

SUPPLEMENTARY DATA

**Supplementary Table S1 . Correlation matrix between biomarkers of subclinical inflammation**

	hsCRP	IL-6	IL-18	TNF $\alpha$	IL-1RA	sICAM-1	Adiponectin	Omentin
hsCRP	1	0.41 <sup>‡</sup>	0.19 <sup>‡</sup>	0.15 <sup>‡</sup>	0.38 <sup>‡</sup>	0.31 <sup>‡</sup>	-0.04	0.03
IL-6		1	0.16 <sup>‡</sup>	0.32 <sup>‡</sup>	0.31 <sup>‡</sup>	0.22 <sup>‡</sup>	-0.10*	0.04
IL-18			1	0.13 <sup>†</sup>	0.29 <sup>‡</sup>	0.31 <sup>‡</sup>	-0.14 <sup>‡</sup>	-0.02
TNF $\alpha$				1	0.18 <sup>‡</sup>	0.24 <sup>‡</sup>	-0.06	0.06
IL-1RA					1	0.28 <sup>‡</sup>	-0.18 <sup>‡</sup>	-0.09*
sICAM-1						1	-0.06	0.09*
Adiponectin							1	0.36 <sup>‡</sup>
Omentin								1

Correlations are based on log<sub>2</sub>-transformed biomarker levels and given as Pearson's correlation coefficients (*r*). \*,  $P \leq 0.05$ ; †,  $P \leq 0.01$ ; ‡  $P \leq 0.001$ .

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**Supplementary Table S2 . Drop-out analysis: baseline characteristics of the KORA F4 study participants stratified by participation in the KORA FF4 study**

Variable	Participation in FF4	No participation in FF4	P
<i>n</i>	615	546	
Age (years)	68.9 ± 4.9	72.0 ± 5.5	<0.001
Sex (% male / female)	52.8 / 47.2	49.3 / 50.7	0.138
BMI (kg/m <sup>2</sup> )	28.2 ± 4.1	29.3 ± 4.8	<0.001
Waist circumference (cm)	97.0 ± 12.1	99.7 ± 12.1	<0.001
Height (cm)	167 ± 9	164 ± 9	0.052
HbA1c (%)	5.73 ± 0.59	5.87 ± 0.78	0.007
HbA1c (mmol/mol)	39 ± 6	41 ± 9	0.007
Glucose tolerance status (NGT / IFG / IGT / IFG&IGT / ndT2D / kT2D) (%)	41.6 / 21.1 / 8.9 / 10.2 / 5.5 / 12.5	33.3 / 14.5 / 10.3 / 11.2 / 7 / 18.7	<0.001
Hypertension (%)*	58.5	68.5	0.052
Total cholesterol (mmol/l) <sup>†</sup>	5.07 ± 0.81	5.17 ± 1.01	0.151
Fasting triglycerides (mmol/l) <sup>†</sup>	1.35 (0.95; 1.84)	1.42 (1.02; 2.06)	0.175
Use of lipid-lowering drugs (%)	23.4	26.2	0.586
eGFR (ml/min per 1.73m <sup>2</sup> )	79.1 ± 13.6	73.0 ± 16.4	0.002
Smoking (never / former / current) (%)	51.9/41.3/6.8	49.5/42.1/8.3	0.012
Alcohol intake (none / moderate / high) (%)	30.1/59.3/10.6	34.4/57.3/8.3	0.676
Physically active (%)	56.6	42.7	0.001
Myocardial infarction (%)	5.2	7.9	0.447
Neurological conditions that might cause nerve damage (%)	18.3	19.5	0.443
Use of nonsteroidal anti-inflammatory drugs (%) <sup>‡</sup>	1.8	7.2	<0.001
MNSI	2.0 (1.0; 2.5)	2.0 (2.0; 3.0)	0.017
hsCRP (mg/l)	1.34 (0.70; 2.71)	1.87 (0.93; 3.97)	<0.001
IL-6 (pg/ml)	1.45 (1.02; 2.21)	1.86 (1.28; 2.79)	<0.001
IL-18 (pg/ml)	317 (252; 414)	317 (250; 422)	0.731
TNFα (pg/ml)	2.02 (1.47; 2.93)	2.03 (1.47; 2.90)	0.095
IL-1RA (pg/ml)	293 (225; 378)	328 (254; 441)	<0.001
sICAM-1 (ng/ml)	229 ± 51	249 ± 72	<0.001
Adiponectin (µg/ml)	9.94 (6.36; 15.20)	10.62 (6.96; 15.29)	0.973
Omentin (ng/ml)	500 ± 153	522 ± 192	0.940

Data are given as mean ± SD, median and 25<sup>th</sup>/75<sup>th</sup> percentiles or percentages. The *P* values are derived from logistic

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regression analysis (likelihood ratio tests comparing models with the respective variable, age and sex as independent variables to models with age and sex only). All analyses were adjusted for age and sex except associations with age (sex-adjusted only) or sex (age-adjusted only). Biomarkers of subclinical inflammation were  $\log_2$ -transformed prior to logistic regression.

