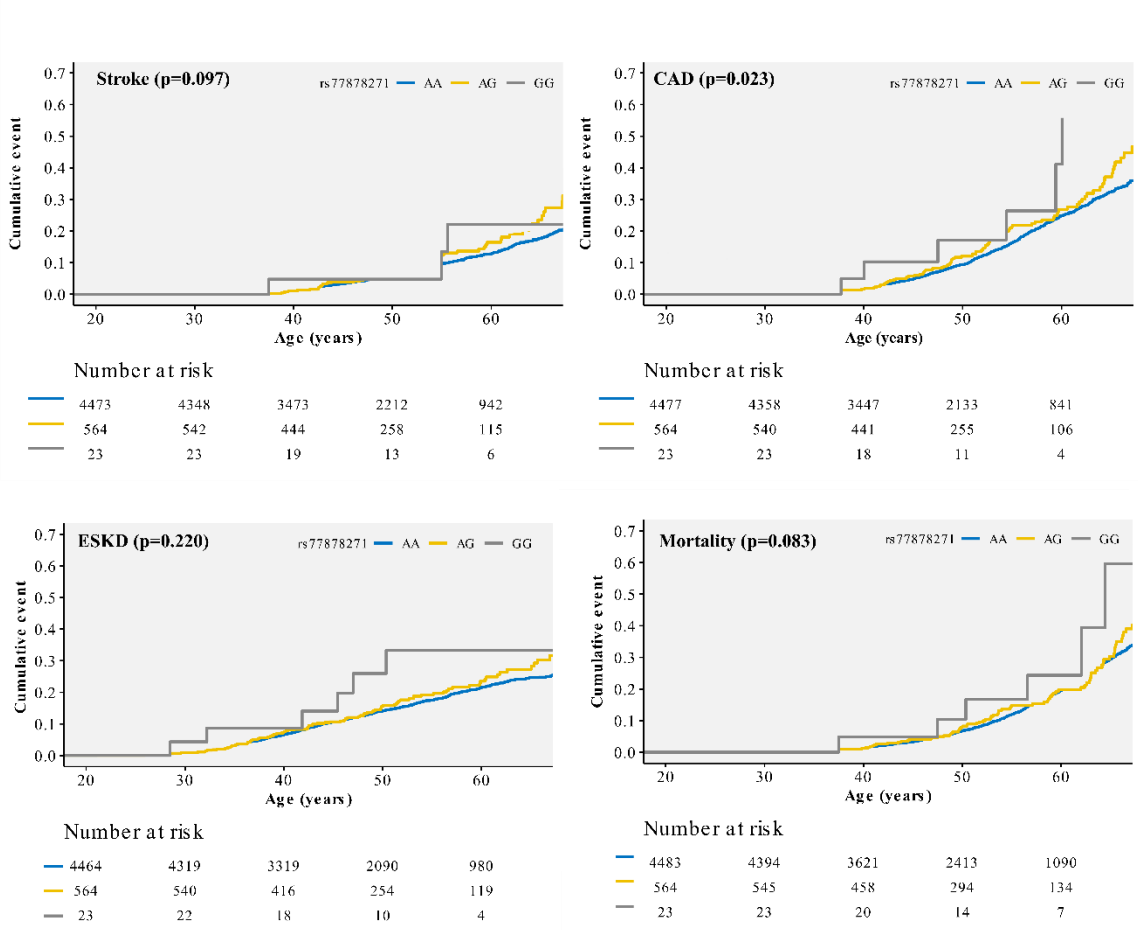
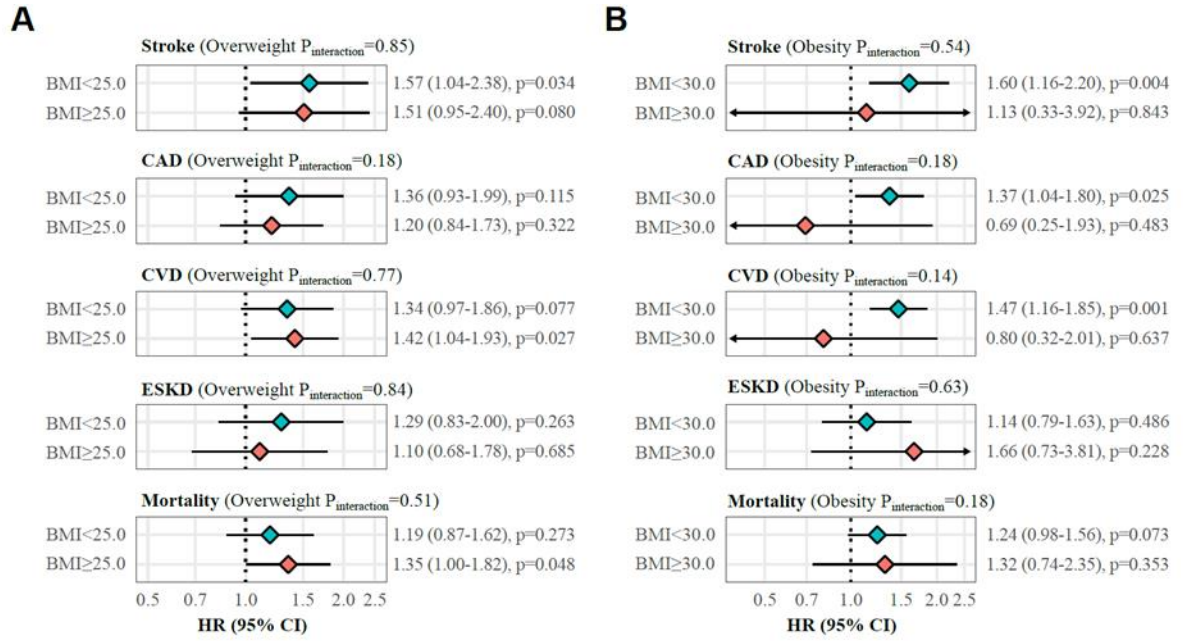
Online Supplemental data

