

**SUPPLEMENTARY MATERIAL**

**BLOOD PRESSURE AND RISK OF CANCER IN THE EUROPEAN PROSPECTIVE**

**INVESTIGATION INTO CANCER AND NUTRITION**

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**SUPPLEMENTARY TABLES****Supplementary Table 1 Definition of cancer locations at anatomical sites and morphological subtypes**

<b>Cancer location Subtype</b>	<b>Topographical codes</b>	<b>Morphology (specific codes)</b>	<b>Rare morphologies (excluded codes)</b>	<b>Note</b>
<b>Head and Neck</b>	C02, C03, C04, C05, C06, C09, C10, C11, C12, C13, C14.0, C30, C32	-	8800, 8850, 9120, 9220, 9591, 9673, 9680, 9690, 9691, 9734	89% (n=605) SCC
Mouth and oropharynx	C02, C03, C04, C05, C06, C09, C10,	-	as for Head & Neck	90% (n=297) SCC
Larynx	C32	-	as for Head & Neck	93% (n=221) SCC
<b>Digestive system</b>				
<b>Esophagus</b>	C15	-	8170, 8720, 9591	
Esophageal AC	C15	8140, 8144	-	
Esophageal SCC	C15	8070, 8071, 8072	-	
<b>Stomach</b>	C16	-	8560, 8800, 8891, 8936, 9590, 9591, 9595, 9663, 9670, 9676, 9680, 9699, 9702, 9711, 9715, 9823	
Gastric AC	C16	8140	-	
<b>Colorectal</b>	C18, C19, C20	-	8240, 8241, 8243, 8245, 8246, 8472, 8743, 8936, 9680, 9699	75% (n=3,489) code 8140
Colon	C18	-	as for Colorectal	72% (n=2,175) code 8140
Rectum and rectosigmoid junction	C19, C20	-	as for Colorectal	81% (n=1,314) code 8140
<b>Liver</b>	C22, C23, C24	-	9120, 9130, 9590, 9680	##
Hepatocellular Cancer	C22.0	8170, 8180	-	
Gallbladder and bile ducts	C22.1, C23, C24			
<b>Pancreas</b>	C25	-	8150, 8151, 8152, 8246, 9591	
<b>Respiratory system</b>				
<b>Lung</b>	C34	-	8710, 8800, 8801, 8990, 9050, 9120, 9133, 9591, 9680, 9699	
Lung AC	C34	8140, 8144, 8230, 8250, 8253, 8254, 8256, 8257, 8260, 8265, 8333, 8480, 8551	-	91% (n=1,027) code 8140
Lung SCC	C34	8070, 8071, 8072, 8083	-	
Lung SmallCC	C34	8041, 8045	-	

Lung (other morphology)	C34	any not excluded and not included above		***
<b>Urinary system</b>				
<b>Kidney</b>	C64	-	8800, 8830, 8890, 8964	
<b>Renal pelvis and ureter</b>	C65, C66	-		*
<b>Bladder</b>	C67	-	8800, 8801, 8980, 9590, 9671	#
<b>Reproductive system</b>				
<b>Prostate (men)</b>	C61	-		
<b>Breast (women)</b>	C50 (women)	-	8801, 8804, 8810, 8980, 8982, 9020, 9120, 9590, 9675, 9690, 9691	
<b>Ovary (women)</b>	C56, C48, C57.0	-	8890, 8980, 9680	
<b>Corpus uteri (women)</b>	C54 (women)	-	8890, 8930, 8931, 8933, 8935, 8950, 8951, 8980, 9100	**
Uterine AC	C54 (women)	8140	-	
Endometroid AC	C54 (women)	8380	-	
<b>Cervix uteri (women)</b>	C53	-	-	
Cervix SCC	C53	8070, 8071, 8072, 8076, 8083	-	###
Cervix AC	C53	8140	-	###
Cervix (other morphology)	C53	any not accounted for above	-	
<b>Anogenital (not cervix)</b>	C21, C51, C52, C60	-	-	
Anogenital SCC	C21, C51, C52, C60	8070, 8071, 8072, 8083	-	
<b>Skin</b>				
<b>Skin (SCC)</b>	C44	8070, 8071, 8072, 8083	-	
<b>Melanoma (skin)</b>	C44	8720 – 8780	-	
<b>Nervous and endocrine system</b>				
<b>Brain and central nervous system</b>	C70, C71, C72	-	8420, 8510, 9120, 9150, 9473, 9490, 9590, 9591, 9680, 9702, 9732	
Glioblastoma	C71	9440		
<b>Thyroid</b>	C73	-	8012, 8021, 8041, 8345, 8510, 8511, 9680	
<b>Hematopoietic system</b>				
<b>Leukemia</b>	C42	9700 – 9709, 9731 – 9989	-	
Multiple myeloma	C42	9731, 9732	-	
<b>Lymphoma (all types)</b>	C77	9590 – 9595, 9650 – 9761, 9820 – 9837, 9940 – 9945	-	
Non-Hodgkin Lymphomas	C77	9591, 9670 – 9719	-	
<b>Other</b>				
<b>Other location AC</b>	any not included above	8140		

