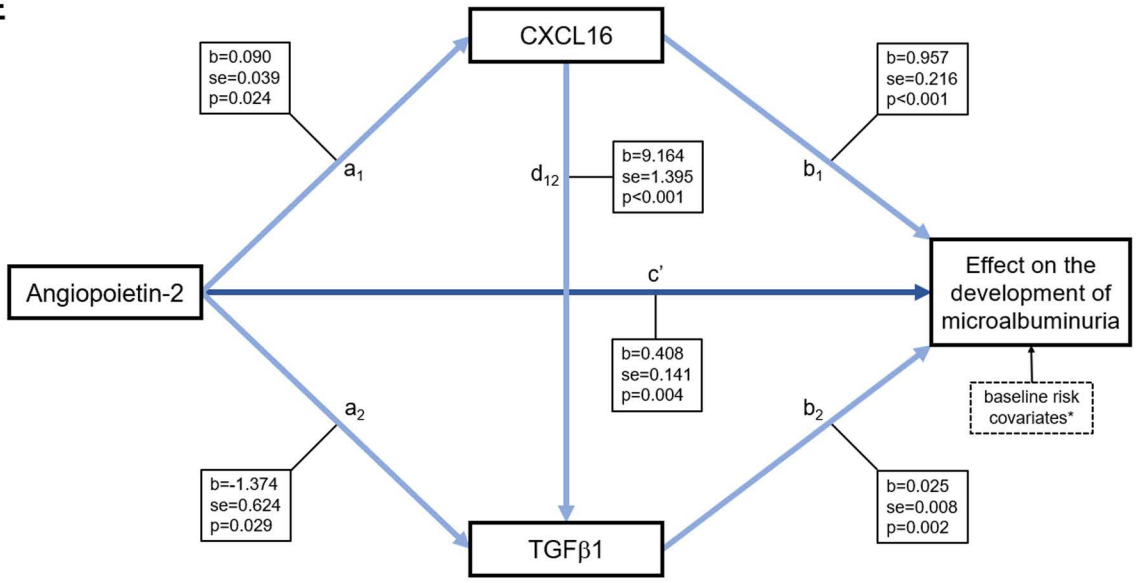
**D**




total Mediated-proportion: 1%

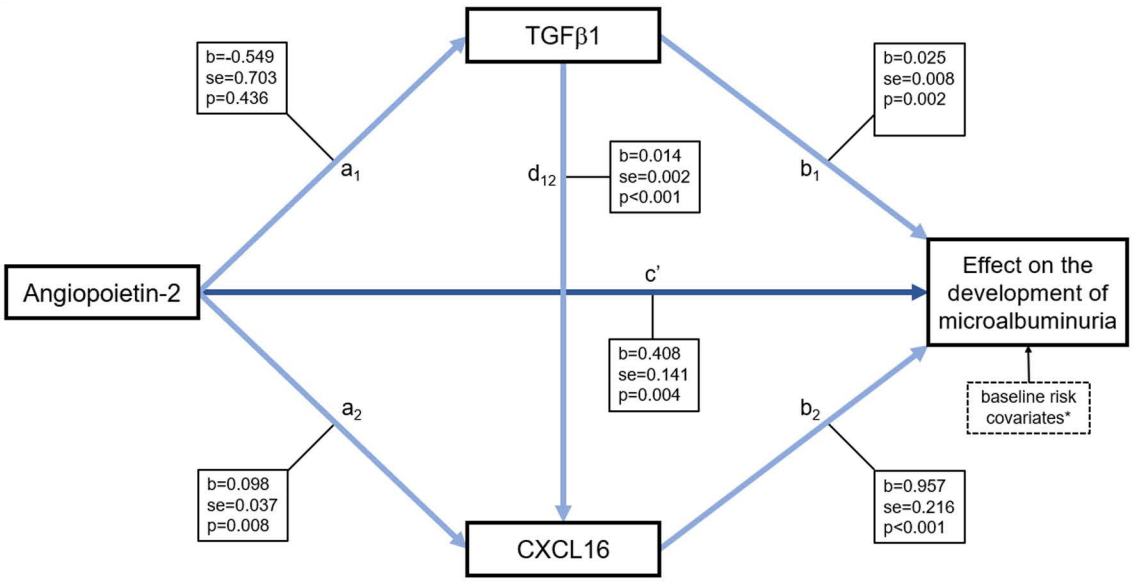
Supplementary Figure 3

**E**




total Mediated-proportion: 7%

**F**




total Mediated-proportion: 7%

Supplementary Figure 3

**Supplementary Table 1.** Univariable association of individual clinical risk factors (top) and measured biomarkers (bottom) with new-onset microalbuminuria.

| Clinical Markers | AUC | 95% CI | p |
|---|---|---|---|
| Age | 0.529 | 0.469 - 0.589 | 0.343 |
| Male sex | 0.489 | 0.430 - 0.549 | 0.727 |
| Tobacco smoking | 0.502 | 0.442 - 0.561 | 0.959 |
| Body-mass index | 0.483 | 0.423 - 0.543 | 0.585 |
| Systolic blood pressure | 0.513 | 0.453 - 0.573 | 0.665 |
| Diastolic blood pressure | 0.475 | 0.415 - 0.535 | 0.412 |
| Mean blood pressure | 0.491 | 0.431 - 0.551 | 0.769 |
| Estimated GFR | 0.486 | 0.427 - 0.546 | 0.656 |
| LDL cholesterol | 0.485 | 0.425 - 0.545 | 0.621 |
| $HbA_{1c}$ | 0.507 | 0.447 - 0.567 | 0.811 |
| Urine albumin-to-creatinine ratio | 0.554 | 0.495 - 0.614 | 0.075 |
| Cardiovascular Disease | 0.539 | 0.479 - 0.599 | 0.203 |
| Duration of diabetes | 0.545 | 0.485 - 0.604 | 0.143 |

AUC indicates area under the ROC curve; CI: 95% Confidence Interval;

| Serum Biomarkers | AUC | 95% CI | p | Bonferroni-Holm correction |
|---|---|---|---|---|
| S100AMRP8 | 0.514 | 0.454 - 0.574 | 0.651 | >0.999 |
| Endostatin | 0.586 | 0.527 - 0.644 | **0.005** | 0.075 |