The low-expression variant of *FABP4* is associated with cardiovascular disease in type 1 diabetes

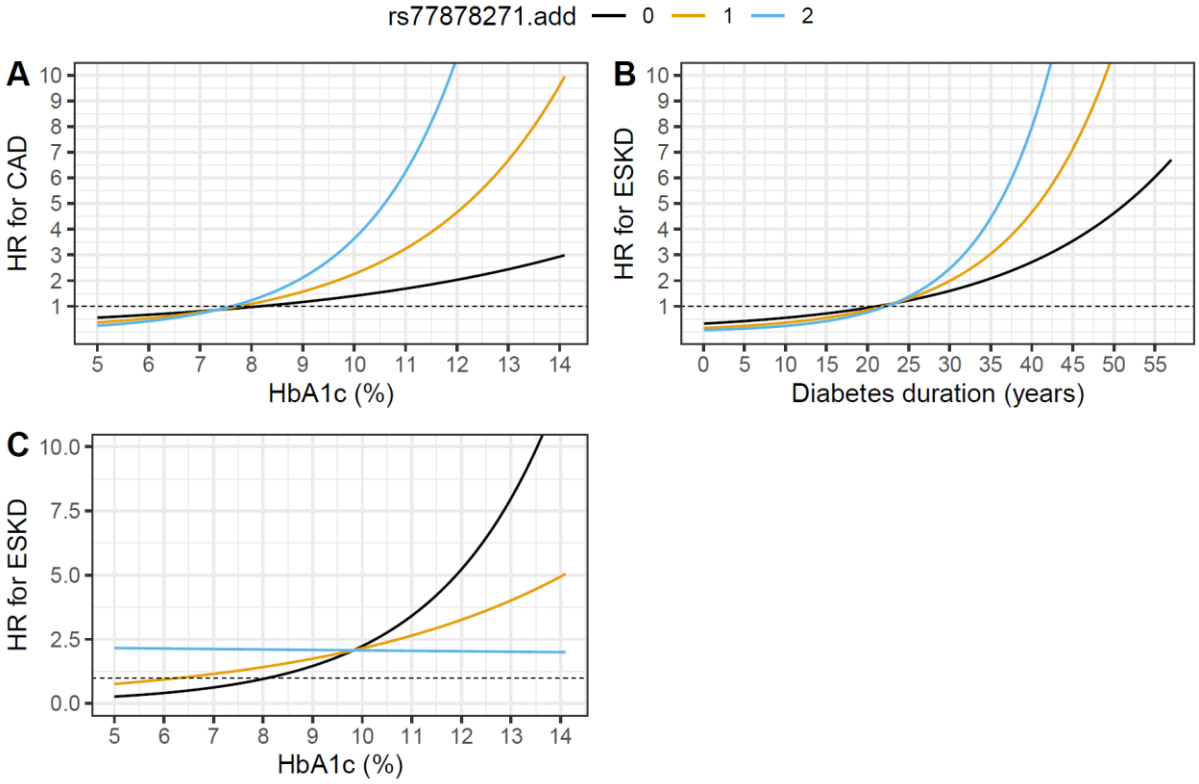
FIGURES



Supplemental Figure 1: Cumulative events for Stroke, CAD, CVD, ESRD followed from birth, stratified by FABP4 rs78778271 genotypes. CAD= coronary artery disease, ESKD=End-stage kidney disease. P-value by Log-rank test.

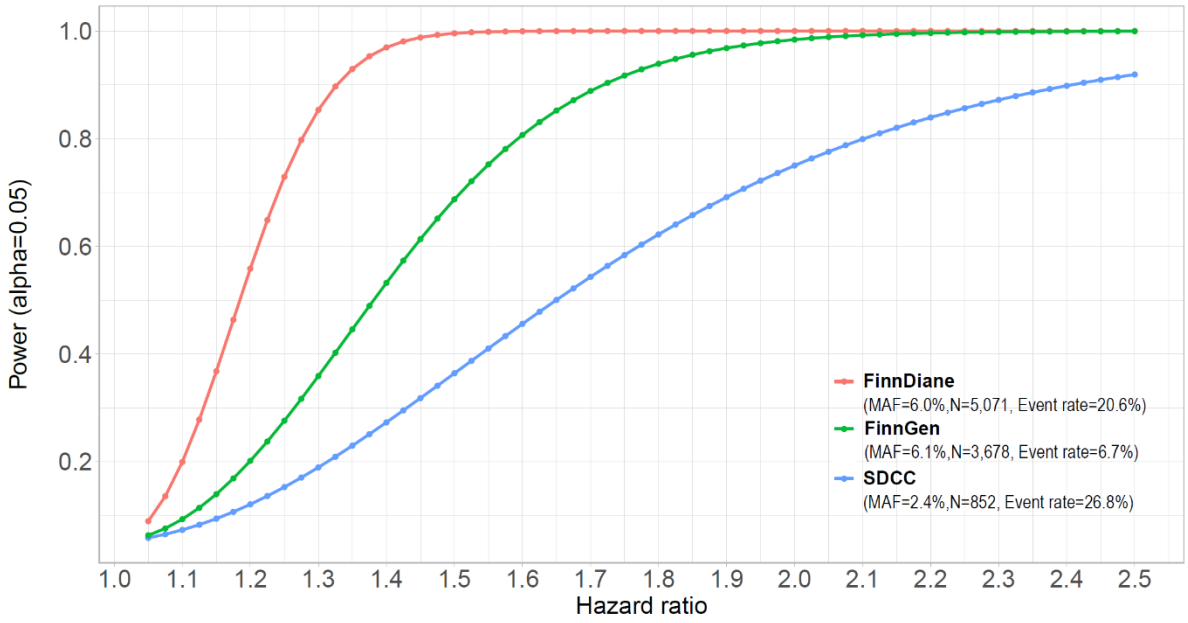


Supplemental Figure 2: **Effect of rs77878271 on outcomes stratified by a) overweight (BMI>25) and b) obesity (BMI>30).** CAD= Coronary artery disease, CVD=Cardiovascular disease, ESKD= End-stage kidney disease. Hazard ratios are from Cox regression analyses adjusted for age, sex and diabetes duration, lipid-lowering medication and RAAS blockers. Participants with underweight (BMI<18.5 kg/m^2) removed prior analysis.