<b>Other location or morphology</b>	any remaining, not accounted for above	any not accounted for above, including rare morphologies		
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The order of the main anatomical sites, as in Figure 2, is according to the hazard ratio estimates for systolic blood pressure from the main adjusted analyses (specific locations and morphologies follow the relevant main anatomical site and other locations are listed last); All morphological codes had behavioural code 3 (xxxx/3) according to the International Classification of Diseases for Oncology (ICD-O) (<http://codes.iarc.fr/abouticdo.php>; Accessed: 24/01/2019); **AC** – adenocarcinoma; **SCC** – squamous cell carcinoma; **SmallCC** – small cell carcinoma; \* renal pelvis and ureter cancers (n=112 cases) were 93% (n=104) with transitional-cell morphology (codes 8120/3 or 8130/3); \*\* corpus uteri cancers (n=1164) included 42% (n=488) AC (code 8140/3) and 47% (n=546) endometroid adenocarcinoma (code 8380/3); \*\*\* lung (other morphology) (n=1107) included: 50% (n=550) undifferentiated or unspecified (codes 8000/3, 8010/3 or 8020/3), 19% (n=207) non-small cell carcinoma (code 8046/3); # bladder cancers (n=1,192) comprised 89% (n=1,058) transitional-cell morphology (codes 8120/3 or 8130/3); ## liver cancers (n=653) comprised: 47% (n=307) cancers of the liver parenchyma (of which 62% (n=191) were with hepatocellular morphology), 11% (n=71) cancers of the intrahepatic bile ducts, 13% (n=86) cancers of the gallbladder, 29% (n=189) cancers of the extrahepatic bile ducts; ### cervical AC (n=37) and cervix (other morphology) (n=41) were considered only in the main analyses for continuous blood pressure variables, due to the small number of cases.

**Supplementary Table 2 Categories of blood pressure and adjustment variables**

Variable (units of measurement)	Categories used in models
hypertension (dichotomous)	SBP $\geq$ 140 mmHg, or DBP $\geq$ 90 mmHg at BP measurement visit, or self-reported hypertension
hypertension (American Society for Hypertension)	pre-hypertension (SBP 120–139 mmHg or DBP in 80–89 mmHg); hypertension stage I (SBP 140-159mmHg or DBP 90-99mmHg); hypertension stage II (SBP >160mmHg or DBP >100mmHg)
hypertension (European Society for Hypertension)	optimal (SBP<120mmHg and DBP<80mmHg); normal (SBP 120-129mmHg and DBP 80-84mmHg); high normal (SBP 130-139mmHg and/or DBP 85-89mmHg); grade I hypertension (SBP 140-159mmHg or DBP 90-99mmHg); grade II hypertension (SBP 160-179mmHg or DBP 100-109mmHg); grade III hypertension (SBP $\geq$ 180mmHg or DBP $\geq$ 110mmHg) and isolated systolic hypertension (elevated SBP with normal DBP)
mean blood pressure (MBP)	Cohort-wide quartiles (cut-points at: 88.8, 96.7, 106.0 mmHg)
sex	men, women
body mass index (kg/m <sup>2</sup> )	cohort-wide quintiles (cut-points at: 22.3, 24.3, 26.2, 28.9 kg/m <sup>2</sup> )
diabetes mellitus (self-reported)	yes, no, missing
educational attainment	none, primary school, technical/professional school, secondary school, longer education, missing
physical activity	inactive, moderately inactive, moderately active, active
smoking status	never, former, current smoker $\leq$ 20 pack years, current smoker >20 pack years, missing
alcohol intake (g/day)	cohort-wide quintiles (cut-points at: 0.6, 3.5, 9.4, 20.6 g/day)
fruit consumption (g/day)	cohort-wide quintiles (cut-points at: 92, 155, 236, 345 g/day)
vegetable consumption (g/day)	cohort-wide quintiles (cut-points at: 93, 137, 193, 290 g/day)
red meat consumption (g/day)	cohort-wide quintiles (cut-points at: 16.5, 32.7, 50.9, 75.6 g/day)
age at first period (menarche) (years)*	<12 years, 12-15 years, >15 years, missing
age at first full-term pregnancy (years)*	$\leq$ 21 years, 21-30 years, >30 years, missing
number of full-term pregnancies *	0, 1, 2, 3, $\geq$ 4, missing
menopausal status *	pre-menopausal (self-reported or age at recruitment <46 years if missing), peri-menopausal or unknown, physiological post-menopausal (self-reported or age $\geq$ 55 years if missing), surgical post-menopausal (self-reported)
age at menopause (years) *	<40 years, 40-46 years, 46-50 years, 50-56 years, >56 years, missing or not relevant
oral contraceptives use *	never, former, current, missing
hormone replacement therapy use *	never, former, current, missing