| VAP-1 | 0.449 | 0.389 - 0.508 | 0.092 | >0.999 |
| CXCL-16 | 0.696 | 0.643 - 0.750 | **<0.001** | **<0.001** |
| sTNF-RI | 0.573 | 0.514 - 0.632 | **0.016** | 0.240 |
| sTNF-RII | 0.544 | 0.484 - 0.603 | 0.153 | >0.999 |
| sST2 | 0.562 | 0.503 - 0.621 | **0.042** | 0.630 |
| sThrombomodulin | 0.530 | 0.470 - 0.589 | 0.329 | >0.999 |
| VEGF | 0.541 | 0.481 - 0.601 | 0.178 | >0.999 |
| RAGE | 0.535 | 0.476 - 0.595 | 0.245 | >0.999 |
| VEGF-R1 | 0.559 | 0.499 - 0.618 | 0.054 | 0.810 |
| TGF-β1 | 0.669 | 0.612 - 0.726 | **<0.001** | **<0.001** |
| Angiopoietin-2 | 0.658 | 0.602 - 0.714 | **<0.001** | **<0.001** |
| Angiopoietin-1 | 0.484 | 0.425 - 0.544 | 0.611 | >0.999 |
| MCP-1 | 0.590 | 0.531 - 0.649 | **0.003** | **0.045** |

AUC indicates area under the ROC curve; CI: 95% Confidence Interval;

**Supplementary Table 2a:** Spearman correlation coefficients between selected serum biomarker levels

| Biomarker | CXCL-16 | TGF-β1 | Angiopoietin-2 | Endostatin | sTNF-RI |
|---|---|---|---|---|---|
| CXCL-16 | - | 0.374** | 0.290** | 0.170** | 0.265** |
| TGF-β1 | 0.374** | - | 0.067 | 0.060 | -0.033 |
| Angiopoietin-2 | 0.290** | 0.067 | - | 0.303** | 0.337** |
| Endostatin | 0.170** | 0.060 | 0.303** | - | **0.519**** |
| sTNF-RI | 0.265** | -0.033 | 0.337** | **0.519**** | - |

* p<0.05; ** p<0.01; CXCL16: C-X-C Motif Chemokine Ligand 16; TGFβ-1: Transforming growth factor beta 1; sTNF-RI: soluble Tumor Necrosis Factor Receptor I.