BMI, body mass index; eGFR, estimated glomerular filtration rate; hsCRP, high-sensitivity C-reactive protein; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; IL, interleukin; IL-1RA, IL-1 receptor antagonist; kT2D, known type 2 diabetes; ndT2D, newly-diagnosed type 2 diabetes; NGT, normal glucose tolerance; sICAM, soluble intercellular adhesion molecule; TNF, tumour necrosis factor.

\*Blood pressure of 140/90 mmHg or higher, or antihypertensive medication given that the subjects were aware of being hypertensive.

† Individuals using lipid-lowering drugs excluded ( $n=286$ ).

‡ Nonsteroidal anti-inflammatory drugs except acetylsalicylic acid used as platelet aggregation inhibitor.

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**Supplementary Table S3. Baseline characteristics of the study participants with DSPN in KORA F4/FF4 stratified by DSPN status**

Variable	No DSPN in KORA F4	DSPN in KORA F4/ No DSPN in KORA FF4	DSPN in KORA F4 and FF4
<i>n</i>	530	28	57
Age (years)	68.5 ± 4.8 * †	70.6 ± 4.6 *	71.4 ± 5.1 †
Sex (% male / female)	50.8 / 49.2 †	57.1 / 42.9	70.2 / 29.8 †
BMI (kg/m <sup>2</sup> )	28.0 ± 3.9 †	29.1 ± 5.2	30.0 ± 4.8 †
Waist circumference (cm)	96.0 ± 11.5 †	100.1 ± 12.5	105.5 ± 13.7 †
Height (cm)	166 ± 9 †	168 ± 8	170 ± 9 †
HbA1c (%)	5.71 ± 0.55 *	6.03 ± 0.86 *	5.78 ± 0.73
HbA1c (mmol/mol)	39 ± 6	42 ± 9	40 ± 8
Glucose tolerance status (NGT / IFG / IGT / IFG&IGT / ndT2D / KT2D) (%)	43.2 / 21.1 / 9.4 / 10.0 / 5.5 / 10.8	28.6 / 21.4 / 3.6 / 10.7 / 7.1 / 28.6	33.3 / 21.1 / 7.0 / 12.3 / 5.3 / 21.1
Hypertension (%) <sup>§</sup>	58.7	53.6	59.6
Total cholesterol (mmol/l) <sup>  </sup>	5.07 ± 0.80	4.70 ± 1.01 †	5.24 ± 0.88 †
Fasting triglycerides (mmol/l) <sup>  </sup>	1.36 (0.97; 1.83)	0.89 (0.87; 1.19)	1.43 (0.95; 2.01)
Use of lipid-lowering drugs (%)	23.8	17.9	22.8
eGFR (ml/min per 1.73m <sup>2</sup> )	79.5 ± 13.4	78.5 ± 13.8	76.3 ± 14.9
Smoking (never / former / current) (%)	52.8 / 40.0 / 7.2	42.9 / 50.0 / 7.1	47.4 / 49.1 / 3.5
Alcohol intake (none / moderate / high) (%)	30.4 / 59.2 / 10.4	25.0 / 64.3 / 10.7	29.8 / 57.9 / 12.3
Physically active (%)	57.4	60.7	47.4
Myocardial infarction (%)	5.5	3.6	3.5
Neurological conditions that might cause nerve damage (%)	16.3 †	25.0	33.3 †
Use of nonsteroidal anti-inflammatory drugs (%) <sup>  </sup>	1.3	3.6	5.3
MNSI	2.0 (1.0; 2.0) * †	4.0 (3.5; 4.5) *	4.0 (4.0; 4.5) †
hsCRP (mg/l)	1.36 (0.70; 2.72)	0.86 (0.50; 1.94)	1.26 (0.74; 2.64)
IL-6 (pg/ml)	1.42 (1.00; 2.13) †	1.41 (1.13; 2.09)	1.96 (1.26; 2.67) †
IL-18 (pg/ml)	312 (251; 409)	330 (266; 416)	371 (280; 464)
TNFα (pg/ml)	1.98 (1.45; 2.89)	2.16 (1.47; 3.32)	2.13 (1.71; 2.98)
IL-1RA (pg/ml)	317 ± 142 †	362 ± 152	372 ± 239 †
sICAM-1 (ng/ml)	228 ± 50	234 ± 50	238 ± 59
Adiponectin (μg/ml)	10.00 (6.35; 15.21)	9.70 (6.94; 13.98)	9.22 (6.27; 14.98)
Omentin (ng/ml)	499 ± 151	518 ± 132	501 ± 178