\* reproductive variables used for adjustment in female cancers (breast, ovary, cervix and corpus uteri)

Supplementary Table 3 EPIC cohort characteristics, cancer cases and blood pressure categories by country

	<b>Total</b>	<b>Denmark</b>	<b>France</b>	<b>Germany</b>	<b>Greece</b>	<b>Italy</b>	<b>Netherlands</b>	<b>Spain</b>	<b>Sweden</b>	<b>UK</b>
<b>Cohort size: N</b>	307318	54961	19195	33048	25854	43109	36517	6273	48184	40177
<b>Age at recruitment, years: mean (SD)</b>	52.5 (9.9)	56.7 (4.4)	52.8 (6.5)	50.3 (8.8)	53.1 (12.6)	50.5 (7.9)	49 (11.9)	50.3 (8.4)	52 (10.9)	54.6 (11.5)
<b>Female: N (%)</b>	194727 (63.4)	28691 (52.2)	19195 (100)	19342 (58.5)	15123 (58.5)	29659 (68.8)	26890 (73.6)	4231 (67.4)	26119 (54.2)	25477 (63.4)
<b>Person years: mean (SD) #</b>	13.7 (4.4)	14.8 (4.1)	9.8 (2.4)	9.6 (2.7)	10.8 (3.7)	14.1 (3.1)	14.4 (3.3)	14.6 (2.8)	16.4 (5)	14.7 (4)
<b>Cancer cases: N</b>										
Any malignant cancer	39298	11043	1256	2551	1266	4551	3767	604	8479	5781
<b>Head and neck</b>										
Head and neck (combined)	683	261	0	51	22	72	69	19	116	73
* Mouth and oropharynx	332	131	0	21	3	31	35	5	67	39
* Larynx	239	95	0	18	16	31	22	9	27	21
<b>Digestive system</b>										
Esophagus	387	133	1	17	4	11	42	4	67	108
* Esophageal AC	176	50	0	7	2	3	15	1	31	67
* Esophageal SCC	149	58	1	7	1	6	18	2	30	26
Stomach	738	169	4	58	62	129	61	15	150	90
* Gastric AC	403	98	1	11	9	52	29	5	123	75
Colorectal	4625	1317	96	267	126	562	510	89	921	737
* Colon	3003	804	63	165	82	417	328	68	592	484
* Rectum and rectosigmoid junction	1622	513	33	102	44	145	182	21	329	253
Liver and bile ducts	653	177	2	57	56	108	42	12	134	65
* HCC	191	48	0	19	14	38	7	1	41	23
* Gallbladder and bile ducts	346	89	2	31	22	48	33	7	74	40
Pancreas	990	325	16	70	44	102	96	13	203	121
<b>Respiratory system</b>										
Lung (combined)	3229	1257	1	193	175	293	338	37	548	387
* Lung AC	1130	485	1	69	33	107	109	8	220	98
* Lung SCC	613	246	0	31	20	46	65	8	108	89
* Lung SmallCC	379	198	0	32	16	21	62	5	2	43
* Lung (other morphology)	1107	328	0	61	106	119	102	16	218	157
<b>Urinary system</b>										
Kidney	758	185	1	96	29	122	70	11	138	106
Renal pelvis and ureter	112	41	0	3	1	8	10	1	29	19
Bladder	1192	260	2	80	56	134	65	32	403	160
<b>Reproductive system</b>										
Prostate	5848	1878	0	495	96	459	214	93	1817	796
Breast (female)	8154	1863	830	478	240	1174	1043	103	1301	1122
* Breast pre-menopausal	256	0	0	39	28	60	42	5	41	41
* Breast post-menopausal	4786	1451	388	263	142	534	582	38	715	673
Ovary	1007	224	55	51	44	129	132	11	175	186