**Supplementary Table 2b.** Spearman correlation coefficients between selected serum biomarker concentrations and clinical risk factors

| Biomarker | MA | Age | Sex | BMI | Duration diabetes | Smoking status | Mean blood pressure | $HbA_{1c}$ | eGFR | LDL | UACR | Cardiac complications |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| CXCL-16 | 0.343** | 0.060 | 0.102 | 0.215** | 0.079 | -0.023 | 0.027 | 0.073 | -0.129* | 0.040 | 0.209** | 0.092 |
| TGF-β1 | 0.294** | -0.077 | 0.129* | 0.093 | 0.093 | -0.084 | 0.057 | 0.114* | 0.098 | 0.023 | 0.209** | 0.061 |
| Angiopoietin-2 | 0.275** | -0.002 | 0.107* | 0.204** | 0.020 | 0.123* | 0.008 | 0.014 | -0.014 | -0.019 | 0.138** | 0.093 |
| Endostatin | 0.147** | 0.218** | 0.024 | 0.093 | 0.087 | -0.007 | 0.043 | -0.103 | -0.274** | 0.069 | -0.056 | 0.033 |
| sTNF-RI | 0.125* | 0.182** | -0.024 | 0.207** | 0.180** | 0.052 | 0.046 | -0.010 | -0.246** | 0.030 | 0.008 | -0.017 |

* p<0.05; ** p<0.01; CXCL16: C-X-C Motif Chemokine Ligand 16; TGFβ-1: Transforming growth factor beta 1; sTNF-RI: soluble Tumor Necrosis Factor Receptor I; MA: microalbuminuria; Cardiovascular disease was defined as history of coronary heart disease, myocardial infarction, stroke or transient ischemic attack, or peripheral vascular disease; eGFR: glomerular filtration rate (calculated with the use of the abbreviated Modification of Diet in Renal Disease formula); $HbA_{1c}$: Glycated hemoglobin; LDL: low density lipoprotein; UACR: urine albumin creatinine ratio.

**Supplementary Table 3:** Clinical characteristics of the available datasets at baseline, split by presence or absence of olmesartan in the ROADMAP trial.

| Characteristics | Olmesartan (n=86) | Placebo (n=96) | P |
|---|---|---|---|
| **Demographic characteristics** | | | |
| Age | | | |
| Median - years (min-max) | 58 (36-75) | 59 (33-74) | 0.431 |
| Male sex - no. (%) | 45 (46,9) | 50 (46.5) | 0.961 |
| Tobacco smoking - no. (%) | | | |
| Non-smoker | 57 (59.4) | 49 (57.0) | 0.866 |
| Current-smoker | 24 (25.0) | 21 (24.4) | |
| Former-smoker | 15 (15.6) | 16 (18.6) | |
| **Physical examination** | | | |
| Body-mass index† | 31.7 ± 4.8 | 32.2 ± 5.1 | 0.915 |
| Mean arterial blood pressure - mmHg | 100.2 ± 10.8 | 99.8 ± 10.5 | 0.808 |
| **Laboratory values** | | | |
| Estimated GFR - ml/min/1.73 $m^2$ | 86.6 ± 18.4 | 86.3 ± 16.0 | 0.829 |
| $HbA_{1c}$ - % | 8.1 ± 1.6 | 7.9 ± 1.6 | 0.323 |
| LDL cholesterol - mmol/l | 2.9 ± 1.0 | 3.3 ± 1.2 | **0.027** |
| Urine albumin-to-creatinine ratio - mg/g | 10.5 ± 6.8 | 10.6 ± 8.3 | 0.585 |
| **Medical history** | | | |
| Cardiovascular disease – no. (%) | 11 (11.5) | 11 (12.8) | 0.783 |
| Duration of diabetes - months | 85.1 ± 72.6 | 83.1 ± 71.2 | 0.673 |
| **Biomarkers** | | | |
| CXCL-16 - ng/ml | 2.65 ± 0.58 | 2.68 ± 0.64 | 0.701 |
| TGF-β1 - ng/ml | 31.50 ± 33.25 | 33.25 ± 14.97 | 0.511 |
| Angiopoietin-2 - ng/ml | 2.12 ± 1.22 | 2.13 ± 1.02 | 0.782 |
| Endostatin - ng/ml | 116.7 ± 41.16 | 111.4 ± 37.52 | 0.324 |
| sTNF-RI - ng/ml | 1.53 ± 0.72 | 1.44 ± 0.62 | 0.352 |

