

## Supplemental material

### Interleukin 6 trans-signalling and the risk of future cardiovascular events in men and women

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#### **Content:**

##### **Supplemental Method**

Supplemental Figure I

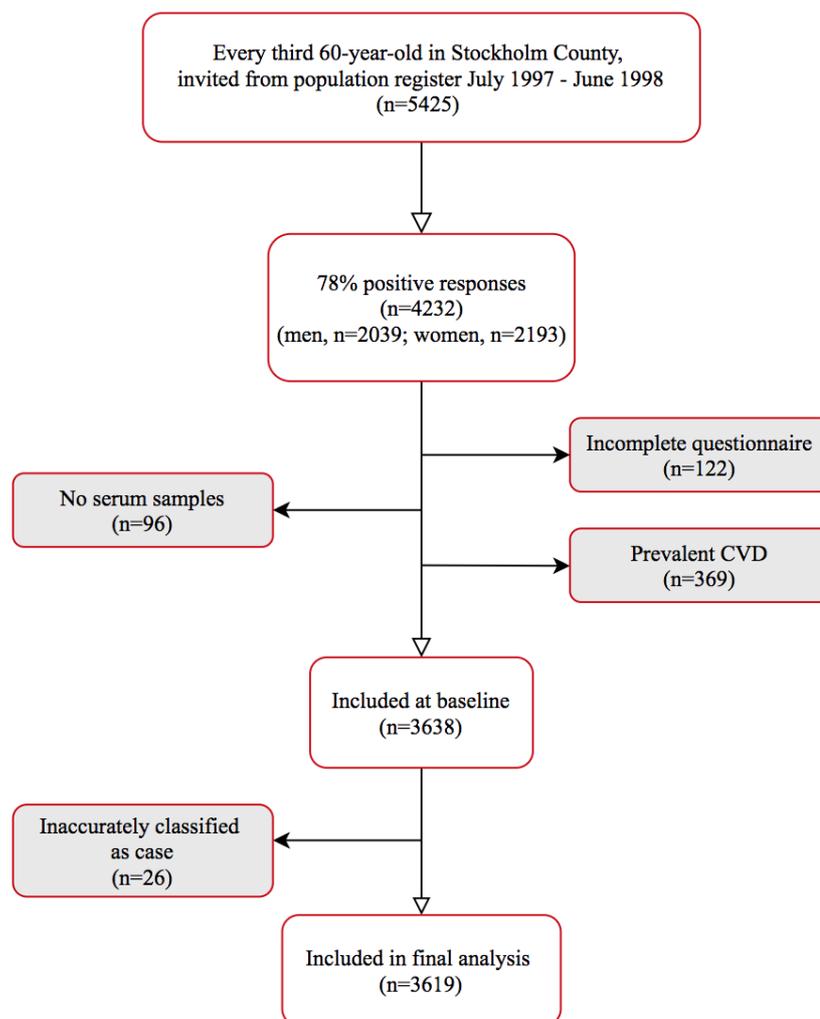
Supplemental Table I

##### **Supplemental Results**

Supplemental Table II-V

## Supplemental Method

### Supplemental figure I. Flow chart of exclusions



**Supplemental Figure I.** Subjects were excluded from the present analyses if they had incomplete questionnaires at enrolment, missing serum samples or if they had prevalent CVD at baseline; defined as self-reported or registered ICD-10 diagnosis codes of either MI (I121), chronic ischemic heart disease (I25) or ischemic stroke (I63). Furthermore, subjects who inaccurately had been categorised as cases with the following diagnosis codes were restricted from the final analysis: carotid artery stenosis (I652) if it was unclear whether the subject had a stroke or not; chronic ischemic heart disease (I259) because former events could not be excluded; old MI (I252) because the time of the event was unknown; and stroke not specified as haemorrhage or infarction (I649) because the underlying cause of the event was not clear.