Supplemental Figure 3 Effect of rs77878271 on A) CAD from Cox model with interaction with HbA1c B) ESKD from Cox model with interaction with Diabetes duration and C) ESKD from Cox model with interaction with HbA1c. Analyses additionally adjusted for age, sex, diabetes

duration (in B diabetes duration was only included as an interaction term), lipid lowering medication and ARBs medication. CAD= coronary artery disease, ESKD=End-stage kidney disease.



Supplemental Figure 4. Power curves for the study cohorts (FinnDiane, SDCC and FinnGen). Additive model assumed.

TABLES

Supplemental Table 1: Classification of diabetic nephropathy stage in the FinnDiane cohort based on the urinary albumin excretion rate (AER) or albumin-to-creatinine ratio (ACR). Albuminuria was confirmed in two out of three timed overnight or 24h urine collections or in morning spot urine samples for ACR. If classified as "normal AER", the participants' medical files were carefully reviewed to assure that regression of albuminuria due to antihypertensive treatment had not taken place.

Urine specimen	**Normal AER**	**Microalbuminuria**	**Macroalbuminuria**
24-hour urine collections	AER<30 mg/24h	AER ≥30 and <300 mg/24h	AER ≥300 mg/24h
Timed overnight	AER<20 µg/min	AER≥20 and <200 µg/min	AER ≥200 µg/min
Morning spot urine samples (men)	ACR<2.5 mg/mmol	ACR≥2.5 and <25 mg/mmol	ACR ≥25 mg/mmol
Morning spot urine samples (women)	ACR <3.5 mg/mmol	ACR≥3.5 and <35 mg/mmol	ACR ≥35 mg/mmol

Supplemental Table 2 Median age at end of follow-up and incidence rates for CVD as well as the MAF and the p-value for deviation from the Hardy Weinberg Equilibrium (P_{HWE}) for rs77878271 in the study cohorts. Median age at follow-up was calculated as years from birth the CVD event date or, if no CVD event occurred, from birth to death date or data retrieval date (December 31, 2014 in FinnDiane, December 31, 2015 in SDCC and December 31, 2019 in FinnGen).

Study cohort	Median age at CVD follow-up	Data retrieval date	CVD incidence rate	MAF	P_{HWE}
FinnDiane	49.4 years (IQR 40.8-57.7)	Dec 31, 2014	20.6%	6.0%	0.30
FinnGen	39.9 years (IQR 32.1-52.1)	Dec 31, 2019	6.7 %	6.1%	0.27
SDCC	55.9 years (IQR 49.1-63.7)	Dec 31, 2015	26.7%	2.4%	0.40

Supplemental Table 3. *FABP4* rs77878271 associations with lipid variables in FinnDiane participants. Unadjusted and adjusted (age, sex, diabetes duration, BMI and lipid-lowering medication) effect estimates from linear regression model.