Data are presented as mean (SD) for normally distributed values, median (min-max) for skewed continuous values and n (%) for categoric values; Cardiovascular disease was defined as history of coronary heart disease, myocardial infarction, stroke or transient ischemic attack, or peripheral vascular disease; eGFR: glomerular filtration rate (calculated with the use of the abbreviated Modification of Diet in Renal Disease formula); $HbA_{1c}$: Glycated hemoglobin; LDL: low density lipoprotein; †: The body-mass index is the weight in kilograms divided by the square of the height in meters.

**Supplementary Table 4:** Odds ratio (OR) for developing microalbuminuria before and after bootstrapped multivariate regression analysis

| Variable | Multivariate | | | Bootstrap resampling | | | | |
|---|---|---|---|---|---|---|---|---|
| | OR | 95% CI | P | OR | BCa 95% CI[a] | P | b[a] | $SE_b$[a] |
| Age | 1.000 | 0.968 - 1.033 | 0.988 | 1.000 | -0.036 - 0.034 | 0.988 | 0.000 | 0.019 |
| Sex | 0.681 | 0.403 - 1.149 | 0.150 | 0.681 | -0.962 - 0.137 | 0.150 | -0.384 | 0.301 |
| BMI | 0.953 | 0.904 - 1.006 | 0.079 | 0.953 | -0.108 - 0.001 | 0.079 | -0.048 | 0.031 |
| Smoking status | 0.930 | 0.662 - 1.306 | 0.674 | 0.930 | -0.438 - 0.283 | 0.674 | -0.073 | 0.191 |
| Mean arterial pressure | 0.995 | 0.972 - 1.019 | 0.685 | 0.995 | -0.030 - 0.018 | 0.685 | -0.005 | 0.013 |
| Estimated GFR | 0.997 | 0.981 - 1.013 | 0.691 | 0.997 | -0.022 - 0.015 | 0.691 | -0.003 | 0.009 |
| $HbA_{1c}$ | 0.938 | 0.797 - 1.103 | 0.436 | 0.938 | -0.256 - 0.103 | 0.436 | -0.064 | 0.095 |
| LDL cholesterol | 0.971 | 0.768 - 1.227 | 0.806 | 0.971 | -0.275 - 0.214 | 0.806 | -0.029 | 0.129 |
| Urine albumin-to-creatinine ratio | 0.996 | 0.963 - 1.030 | 0.817 | 0.996 | -0.047 - 0.037 | 0.817 | -0.004 | 0.020 |
| Cardiovascular disease | 1.516 | 0.703 - 3.271 | 0.288 | 1.516 | -0.459 - 10.389 | 0.288 | 0.416 | 0.434 |
| Duration of diabetes | 1.001 | 0.997 - 1.004 | 0.633 | 1.001 | -0.003 - 0.005 | 0.633 | 0.001 | 0.002 |
| Duration of follow-up | 0.992 | 0.977 - 1.006 | 0.248 | 0.992 | -0.025 - 0.007 | 0.248 | -0.009 | 0.008 |
| CXCL-16 | 2.603 | 1.705 - 3.957 | **<0.001** | 2.603 | 0.472 - 10.626 | **<0.001** | 0.957 | 0.233 |
| TGF-β1 | 1.026 | 1.010 - 1.042 | **0.001** | 1.026 | 0.007 - 0.049 | **0.001** | 0.025 | 0.009 |
| Angiopoietin-2 | 1.504 | 1.141 - 1.983 | **0.004** | 1.504 | 0.106 - 0.968 | **0.004** | 0.408 | 0.177 |