### Quartile boundaries for individual biomarkers

**Supplemental Table I.** Quartile boundaries for IL6 trans-signalling biomarkers in men and women

	$\leq 25^{\text{th}}$	$>25-\leq 50^{\text{th}}$	$>50-\leq 75^{\text{th}}$	$>75^{\text{th}}$
<b>Men</b>				
<b>IL6</b> (pg/ml)	$\leq 0.44$	$>0.44 \leq 0.62$	$>0.62 \leq 0.90$	$> 0.90$
<b>sIL6R</b> (ng/ml)	$\leq 28.98$	$> 28.98 \leq 35.76$	$> 35.76 \leq 44.36$	$> 44.36$
<b>sgp130</b> (ng/ml)	$\leq 338.4$	$> 338.4 \leq 395.7$	$> 395.7 \leq 459.1$	$> 459.1$
<b>B/T ratio</b>	$\leq 1.56$	$>1.56 \leq 1.59$	$>1.59 \leq 1.62$	$>1.62$
<b>Women</b>				
<b>IL6</b> (pg/ml)	$\leq 0.39$	$>0.39 \leq 0.56$	$> 0.56 \leq 0.88$	$> 0.88$
<b>sIL6R</b> (ng/ml)	$\leq 25.68$	$> 25.68 \leq 31.41$	$> 31.41 \leq 38.43$	$> 38.43$
<b>sgp130</b> (ng/ml)	$\leq 306.4$	$> 306.4 \leq 367.6$	$> 367.6 \leq 443.2$	$> 443.2$
<b>B/T ratio</b>	$\leq 1.54$	$>1.54 \leq 1.58$	$>1.58 \leq 1.61$	$>1.61$

**Supplemental Table I.** Quartile boundaries for each IL6 trans-signalling biomarker in men and women, respectively

## Supplemental results

### IL6, sIL6R, sgp130 and the risk of future CVE

**Supplemental Table II: IL6, sIL6R, sgp130 and B/T ratio and risk of CVE in men**

	<b>Crude</b>	<b>P</b>	<b>Adjusted</b>	<b>P</b>
<b>IL6</b>				
≤25 <sup>th</sup> perc	1.00 (ref)	-	1.00 (ref)	-
25-50 <sup>th</sup> perc	1.27 (0.95-1.70)	0.11	1.19 (0.89-1.60)	0.24
50-75 <sup>th</sup> perc	1.19 (0.89-1.60)	0.24	1.03 (0.76-1.39)	0.85
>75 <sup>th</sup> perc	1.66 (1.26-2.20)	<0.001	1.35 (1.00-1.81)	0.05
<b>sIL6R</b>				
≤25 <sup>th</sup> perc	1.00 (ref)	-	1.00 (ref)	-
25-50 <sup>th</sup> perc	1.21 (0.93-1.66)	0.24	1.21 (0.89-1.66)	0.22
50-75 <sup>th</sup> perc	1.73 (1.30-2.32)	<0.001	1.69 (1.26-2.27)	<0.001
>75 <sup>th</sup> perc	1.78 (1.33-2.38)	<0.001	1.61 (1.20-2.15)	0.002
<b>sgp130</b>				
≤25 <sup>th</sup> perc	1.00 (ref)	-	1.00 (ref)	-
25-50 <sup>th</sup> perc	1.24 (0.84-1.57)	0.14	1.20 (0.90-1.61)	0.21
50-75 <sup>th</sup> perc	1.21 (0.91-1.61)	0.20	1.19 (0.89-1.60)	0.23
>75 <sup>th</sup>	1.32 (0.99-1.75)	0.06	1.21 (0.91-1.62)	0.19
<b>B/T ratio</b>				
≤25 <sup>th</sup> perc	1.00 (ref)	-	1.00 (ref)	-
25-50 <sup>th</sup> perc	0.98 (0.72-1.34)	0.91	1.0 (0.73-1.37)	0.99
50-75 <sup>th</sup> perc	1.63 (1.22-2.17)	0.001	1.58 (1.19-2.11)	0.002
>75 <sup>th</sup>	1.72 (1.30-2.29)	<0.001	1.58 (1.19-2.10)	0.002

**Supplemental Table II:** Risk of CVE, expressed as hazard ratio (HR) with 95% confidence interval (CI) associated with the individual biomarkers involved in IL6 trans-signalling in men. Reference group: ≤25<sup>th</sup> percentile. The analysis is adjusted for diabetes, hypertension, hypercholesterolemia, BMI and smoking.