	Total	Denmark	France	Germany	Greece	Italy	Netherlands	Spain	Sweden	UK
Corpus uteri	1164	262	68	64	19	175	140	35	243	158
* Uterine AC	488	22	21	4	6	103	37	8	229	58
* Endometroid AC	546	204	42	52	5	52	87	22	4	78
Cervix uteri	223	56	2	21	21	26	32	7	33	25
* Cervix SCC	145	44	0	14	7	16	22	6	23	13
* Cervix AC	37	8	1	2	2	6	5	0	8	5
* Cervix (other morphology)	41	4	1	5	12	4	5	1	2	7
Anogenital (not cervix)	244	66	4	25	12	24	19	0	56	38
* Anogenital SCC	173	45	3	15	5	12	17	0	49	27
<b>Skin</b>										
Skin SCC	1399	400	16	13	2	40	124	15	430	359
Melanoma (skin)	1617	444	80	107	22	143	171	15	379	256
<b>Nervous and endocrine system</b>										
Brain and CNS	591	160	1	45	19	91	58	13	105	99
* Glioblastoma	297	95	0	26	6	39	17	2	51	61
Thyroid	420	41	59	65	37	118	17	20	39	24
<b>Hematopoietic system</b>										
Leukemia	1308	315	0	88	41	170	143	24	305	222
* Multiple myeloma	475	110	0	35	14	69	39	3	131	74
Lymphoma (all types)	1058	329	0	39	24	99	65	10	276	216
* Non-Hodgkin lymphomas	882	287	0	31	18	86	59	10	208	183
<b>Other</b>										
Other location AC	406	109	0	15	4	47	54	2	118	57
Other location or other morphology	2492	771	18	153	110	315	252	23	493	357
<b>Systolic Blood Pressure, N (%)</b>										
< 120 mmHg	86141 (28.0)	8691 (15.8)	7918 (41.3)	10421 (31.5)	8151 (31.5)	12446 (28.9)	14872 (40.7)	2202 (35.1)	10487 (21.8)	10953 (27.3)
120-129 mmHg	66446 (21.6)	9787 (17.8)	4351 (22.7)	8117 (24.6)	5511 (21.3)	10206 (23.7)	8108 (22.2)	1414 (22.5)	10182 (21.1)	8770 (21.8)
130-139 mmHg	57482 (18.7)	10356 (18.8)	3412 (17.8)	6653 (20.1)	4180 (16.2)	8812 (20.4)	6074 (16.6)	1163 (18.5)	8935 (18.5)	7897 (19.7)
140-159 mmHg	68235 (22.2)	17674 (32.2)	2787 (14.5)	5894 (17.8)	5392 (20.9)	8746 (20.3)	5242 (14.4)	1124 (17.9)	12192 (25.3)	9184 (22.9)
160-179 mmHg	22656 (7.4)	6266 (11.4)	607 (3.2)	1607 (4.9)	2056 (8.0)	2334 (5.4)	1781 (4.9)	303 (4.8)	4953 (10.3)	2749 (6.8)
>= 180 mmHg	6358 (2.1)	2187 (4.0)	120 (0.6)	356 (1.1)	564 (2.2)	565 (1.3)	440 (1.2)	67 (1.1)	1435 (3.0)	624 (1.6)
SBP, mmHg: mean (SD)	131.5 (19.7)	139.6 (20.5)	125 (17.2)	129.2 (17.7)	129.8 (20.6)	129.5 (18.1)	126.2 (18.9)	128.2 (18.6)	134 (20)	131.2 (19.2)
<b>Diastolic Blood Pressure, N (%)</b>										
< 80 mmHg	132590 (43.1)	20292 (36.9)	12372 (64.5)	12577 (38.1)	10656 (41.2)	15892 (36.9)	21394 (58.6)	3192 (50.9)	17028 (35.3)	19187 (47.8)
80-84 mmHg	64872 (21.1)	11599 (21.1)	3031 (15.8)	6293 (19.0)	6189 (23.9)	11721 (27.2)	6246 (17.1)	1123 (17.9)	10667 (22.1)	8003 (19.9)
85-89 mmHg	41500 (13.5)	8863 (16.1)	1901 (9.9)	5522 (16.7)	2738 (10.6)	5779 (13.4)	4081 (11.2)	818 (13.0)	6853 (14.2)	4945 (12.3)
90-99 mmHg	51196 (16.7)	10521 (19.1)	1544 (8.0)	6362 (19.3)	4784 (18.5)	7440 (17.3)	3685 (10.1)	828 (13.2)	10117 (21.0)	5915 (14.7)
100-109 mmHg	13896 (4.5)	2955 (5.4)	269 (1.4)	1874 (5.7)	1204 (4.7)	1822 (4.2)	916 (2.5)	222 (3.5)	2952 (6.1)	1682 (4.2)
>= 110 mmHg	3264 (1.1)	731 (1.3)	78 (0.4)	420 (1.3)	283 (1.1)	455 (1.1)	195 (0.5)	90 (1.4)	567 (1.2)	445 (1.1)
DBP, mmHg: mean (SD)	81.1 (10.9)	83.1 (10.6)	76.7 (10)	83.5 (10.6)	80.5 (10.6)	81.7 (10.1)	77.8 (10.7)	80.3 (11.7)	82.2 (10.9)	80.1 (11.5)