OR: odds ratio; CI: confidence interval; BCa CI: bias-corrected and accelerated (BCa) bootstrap interval; b: regression coefficients; SE0. standard error; a: bootstrap results are based on 10.000 bootstrap samples; CXCL16: C-X-C Motif Chemokine Ligand 16; TGFβ-1: Transforming growth factor beta 1; sTNF-RI: soluble Tumor Necrosis Factor Receptor I. Cardiovascular disease was defined as history of coronary heart disease, myocardial infarction, stroke or transient ischemic attack, or peripheral vascular disease; eGFR: glomerular filtration rate (calculated with the use of the abbreviated Modification of Diet in Renal Disease formula); HbA1c: Glycated hemoglobin; LDL: low density lipoprotein; UACR: urine albumin creatinine ratio.

**Supplementary Table 5:** Log-rank test of comparing the different quartiles of all 3 biomarkers associated with an increasing incidence of the composite outcome (de novo microalbuminuria).

| Log-rank text (Mantel-Cox) | Q1 | Q2 | Q3 | Q4 |
|---|---|---|---|---|
| **CXCL-16-quartiles** | | | | |
| Q1 (< 1.953 ng/ml) | - | <0.001 | <0.001 | <0.001 |
| Q2: (1.953 - 2.390 ng/ml) | <0.001 | - | 0.493 | 0.038 |
| Q3: (2.390 - 2.883 ng/ml) | <0.001 | 0.493 | - | 0.142 |
| Q4: (> 2.883 ng/ml) | <0.001 | 0.038 | 0.142 | - |
| **TGF-β1-quartiles** | | | | |
| Q1 < 11.745 ng/ml) | - | <0.001 | <0.001 | <0.001 |
| Q2: (11.745- 29.341 ng/ml) | <0.001 | - | 0.048 | 0.184 |
| Q3: (29.341- 40.575 ng/ml) | <0.001 | 0.048 | - | 0.939 |
| Q4: (> 40.575 ng/ml) | <0.001 | 0.184 | 0.939 | - |
| **Angiopoietin-2-quartiles** | | | | |
| Q1 (< 1.416 ng/ml) | - | 0.017 | <0.001 | <0.001 |
| Q2: (1.416 - 1.831 ng/ml) | 0.017 | - | 0.035 | 0.079 |
| Q3: (1.831 - 2.378 ng/ml) | <0.001 | 0.035 | - | 0.739 |
| Q4: (> 2.378 ng/ml) | <0.001 | 0.079 | 0.739 | - |

**Supplementary Table 6.** Calibration and sensitivity analysis of the risk prediction models

| Model | Omnibus Tests | Nagelkerke's $R^2$ | Hosmer and Lemeshow Test |
|---|---|---|---|
| Model 1 | 0.096 | 0.068 | 0.031 |
| Model 2 | <0.001 | 0.235 | 0.027 |
| Model 3 | <0.001 | 0.267 | 0.016 |

**Model 1:** Age, Sex, BMI, Duration diabetes, Smoking status, Mean blood pressure, $HbA_{1c}$, eGFR, LDL, Time of follow-up, UACR, Cardiac Complications
**Model 2:** CXCL16, TGFβ1, Angiopoietin-2
**Model 3:** Model 1 + 2