Lipid	Model	Effect size (95%CI)	P-value
HDL cholesterol, mmol/l	unadjusted	-0.017 (-0.051-0.018)	0.34
	adjusted	-0.009 (-0.042-0.023)	0.57
Triglycerides, mmol/l	unadjusted	-0.021 (-0.108-0.033)	0.30
	adjusted	-0.021 (-0.135-0.005)	0.07
Total cholesterol, mmol/l	unadjusted	-0.021 (-0.103-0.060)	0.61
	adjusted	-0.021 (-0.103-0.061)	0.62
LDL cholesterol, mmol/l	unadjusted	0.005 (-0.068-0.078)	0.90
	adjusted	0.011 (-0.062-0.085)	0.76
Apo B, g/l	unadjusted	0.053 (-1.955-2.061)	0.96
	adjusted	-0.366 (-2.342-1.610)	0.72
Apo A1, g/l	unadjusted	-1.034 (-3.031-0.963)	0.31
	adjusted	-0.597 (-2.521-1.327)	0.54
HDL-2 cholesterol, mmol/l	unadjusted	-0.006 (-0.031-0.018)	0.62
	adjusted	-0.003 (-0.026-0.021)	0.82
HDL-3 cholesterol, mmol/l	unadjusted	0.005 (-0.013-0.024)	0.55
	adjusted	0.008 (-0.010-0.026)	0.40

Supplemental Table 4. Clinical characteristics of SDCC participants genotype at the baseline examination. For continuous variables, data are reported as median with 1st and 3rd quartiles. For categorical variables, data are reported as number and percentage

Clinical characteristics	SDCC (n = 852)	FinnDiane (n =5,077)
Men, n (%)	490 (57.5)	2661 (52.4)
Age, years	42.5 (35.0-51.2)	38.9 (29.7-48.2)
Diabetes duration, years	26.0 (20.5-34.0)	22.8 (13.1-32.3)

Diabetes onset age, years	14.1 (8.9-22.5)	14.0 (9.0-22.3)
Systolic blood pressure, mmHg	137 (124 -151)	132 (121-145)
Diastolic blood pressure, mmHg	79 (72-86)	80.0 (72-86)
Ever smoked, n (%)	736 (86.4)	2152 (47.4)
HbA_{1c}, %	8.80 (7.90-9.60)	8.3 (7.4-9.3)
eGFR, ml/min/1.73m^2	96.75 (74.3-109.5)	88.6 (69.4-106.0)
BMI, kg/m^2	23.88 (22.1-25.9)	24.7 (22.6-27.0)
Overweight, n (%)	246 (28.9)	1768 (36.8)
Obesity, n (%)	49 (5.8)	451 (9.4)
Antihypertensive medication, n (%)	371 (45.8)	1991 (41.8)
RAAS-blockers (ACEi+ARBs), n (%)	258 (31.8)	1618 (33.0)
Lipid-lowering medication, n (%)	688 (84.7)	737 (15.1)
Total cholesterol, mmol/l	5.10 (4.50-5.90)	4.85 (4.24-5.50)
HDL cholesterol, mmol/l	1.49 (1.20-1.85)	1.31 (1.09-1.59)
Triglycerides, mmol/l	0.96 (0.70-1.46)	1.03 (0.77-1.48)
Normal AER, n (%)	425 (50.3)	3007 (62.7)
Microalbuminuria, n (%)	113 (13.4)	608 (12.7)
Macroalbuminuria, n (%)	307 (36.3)	758 (15.8)
ESKD, n (%)	0 (0.0)	785 (15.5)

Supplemental Table 5: FABP4 rs77878271 and risk of outcomes in the SDCC study.