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Data are given as mean  $\pm$  SD, median and 25<sup>th</sup>/75<sup>th</sup> percentiles or percentages. The *P* values are derived from logistic regression analysis (likelihood ratio tests comparing models with the respective variable, age and sex as independent variables to models with age and sex only). All analyses were adjusted for age and sex except associations with age (sex-adjusted only) or sex (age-adjusted only). Biomarkers of subclinical inflammation were log<sub>2</sub>-transformed prior to logistic regression.

BMI, body mass index; eGFR, estimated glomerular filtration rate; hsCRP, high-sensitivity C-reactive protein; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; IL, interleukin; IL-1RA, IL-1 receptor antagonist; kT2D, known type 2 diabetes; ndT2D, newly-diagnosed type 2 diabetes; NGT, normal glucose tolerance; sICAM, soluble intercellular adhesion molecule; TNF, tumour necrosis factor.

\* *P*<0.05 for the comparison of individuals without DSPN in KORA F4 (data column 1) vs individuals with DSPN in KORA F4, but not in in KORA FF4 (data column 2).

† *P*<0.05 for the comparison of individuals without DSPN in KORA F4 (data column 1) vs individuals with DSPN in KORA F4 and FF4 (data column 3).

‡ *P*<0.05 for the comparison of individuals with DSPN in KORA F4, but not in in KORA FF4 (data column 2) vs individuals with DSPN in KORA F4 and FF4 (data column 3).

§ Blood pressure of 140/90 mmHg or higher, or antihypertensive medication given that the subjects were aware of being hypertensive.

|| Individuals using lipid-lowering drugs excluded (*n*=144).

¶ Nonsteroidal anti-inflammatory drugs except acetylsalicylic acid used as platelet aggregation inhibitor.

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**Supplementary Table S4. Associations between biomarkers of subclinical inflammation and progression of DSPN assessed by changes in MNSI in individuals with DSPN in KORA F4**

Variable	Model 1		Model 2		Model 3	
	$\beta$ (95% CI)	<i>P</i>	$\beta$ (95% CI)	<i>P</i>	$\beta$ (95% CI)	<i>P</i>
hsCRP	0.111 (-0.076; 0.298)	0.240	<b>0.261 (0.012; 0.510)</b>	<b>0.041</b>	0.247 (-0.002; 0.496)	0.052
IL-6	0.098 (-0.151; 0.348)	0.432	0.321 (-0.043; 0.684)	0.082	0.286 (-0.085; 0.658)	0.127
IL-18	0.310 (-0.113; 0.733)	0.148	0.388 (-0.098; 0.875)	0.114	0.274 (-0.233; 0.781)	0.281
TNF $\alpha$	0.149 (-0.114; 0.411)	0.261	0.163 (-0.143; 0.469)	0.288	0.195 (-0.118; 0.507)	0.215
sICAM-1	<b>0.776 (0.048; 1.504)</b>	<b>0.037</b>	0.836 (-0.006; 1.678)	0.051	<b>1.075 (0.218; 1.932)</b>	<b>0.015</b>
IL-1RA	<b>0.433 (0.082; 0.784)</b>	<b>0.016</b>	<b>0.892 (0.437; 1.347)</b>	<b>&lt;0.001</b>	<b>0.792 (0.292; 1.293)</b>	<b>0.003</b>
Adiponectin	0.087 (-0.249; 0.423)	0.604	0.090 (-0.369; 0.550)	0.694	-0.094 (-0.586; 0.398)	0.701
Omentin	-0.081 (-0.617; 0.455)	0.762	-0.038 (-0.649; 0.573)	0.901	0.016 (-0.589; 0.622)	0.957

Regression coefficients ( $\beta$ ), 95% CI and corresponding *P* values for changes in MNSI (MNSI<sub>FF4</sub> minus MNSI<sub>F4</sub>) are given for a doubling in circulating levels of biomarkers.

Model 1: adjusted for age and sex.

Model 2: model 1 + waist circumference, height, hypertension, total cholesterol, HbA1c, alcohol intake, smoking, physical activity.

Model 3: model 2 + use of lipid-lowering drugs, use of non-steroidal anti-inflammatory drugs, estimated glomerular filtration rate, prevalent myocardial infarction and neurological conditions that might cause nerve damage.

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Supplementary Figure S1. Description of the study design and population