**Supplementary Table 7:** Prediction performance analysis for individual and combined biomarkers

| Models | AUC | 95% CI | SEM | NRI | SEM | Z | P |
|---|---|---|---|---|---|---|---|
| Model 1 | 0.638 | 0.580 - 0.695 | 0.029 | - | - | - | - |
| Model 1 plus each biomarker individually | | | | | | | |
| CXCL-16 | 0.715 | 0.662 - 0.767 | 0.027 | 0.238 | 0.059 | 4.002 | **<0.001** |
| TGF-β1 | 0.664 | 0.607 - 0.721 | 0.029 | 0.161 | 0.056 | 2.884 | **0.004** |
| Angiopoietin-2 | 0.678 | 0.623 - 0.733 | 0.028 | 0.215 | 0.043 | 5.043 | **<0.001** |
| Model 3 | 0.760[a] | 0.711 - 0.809 | 0.025 | 0.341 | 0.065 | 5.269 | **<0.001** |

[a] *P* value for Delong test comparing biomarker plus clinical model to clinical model alone was <0,001; AUC: Area under the curve; SEM: Standard Error of the Mean; NRI: Net Reclassification Improvement; Z: z value (z statistic for NRI) and the corresponding p-Value (with alpha error set to 0.05).

**Model 1:** Age, Sex, BMI, Duration diabetes, Smoking status, Mean blood pressure, $HbA_{1c}$, eGFR, LDL, Time of follow-up, UACR, Cardiovascular disease
**Model 2:** CXCL16, TGFβ1, Angiopoetin2
**Model 3:** Model 1 + 2

**Supplementary Table 8:** Biomarkers of interest**.** Relevant clinical studies in patients with early stage cardiovascular disease or cardiovascular risk factors. Supposed pathways and underlying molecular mechanisms.

| Biomarker | Primary Pathway | Secondary pathway | Molecular Mechanism | References |
|---|---|---|---|---|
| **CXCL-16** | Inflammation | Fibrosis | Chemokine-Ligand of the CXCR6<br>Scavenger Receptor for oxidized LDL | 1-4 |
| **ANGP-2** | Inflammation | Angiogenesis | Partial antagonist of Tie2 | 5-14 |
| **TGF-β1** | Fibrosis | Inflammation | Strong pro-fibrotic growth factor | 15-19 |
| **sVEGF-R1 (sFlt-1)** | Angiogenesis | Inflammation | Antagonist of VEGF-A | 20-28 |
| **C1qR1 (sCD93)** | Inflammation | Apoptosis | C-Type lectin-like domain signaling<br>Monocytes and endothelial cells | 29-31 |
| **Endostatin** | Angiogenesis | Fibrosis | Inhibitor of Angiogenesis<br>C-terminal fragment of collagen XVIII | 32-37 |
| **Galectin-3** | Fibrosis | Inflammation | Lectin signaling | 38-44 |
| **VAP-1** | Inflammation | Oxidative stress | Leukocyte trafficking<br>Amine Oxidase | 45-49 |
| **sThrombomodulin** | Inflammation | Coagulation | Cofactor for activating Protein C<br>Binding of HMGB-1 | 50-58 |
| **MCP-1** | Inflammation | Fibrosis | Chemokine-Ligand of the CCR2 | 59-65 |
| **sTNF-RII** | Inflammation | Fibrosis | High affinity for the membrane-bound TNF. Restricted more to endothelial cells | 66-74 |
| **sTNF-RI** | Inflammation | Fibrosis | High affinity for the soluble form of TNFa | 66-70,72-78 |
| **sST-2** | Inflammation | Myocardial fibrosis | Decoy receptor of IL-33 | 79-86 |
| **Osteopontin** | Inflammation | Calcification | Cell adhesion and migration<br>Macrophage & Lymphocyte activation | 87-90 |
| **S100A8** | Inflammation | Angiogenesis | Leukocyte trafficking | 91-95 |
| **RAGE** | Inflammation | Oxidative stress | Multiligand cell surface molecule belonging to the IG superfamily | 95-100 |
| **VEGF-A** | Angiogenesis | Inflammation | Binds to VEGFR1 and VEGFR2 | 101-103 |
| **ANGP-1** | Angiogenesis | Inflammation | Pure agonist of Tie2 | 102-105 |
| **Copeptin** | Inflammation | Fluid homeostasis | V1 (V1a & V1b) and V2 receptor agonist | 106-113 |