Outcome	Model	Time scale	N events	HR (95%CI)	P-value
Follow-up time from birth:					
CAD	unadjusted	years from birth	145	1.32 (0.72-2.40)	0.37
	Adjusted*	years from birth	145	1.51 (0.83-2.74)	0.17
Stroke	unadjusted	years from birth	108	1.30 (0.66-2.54)	0.45
	Adjusted*	years from birth	108	1.44 (0.75-2.79)	0.28
CVD	unadjusted	years from birth	228	1.32 (0.82-2.12)	0.25
	Adjusted*	years from birth	228	1.49 (0.94-2.38)	0.09
ESKD	unadjusted	years from birth	148	1.29 (0.70-2.37)	0.41
	Adjusted*	years from birth	148	1.43 (0.78-2.62)	0.25
Mortality	unadjusted	years from birth	346	0.91 (0.58-1.44)	0.69
	Adjusted*	years from birth	346	1.03 (0.66-1.61)	0.90
Follow-up time from visit:					
CAD	unadjusted	years from visit	145	1.59 (0.86-2.93)	0.14
	model 1	years from visit	145	1.48 (0.81-2.71)	0.20
	model 2	years from visit	136	1.42 (0.77-2.64)	0.26
	model 3	years from visit	144	1.3 (0.71-2.38)	0.40
Stroke	unadjusted	years from visit	108	1.61 (0.81-3.21)	0.17
	model 1	years from visit	108	1.51 (0.77-2.94)	0.23
	model 2	years from visit	105	1.41 (0.71-2.79)	0.33
	model 3	years from visit	106	1.28 (0.66-2.49)	0.46
CVD	unadjusted	years from visit	228	1.51 (0.95-2.39)	0.08
	model 1	years from visit	228	1.51 (1.02-1.05)	0.09
	model 2	years from visit	217	1.45 (0.90-2.35)	0.13
	model 3	years from visit	225	1.33 (0.83-2.13)	0.23
Mortality	unadjusted	years from visit	346	1.12 (0.71-1.77)	0.63
	model 1	years from visit	346	1.02 (0.65-1.59)	0.95
	model 2	years from visit	323	0.9 (0.56-1.45)	0.68
	model 3	years from visit	341	0.83 (0.53-1.30)	0.41

*Adjusted for diabetes diagnosis age and sex. CAD= Coronary artery disease, CVD=Cardiovascular disease, ESKD= End-stage kidney disease. Model 1: adjusted for age, sex, diabetes duration. Model 2: Model 1+ lipid lowering medication and ARBs medication. Model 3: Model 1+ nephropathy stage (normo-, micro-, macroalbuminuria or ESKD).

Supplemental Table 6: P-values for interactions between FABP4 rs77878271 and diabetes onset age on the risk of stroke, coronary artery disease (CAD), cardiovascular disease (CVD; combined stroke+CAD), end-stage kidney disase (ESKD) and mortality. Other covariates in the cox regression

model: diabetes duration (in interaction analyses with diabetes duration; diabetes duration was only included only as an interaction term), lipid lowering medication and ARBs medication.

Interaction term	Outcome	P interaction
rs77878271 * diabetes onset age	Stroke	0.25
rs77878271 * diabetes onset age	CAD	0.72
rs77878271 * diabetes onset age	CVD	0.28
rs77878271 * diabetes onset age	ESRD	0.55
rs77878271 * diabetes onset age	Mortality	0.46
rs77878271 * diabetes duration	Stroke	0.55
rs77878271 * diabetes duration	CAD	0.74
rs77878271 * diabetes duration	CVD	0.83
rs77878271 * diabetes duration	ESRD	0.03
rs77878271 * diabetes duration	Mortality	0.08
rs77878271 * HbA1c	Stroke	0.55
rs77878271 * HbA1c	CAD	0.04
rs77878271 * HbA1c	CVD	0.14
rs77878271 * HbA1c	ESRD	0.04
rs77878271 * HbA1c	Mortality	0.41
rs77878271 * BMI	Stroke	0.93
rs77878271 * BMI	CAD	0.86
rs77878271 * BMI	CVD	0.44
rs77878271 * BMI	ESKD	0.47
rs77878271 * BMI	Mortality	0.89

CAD= Coronary artery disease, CVD=Cardiovascular disease, ESKD= End-stage kidney disease, BMI= Body Mass Index.

Supplemental Table 7: Physicians and nurses at health care centers participating in the collection of FinnDiane patients.