	Total	Denmark	France	Germany	Greece	Italy	Netherlands	Spain	Sweden	UK
<b>Mean Blood Pressure, N (%)</b>										
50.0-88.3 mmHg	76991 (25.1)	8532 (15.5)	7505 (39.1)	7052 (21.3)	7108 (27.5)	9839 (22.8)	13546 (37.1)	1879 (30.0)	10381 (21.5)	11149 (27.7)
88.5-96.6 mmHg	77727 (25.3)	11503 (20.9)	5146 (26.8)	8266 (25.0)	7003 (27.1)	12659 (29.4)	9409 (25.8)	1525 (24.3)	12282 (25.5)	9934 (24.7)
96.8-105.5 mmHg	76327 (24.8)	15558 (28.3)	4230 (22.0)	9455 (28.6)	5777 (22.3)	11080 (25.7)	7862 (21.5)	1594 (25.4)	11192 (23.2)	9579 (23.8)
105.6-216.6 mmHg	76273 (24.8)	19368 (35.2)	2314 (12.1)	8275 (25.0)	5966 (23.1)	9531 (22.1)	5700 (15.6)	1275 (20.3)	14329 (29.7)	9515 (23.7)
MBP, mmHg: mean (SD)	97.9 (12.9)	101.9 (12.9)	92.8 (11.4)	98.7 (12.2)	96.9 (12.8)	97.7 (11.9)	94 (12.5)	96.2 (13.1)	99.5 (13)	97.2 (13.3)
<b>Hypertension (yes/no), N (%)</b>										
No hypertension	174179 (56.7)	25551 (46.5)	13495 (70.3)	17799 (53.9)	14383 (55.6)	26131 (60.6)	23286 (63.8)	3740 (59.6)	25183 (52.3)	24611 (61.3)
Hypertension	133139 (43.3)	29410 (53.5)	5700 (29.7)	15249 (46.1)	11471 (44.4)	16978 (39.4)	13231 (36.2)	2533 (40.4)	23001 (47.7)	15566 (38.7)
<b>Treatment of hypertension (yes/no), N (%)</b>										
Untreated hypertension	73714 (66.6)	18458 (73.3)	3980 (74.2)	7681 (50.5)	6179 (54.3)	11495 (68.5)	8603 (67.9)	1661 (66.0)	12992 (68.6)	2665 (100.0)
Treated hypertension	37017 (33.4)	6733 (26.7)	1382 (25.8)	7525 (49.5)	5204 (45.7)	5292 (31.5)	4070 (32.1)	854 (34.0)	5957 (31.4)	0 (0.0)

**EPIC** - European Prospective Investigation into Cancer and Nutrition; **N** - number of individuals; **(%)** - percentage from total number per country; **SD** - standard deviation; **DBP** – diastolic blood pressure; **SBP** – systolic blood pressure; **MBP (Mean Blood Pressure)**: calculated as  $(1/3)*SBP+(2/3)*DBP$ ; **#** - person years of follow-up in the study from the date of blood pressure measurement; **Hypertension**: defined as  $SBP \geq 140$  mmHg, or  $DBP \geq 90$  mmHg, or self-reported; **Treatment of hypertension**: summary of self-reported antihypertensive treatment (yes/no) for individuals with hypertension as defined above; The order of the main cancer locations corresponds to Figure 2 (by body system); \* - specific cancer location or morphology (cancer morphologies and locations are defined in Supplementary Table 1); **AC** - adenocarcinoma; **SCC** - squamous cell carcinoma; **SmallCC** - small cell carcinoma; **HCC** - hepatocellular carcinoma.



Supplementary Table 4 Baseline demographic, lifestyle and reproductive characteristics by blood pressure category