**Supplemental Table III: IL6, sIL6R, sgp130 and B/T ratio and risk of CVE in women**

	<b>Crude</b>	<b>P</b>	<b>Adjusted</b>	<b>P</b>
<b>IL6</b>				
≤25 <sup>th</sup> perc	1.00 (ref)	-	1.00 (ref)	-
25-50 <sup>th</sup> perc	0.93 (0.63-1.38)	0.72	0.89 (0.60-1.32)	0.55
50-75 <sup>th</sup> perc	1.27 (0.88-1.84)	0.20	1.07 (0.73-1.56)	0.74
>75 <sup>th</sup> perc	1.48 (1.03-2.11)	0.03	1.15 (0.79-1.69)	0.46
<b>sIL6R</b>				
≤25 <sup>th</sup> perc	1.00 (ref)	-	1.00 (ref)	-
25-50 <sup>th</sup> perc	0.97 (0.66-1.44)	0.89	0.92 (0.62-1.37)	0.70
50-75 <sup>th</sup> perc	1.15 (0.79-1.68)	0.46	1.06 (0.73-1.55)	0.75
>75 <sup>th</sup> perc	1.52 (1.07-2.17)	0.02	1.34 (0.95-1.95)	0.10
<b>sgp130</b>				
≤25 <sup>th</sup> perc	1.00 (ref)	-	1.00 (ref)	-
25-50 <sup>th</sup> perc	1.41 (0.97-2.05)	0.08	1.42 (0.97-2.06)	0.07
50-75 <sup>th</sup> perc	1.45 (1.0-2.11)	0.05	1.36 (0.93-1.98)	0.11
>75 <sup>th</sup>	1.22 (0.83-1.80)	0.32	1.13 (0.76-1.68)	0.53
<b>B/T ratio</b>				
≤25 <sup>th</sup> perc	1.00 (ref)	-	1.00 (ref)	-
25-50 <sup>th</sup> perc	1.03 (0.69-1.51)	0.90	0.97 (0.65-1.43)	0.87
50-75 <sup>th</sup> perc	1.40 (0.97-2.01)	0.07	1.30 (0.90-1.88)	0.16
>75 <sup>th</sup> perc	1.31 (0.91-1.90)	0.15	1.16 (0.80-1.69)	0.42

**Supplemental Table III:** Risk of CVE, expressed as hazard ratio (HR) with 95% confidence interval (CI) associated with the individual biomarkers involved in IL6 trans-signalling in women. Reference group: ≤25<sup>th</sup> percentile. The analysis is adjusted for diabetes, hypertension, hypercholesterolemia, BMI, smoking and hormone replacement therapy.

**B/T ratio as a continuous variable and the risk of future CVE****Supplemental Table IV.** B/T ratio and the risk of CVE in men and women

<b>B/T ratio</b>	<b>Crude</b>	<b>P</b>	<b>Adjusted</b>	<b>P</b>
<b>Men</b>				
0.1 unit	1.71 (1.37-2.13)	<0.001	1.58 (1.27-1.97)	<0.001
Quartile	1.24 (1.13-1.35)	<0.001	1.20 (1.10-1.31)	<0.001
<b>Women</b>				
0.1 unit	1.19 (0.97-1.47)	0.10	1.11 (0.90-1.38)	0.32
Quartile	1.12 (1.0-1.25)	0.06	1.08 (0.96-1.21)	0.21

**Supplemental Table IV:** The risk of future cardiovascular events (CVE), expressed as hazard ratio (95% confidence interval), associated with the B/T ratio per 0.1 unit and quartile increase, respectively. The analysis is performed in men and women, separately and adjusted for diabetes, hypertension, hypercholesterolemia, BMI and smoking. Further adjustments were made for hormone replacement therapy in women.

**Interaction analysis****Supplemental Table V:** Interaction analysis of the risk of future CVE associated with combined exposures of sex and IL6 trans-signalling

	<b>Women</b>		<b>Men</b>	
	N with/without CVE	RR (95% CI); P	N with/without CVE	RR (95% CI); P
<b>B/T ≤median</b>	117/952	1.0	130/610	1.69 (1.31-2.17); P<0.001
<b>B/T &gt;median</b>	116/729	1.20 (0.93-1.56); P= 0.16	267/698	2.74 (2.20-3.41); P<0.001

**RERI** (95% CI) = 0.85 (0.36 - 1.35); P<0.001

**AP** (95% CI) = 0.31 (0.14-0.48); P<0.001

**Supplemental Table V.** Risk of CVE, expressed as hazard ratio (HR) with 95% confidence interval (CI), for combined exposures of sex and the B/T ratio. Reference group: women; B/T ratio ≤median (HR=1.0). HR, relative excess risk due to interaction (RERI) and attributable proportion (AP) are adjusted for diabetes, hypertension, hypercholesterolemia, BMI, smoking and hormone replacement therapy (in women).