FinnDiane Study Centers	Physicians and nurses
Anjalankoski Health Centre	S. Koivula, T. Uggeldahl
Central Finland Central Hospital, Jyväskylä	T. Forslund, A. Halonen, A. Koistinen, P. Koskiaho, M. Laukkanen, J. Saltevo, M. Tiihonen
Central Hospital of Åland Islands, Mariehamn	M. Forsen, H. Granlund, A-C. Jonsson, B. Nyroos
Central Hospital of Kanta-Häme, Hämeenlinna	P. Kinnunen, A. Orvola, T. Salonen, A. Vähänen
Central Hospital of Länsi-Pohja, Kemi	H. Laukkanen, P. Nyländen, A. Sademies

Central Ostrabothnian Hospital District, Kokkola	S. Anderson, B. Asplund, U. Byskata, P. Liedes, M. Kuusela, T. Virkkala
City of Espoo Health Centre	
Espoonlahti	A. Nikkola, E. Ritola
Tapiola	M. Niska, H. Saarinen
Samaria	E. Oukko-Ruponen, T. Virtanen
Viherlaakso	A. Lyytinen
City of Helsinki Health Centre	
Puistola	H. Kari, T. Simonen
Suutarila	A. Kaprio, J. Kärkkäinen, B. Rantaeskola
Töölö	P. Kääriäinen, J. Haaga, A-L. Pietiläinen
City of Hyvinkää Health Centre	S. Klemetti, T. Nyandoto, E. Rontu, S. Satuli-Autere
City of Vantaa Health Centre	
Korso	R. Toivonen, H. Virtanen
Länsimäki	R. Ahonen, M. Ivaska-Suomela, A. Jauhiainen
Martinlaakso	M. Laine, T. Pellonpää, R. Puranen
Myyrmäki	A. Airas, J. Laakso, K. Rautavaara
Rekola	M. Erola, E. Jatkola
Tikkurila	R. Lönnblad, A. Malm, J. Mäkelä, E. Rautamo
Heinola Health Centre	P. Hentunen, J. Lagerstam
Helsinki University Central Hospital, Department of Medicine, Division of Nephrology	A. Ahola, J. Fagerudd, M. Feodoroff, D. Gordin, O. Heikkilä, K Hietala, L. Kyllönen, J. Kytö, S. Lindh, K. Pettersson-Fernholm, M. Rosengård-Bärlund, M. Rönnback, A. Sandelin, A-R Salonen, L. Salovaara, L. Thorn, J. Tuomikangas, T. Vesisenaho, J. Wadén
Herttoniemi Hospital, Helsinki	V. Sipilä
Hospital of Lounais-Häme, Forssa	T. Kalliomäki, J. Koskelainen, R. Nikkanen, N. Savolainen, H. Sulonen, E. Valtonen
Iisalmi Hospital	E. Toivanen
Jokilaakso Hospital, Jämsä	A. Parta, I. Pirttiniemi
Jorvi Hospital, Helsinki University Central Hospital	S. Aranko, S. Ervasti, R. Kauppinen-Mäkelin, A. Kuusisto, T. Leppälä, K. Nikkilä, L. Pekkonen
Jyväskylä Health Centre, Kyllö	K. Nuorva, M. Tiihonen
Kainuu Central Hospital, Kajaani	S. Jokelainen, P. Kemppainen, A-M. Mankinen, M. Sankari
Kerava Health Centre	H. Stuckey, P. Suominen
Kirkkonummi Health Centre	A. Lappalainen, M. Liimatainen, J. Santaholma
Kivelä Hospital, Helsinki	A. Aimolahti, E. Huovinen
Koskela Hospital, Helsinki	V. Ilkka, M. Lehtimäki
Kotka Heath Centre	E. Pälikkö-Kontinen, A. Vanhanen
Kouvola Health Centre	E. Koskinen, T. Siitonen
Kuopio University Hospital	E. Huttunen, R. Ikäheimo, P. Karhapää, P. Kekäläinen, M. Laakso, T. Lakka, E. Lampainen, L. Moilanen, L. Niskanen, U. Tuovinen, I. Vauhkonen, E. Voutilainen
Kuusamo Health Centre	T. Kääriäinen, E. Isopoussu
Kuusankoski Hospital	E. Kilkki, I. Koskinen, L. Riihelä
Laakso Hospital, Helsinki	T. Meriläinen, P. Poukka, R. Savolainen, N. Uhlenius
Lahti City Hospital	A. Mäkelä, M. Tanner
Lapland Central Hospital, Rovaniemi	L. Hyvärinen, S. Severinkangas, T. Tulokas
Lappeenranta Health Centre	P. Linkola, I. Pulli
Lohja Hospital	T. Granlund, M. Saari, T. Salonen