Characteristics	Total	Systolic Blood Pressure					
		< 120 mmHg	120-129 mmHg	130-139 mmHg	140-159 mmHg	160-179 mmHg	≥ 180 mmHg
Cohort size: N	307318	86141	66446	57482	68235	22656	6358
Female: N (%)	194727 (63.4)	65461 (76.0)	40944 (61.6)	33415 (58.1)	38168 (55.9)	13066 (57.7)	3673 (57.8)
Age at recruitment, years: mean (SD)	52.5 (9.9)	47.3 (9.8)	50.9 (9.4)	53.6 (8.9)	56.8 (8.0)	59.5 (7.3)	60.5 (7.1)
Body Mass Index, kg/m <sup>2</sup> : mean (SD)	25.8 (4.2)	24.1 (3.6)	25.5 (3.9)	26.3 (4.1)	27.0 (4.4)	27.6 (4.6)	27.9 (4.8)
Alcohol intake, g/day: mean (SD)	12.4 (17.1)	9.7 (13.5)	11.9 (15.9)	13.1 (17.6)	14.5 (19.5)	14.5 (20.3)	15.8 (22.3)
Fruit consumption, g/day: mean (SD)	230.6 (176.7)	237.9 (185.0)	233.0 (179.0)	229.4 (176.2)	225.0 (169.2)	220.2 (163.3)	214.6 (162.4)
Vegetable consumption, g/day: mean (SD)	200.9 (145.4)	209.0 (155.5)	201.4 (148.8)	197.2 (138.8)	197.1 (138.0)	193.6 (135.5)	188.2 (134.1)
Red meat consumption, g/day: mean (SD)	48.2 (36.3)	44.0 (34.6)	47.3 (36.0)	49.3 (36.2)	51.7 (37.6)	52.1 (37.3)	53.5 (37.5)
<b>Diabetes: N (%)</b>							
Self-reported diabetes	8588 (2.8)	1034 (1.2)	1365 (2.1)	1582 (2.8)	2837 (4.2)	1317 (5.8)	453 (7.1)
Missing information	30147 (9.8)	5934 (6.9)	6280 (9.5)	6226 (10.8)	8421 (12.3)	2612 (11.5)	674 (10.6)
<b>Smoking status: N (%)</b>							
Never smoker	141931 (46.2)	39958 (46.4)	30980 (46.6)	26660 (46.4)	31153 (45.7)	10419 (46.0)	2761 (43.4)
Former smoker	86314 (28.1)	21204 (24.6)	18180 (27.4)	16751 (29.1)	21025 (30.8)	7147 (31.5)	2007 (31.6)
Current smoker (≤ 20 pack-years)	32226 (10.5)	12765 (14.8)	7333 (11.0)	5130 (8.9)	5093 (7.5)	1457 (6.4)	448 (7.0)
Current smoker (> 20 pack-years)	34907 (11.4)	8959 (10.4)	7386 (11.1)	6629 (11.5)	8221 (12.0)	2787 (12.3)	925 (14.5)
Missing information	11940 (3.9)	3255 (3.8)	2567 (3.9)	2312 (4.0)	2743 (4.0)	846 (3.7)	217 (3.4)
<b>Physical activity: N (%)</b>							
Inactive	67194 (21.9)	15201 (17.6)	13228 (19.9)	12770 (22.2)	17521 (25.7)	6542 (28.9)	1932 (30.4)
Moderately inactive	100295 (32.6)	28544 (33.1)	21835 (32.9)	18840 (32.8)	21753 (31.9)	7291 (32.2)	2032 (32.0)
Moderately active	70977 (23.1)	21409 (24.9)	15862 (23.9)	13326 (23.2)	14685 (21.5)	4467 (19.7)	1228 (19.3)
Active	62152 (20.2)	17801 (20.7)	14093 (21.2)	11555 (20.1)	13446 (19.7)	4123 (18.2)	1134 (17.8)
Missing information	6700 (2.2)	3186 (3.7)	1428 (2.1)	991 (1.7)	830 (1.2)	233 (1.0)	32 (0.5)
<b>Education: N (%)</b>							
None	9377 (3.1)	1661 (1.9)	1649 (2.5)	1786 (3.1)	2790 (4.1)	1164 (5.1)	327 (5.1)
Primary school completed	90254 (29.4)	18049 (21.0)	17950 (27.0)	17702 (30.8)	24700 (36.2)	9155 (40.4)	2698 (42.4)
Technical/professional school	77398 (25.2)	20712 (24.0)	16789 (25.3)	14704 (25.6)	17822 (26.1)	5759 (25.4)	1612 (25.4)
Secondary school	53830 (17.5)	19078 (22.1)	12696 (19.1)	9691 (16.9)	9148 (13.4)	2546 (11.2)	671 (10.6)
Longer education (incl. University degree)	67606 (22.0)	24418 (28.3)	15466 (23.3)	11838 (20.6)	11689 (17.1)	3335 (14.7)	860 (13.5)
Missing information	8853 (2.9)	2223 (2.6)	1896 (2.9)	1761 (3.1)	2086 (3.1)	697 (3.1)	190 (3.0)
<b>Antihypertensive treatment: N (%)</b>							
No treatment	227336 (74.0)	75558 (87.7)	53631 (80.7)	42212 (73.4)	42214 (61.9)	11150 (49.2)	2571 (40.4)
Treated	37017 (12.0)	2065 (2.4)	4241 (6.4)	6737 (11.7)	13884 (20.3)	7462 (32.9)	2628 (41.3)
Missing information	42965 (14.0)	8518 (9.9)	8574 (12.9)	8533 (14.8)	12137 (17.8)	4044 (17.8)	1159 (18.2)