CXCL16: C-X-C Motif Chemokine Ligand 16; TGFβ-1: Transforming growth factor beta 1; VEGF-R1: Vascular Endothelial Growth Factor-A Receptor 1; ANGP-2: Angiopoietin-2; C1qR1: Complement component C1q Receptor1; VAP-1: Vascular Adhesion Protein 1; MCP-1: Monocyte Chemotactic Protein 1; sTNF-RII: soluble Tumor Necrosis Factor Receptor II; sTNF-RI: soluble Tumor Necrosis Factor Receptor I; sST2: soluble ST2; S100A8/MRP8: S100 calcium binding protein A/Myeloid Related Protein 8; RAGE: Receptor for Advanced Glycation Endproducts; VEGF-A: Vascular Endothelial Growth Factor-A. C1qR1, Galectin-3, Osteopontin and Copeptin were measured but not included in the analysis due to the high proportion of missing values (>3% and >15%).

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**Modified STROBE Statement—checklist of items that should be included in reports of observational studies (Cohort/Cross-sectional and case-control studies)**

| | Item No | Recommendation | Reported on Page No |
|---|---|---|---|
| **Title and abstract** | 1 | (*a*) Indicate the study's design with a commonly used term in the title or the abstract | Page 1-2 |
| | | (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found | Page 2 |
| **Introduction** | | | |
| Background/rationale | 2 | Explain the scientific background and rationale for the investigation being reported | Page 3 |
| Objectives | 3 | State specific objectives, including any prespecified hypotheses | Page 3 |
| **Methods** | | | |
| Study design | 4 | Present key elements of study design early in the paper | Page 4 |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | Page 4-5 |
| Participants | 6 | (*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up<br>*Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls<br>*Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants | Page 4-5 |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable | Page 4-5 |
| Data sources/ measurement | 8* | For each variable of interest, give sources of data and details of methods of assessment (measurement). | Page 5-6<br>Supplementary Table 6 |
| Bias | 9 | Describe any efforts to address potential sources of bias | Page 4-6<br>Page 9-12 |
| Study size | 10 | Explain how the study size was arrived at (if applicable) | Page 4 |
| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why | Page 4-6 |
| Statistical methods | 12 | (*a*) Describe all statistical methods, including those used to control for confounding | Page 6-7 |
| | | (*b*) Describe any methods used to examine subgroups and interactions | Page 6-7 |
| | | (*c*) Explain how missing data were addressed | Page 6-7 |
| | | (*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed<br>*Case-control study*—If applicable, explain how matching of cases and controls was addressed<br>*Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy | Page 4 |
| | | (*e*) Describe any sensitivity analyses | Page 6-7 |
| **Results** | | | |
| Participants | 13* | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for | Page 8 |

| | | | |
|---|---|---|---|
| | | eligibility, confirmed eligible, included in the study, completing follow-up, and analyzed | |
| | | (c) **Use of a flow diagram** | Supplementary Figure 1 |
| Descriptive data | 14* | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders | Page 8<br>Table 1 |
| | | (b) Indicate number of participants with missing data for each variable of interest | Page 4-6 |
| | | (c) *Cohort study*—Summarise follow-up time (eg, average and total amount) | Page 4 |
| Outcome data | 15* | *Cohort study*—Report numbers of outcome events or summary measures over time | - |
| | | *Case-control study*—Report numbers in each exposure category, or summary measures of exposure | Page 8-10 |
| | | *Cross-sectional study*—Report numbers of outcome events or summary measures | - |
| Main results | 16 | (*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included | Page 8-10 |
| Other analyses | 17 | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses | Page 8-10 |
| **Discussion** | | | |
| Key results | 18 | Summarise key results with reference to study objectives | Page 10-13 |
| Limitations | 19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias | Page 10-13 |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence | Page 10-13 |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results | Page 10-13 |

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.