Loimaa Health Centre	A. Mäkelä, P. Eloranta
Länsi-Uusimaa Hospital, Tammisaari	I-M. Jousmaa, J. Rinne
Malmi Hospital, Helsinki	H. Lanki, S. Moilanen, M. Tilly-Kiesi
Mikkeli Central Hospital	A. Gynther, R. Manninen, P. Nironen, M. Salminen, T. Vänttinen
Mänttä Regional Hospital	I. Pirttiniemi, A-M. Hänninen
North Karelian Hospital, Joensuu	U-M. Henttula, P. Kekäläinen, M. Pietarinen, A. Rissanen, M. Voutilainen
Nurmijärvi Health Centre	A. Burgos, K. Urtamo
Oulankangas Hospital, Oulainen	E. Jokelainen, P-L. Jylkkä, E. Kaarlela, J. Vuolaspuro
Oulu Health Centre	L. Hiltunen, R. Häkkinen, S. Keinänen-Kiukaanniemi
Oulu University Hospital	R. Ikäheimo
Päijät-Häme Central Hospital	H. Haapamäki, A. Helanterä, S. Hämäläinen, V. Ilvesmäki, H. Miettinen
Palokka Health Centre	P. Sopanen, L. Welling
Pieksämäki Hospital	V. Javtsenko, M. Tamminen
Pietarsaari Hospital	M-L. Holmbäck, B. Isomaa, L. Sarelin
Pori City Hospital	P. Ahonen, P. Merensalo, K. Sävelä
Porvoo Hospital	M. Kallio, B. Rask, S. Rämö
Raahe Hospital	A. Holma, M. Honkala, A. Tuomivaara, R. Vainionpää
Rauma Hospital	K. Laine, K. Saarinen, T. Salminen
Riihimäki Hospital	P. Aalto, E. Immonen, L. Juurinen
Salo Hospital	A. Alanko, J. Lapinleimu, P. Rautio, M. Virtanen
Satakunta Central Hospital, Pori	M. Asola, M. Juhola, P. Kunelius, M-L. Lahdenmäki, P. Pääkkönen, M. Rautavirta
Savonlinna Central Hospital	E. Korpi-Hyövälti, T. Latvala, E. Leijala
South Karelia Central Hospital, Lappeenranta	T. Ensala, E. Hussi, R. Härkönen, U. Nyholm, J. Toivanen
Tampere Health Centre	A. Vaden, P. Alarotu, E. Kujansuu, H. Kirkkopelto-Jokinen, M. Helin, S. Gummerus, L. Calonius, T. Niskanen, T. Kaitala, T. Vatanen
Tampere University Hospital	I. Ala-Houhala, T. Kuningas, P. Lampinen, M. Määttä, H. Oksala, T. Oksanen, K. Salonen, H. Tauriainen, S. Tulokas
Tiirismaa Health Centre, Hollola	T. Kivelä, L, Petlin, L. Savolainen
Turku Health Centre	I. Hämäläinen, H. Virtamo, M. Vähätalo
Turku University Central Hospital	K. Breitholz, R. Eskola, K. Metsärinne, U. Pietilä, P. Saarinen, R. Tuominen, S. Äyräpää
Vaajakoski Health Centre	K. Mäkinen, P. Sopanen
Valkeakoski Regional Hospital	S. Ojanen, E. Valtonen, H. Ylönen, M. Rautiainen, T. Immonen
Vammala Regional Hospital	I. Isomäki, R. Kroneld, M. Tapiolinna-Mäkelä
Vaasa Central Hospital	S. Bergkulla, U. Hautamäki, V-A. Myllyniemi, I. Rusk