Continues on next page

<b>Reproductive factors (women)</b>	<b>Total</b>	<b>&lt; 120 mmHg</b>	<b>120-129 mmHg</b>	<b>130-139 mmHg</b>	<b>140-159 mmHg</b>	<b>160-179 mmHg</b>	<b>≥ 180 mmHg</b>
<b>Age at first menstrual period: N (%)</b>							
< 12 years	27085 (13.9)	9595 (14.7)	5733 (14.0)	4716 (14.1)	5074 (13.3)	1514 (11.6)	453 (12.3)
≥ 12 and < 15 years	125828 (64.6)	42585 (65.1)	26680 (65.2)	21625 (64.7)	24337 (63.8)	8287 (63.4)	2314 (63.0)
≥ 15 years	32391 (16.6)	9329 (14.3)	6418 (15.7)	5762 (17.2)	7319 (19.2)	2794 (21.4)	769 (20.9)
Missing information	9423 ( 4.8)	3952 (6.0)	2113 (5.2)	1312 (3.9)	1438 (3.8)	471 (3.6)	137 (3.7)
<b>Age at first full term pregnancy: N (%)</b>							
≤ 21 years	36839 (18.9)	11093 (16.9)	7757 (18.9)	6509 (19.5)	7915 (20.7)	2769 (21.2)	796 (21.7)
> 21 and ≤ 30 years	106230 (54.6)	33698 (51.5)	22395 (54.7)	19006 (56.9)	21669 (56.8)	7421 (56.8)	2041 (55.6)
> 30 years	15709 ( 8.1)	5588 (8.5)	3297 (8.1)	2535 (7.6)	2964 (7.8)	1035 (7.9)	290 (7.9)
Missing information	35949 (18.5)	15082 (23.0)	7495 (18.3)	5365 (16.1)	5620 (14.7)	1841 (14.1)	546 (14.9)
<b>Number of full-term pregnancies: N (%)</b>							
None	25571 (13.1)	10307 (15.7)	5226 (12.8)	3944 (11.8)	4227 (11.1)	1438 (11.0)	429 (11.7)
One	28796 (14.8)	9326 (14.2)	6139 (15.0)	5018 (15.0)	5771 (15.1)	1977 (15.1)	565 (15.4)
Two	75357 (38.7)	24211 (37.0)	16178 (39.5)	13358 (40.0)	15223 (39.9)	5037 (38.6)	1350 (36.8)
Three	33031 (17.0)	9387 (14.3)	6941 (17.0)	6026 (18.0)	7340 (19.2)	2624 (20.1)	713 (19.4)
Four or more	14897 ( 7.7)	3448 (5.3)	2883 (7.0)	2861 (8.6)	3732 (9.8)	1484 (11.4)	489 (13.3)
Missing information	17075 ( 8.8)	8782 (13.4)	3577 (8.7)	2208 (6.6)	1875 (4.9)	506 (3.9)	127 (3.5)
<b>Menopausal status: N (%)</b>							
Pre-menopausal	58190 (29.9)	32401 (49.5)	13167 (32.2)	7060 (21.1)	4551 (11.9)	825 (6.3)	186 (5.1)
Post-menopausal	96806 (49.7)	20155 (30.8)	18714 (45.7)	18853 (56.4)	26087 (68.3)	10027 (76.7)	2970 (80.9)
Peri-menopausal or unknown	33371 (17.1)	11425 (17.5)	7789 (19.0)	6270 (18.8)	5912 (15.5)	1607 (12.3)	368 (10.0)
Surgical post-menopausal	6360 ( 3.3)	1480 (2.3)	1274 (3.1)	1232 (3.7)	1618 (4.2)	607 (4.6)	149 (4.1)
<b>Age at menopause: N (%)</b>							
< 40 years	4301 ( 2.2)	950 (1.5)	853 (2.1)	821 (2.5)	1128 (3.0)	436 (3.3)	113 (3.1)
≥ 40 and ≤ 46 years	18912 ( 9.7)	4218 (6.4)	3594 (8.8)	3621 (10.8)	5030 (13.2)	1893 (14.5)	556 (15.1)
> 46 and ≤ 50 years	31996 (16.4)	6636 (10.1)	6298 (15.4)	6257 (18.7)	8493 (22.3)	3299 (25.2)	1013 (27.6)
> 50 and ≤ 56 years	29427 (15.1)	5220 (8.0)	5427 (13.3)	5940 (17.8)	8462 (22.2)	3415 (26.1)	963 (26.2)
> 56 years	1997 ( 1.0)	267 (0.4)	326 (0.8)	364 (1.1)	652 (1.7)	287 (2.2)	101 (2.7)
Missing information or not applicable	108094 (55.5)	48170 (73.6)	24446 (59.7)	16412 (49.1)	14403 (37.7)	3736 (28.6)	927 (25.2)
<b>Oral contraceptive use: N (%)</b>							
Never	82568 (42.4)	20931 (32.0)	16050 (39.2)	15231 (45.6)	20282 (53.1)	7760 (59.4)	2314 (63.0)
Former	91622 (47.1)	34372 (52.5)	20156 (49.2)	15415 (46.1)	15725 (41.2)	4735 (36.2)	1219 (33.2)
Current	10050 ( 5.2)	5228 (8.0)	2345 (5.7)	1353 (4.0)	879 (2.3)	207 (1.6)	38 (1.0)
Missing information	10487 ( 5.4)	4930 (7.5)	2393 (5.8)	1416 (4.2)	1282 (3.4)	364 (2.8)	102 (2.8)
<b>Hormone replacement therapy: N (%)</b>							
Never	129049 (66.3)	46653 (71.3)	26815 (65.5)	21277 (63.7)	23675 (62.0)	8205 (62.8)	2424 (66.0)
Former	16259 ( 8.3)	4161 (6.4)	3354 (8.2)	3188 (9.5)	3917 (10.3)	1310 (10.0)	329 (9.0)
Current	30133 (15.5)	8768 (13.4)	6600 (16.1)	5701 (17.1)	6533 (17.1)	2014 (15.4)	517 (14.1)
Missing information	19286 ( 9.9)	5879 (9.0)	4175 (10.2)	3249 (9.7)	4043 (10.6)	1537 (11.8)	403 (11.0)

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Characteristics	Total	Diastolic Blood Pressure					
		< 80 mmHg	80-84 mmHg	85-89 mmHg	90-99 mmHg	100-109 mmHg	≥ 110 mmHg
Cohort size: N	307318	132590	64872	41500	51196	13896	3264
Female: N (%)	194727 (63.4)	96352 (72.7)	39059 (60.2)	23956 (57.7)	27199 (53.1)	6720 (48.4)	1441 (44.1)
Age at recruitment, years: mean (SD)	52.5 (9.9)	50.2 (10.5)	52.9 (9.6)	54.2 (8.7)	55.4 (8.4)	56.4 (8.0)	56.6 (7.9)
Body Mass Index, kg/m <sup>2</sup> : mean (SD)	25.8 (4.2)	24.6 (3.8)	26.0 (4.1)	26.6 (4.2)	27.3 (4.4)	28.1 (4.7)	28.8 (5.1)
Alcohol intake, g/day: mean (SD)	12.4 (17.1)	10.4 (14.3)	12.7 (17.1)	13.6 (18.2)	14.8 (19.9)	16.2 (22.0)	17.2 (23.5)
Fruit consumption, g/day: mean (SD)	230.6 (176.7)	234.0 (178.4)	238.6 (184.6)	222.9 (170.7)	223.5 (169.3)	214.8 (166.0)	211.6 (163.5)
Vegetable consumption, g/day: mean (SD)	200.9 (145.4)	206.9 (149.3)	202.5 (146.6)	191.8 (138.5)	194.8 (140.7)	189.0 (138.7)	190.4 (138.4)
Red meat consumption, g/day: mean (SD)	48.2 (36.3)	46.1 (35.5)	48.3 (35.9)	50.1 (36.8)	50.6 (37.4)	51.9 (37.9)	53.9 (39.4)
<b>Diabetes: N (%)</b>							
Self-reported diabetes	8588 (2.8)	2794 (2.1)	1897 (2.9)	1280 (3.1)	1920 (3.8)	539 (3.9)	158 (4.8)
Missing information	30147 (9.8)	11973 (9)	5761 (8.9)	4547 (11)	5692 (11.1)	1738 (12.5)	436 (13.4)
<b>Smoking status: N (%)</b>							
Never smoker	141931 (46.2)	62146 (46.9)	30071 (46.4)	19076 (46.0)	23182 (45.3)	6030 (43.4)	1426 (43.7)
Former smoker	86314 (28.1)	34090 (25.7)	18378 (28.3)	12433 (30.0)	15817 (30.9)	4547 (32.7)	1049 (32.1)
Current smoker (≤ 20 pack-years)	32226 (10.5)	16753 (12.6)	6505 (10.0)	3576 (8.6)	4080 (8.0)	1066 (7.7)	246 (7.5)
Current smoker (> 20 pack-years)	34907 (11.4)	14418 (10.9)	7493 (11.6)	4820 (11.6)	6068 (11.9)	1704 (12.3)	404 (12.4)
Missing information	11940 (3.9)	5183 (3.9)	2425 (3.7)	1595 (3.8)	2049 (4.0)	549 (4.0)	139 (4.3)
<b>Physical activity: N (%)</b>							
Inactive	67194 (21.9)	25354 (19.1)	14642 (22.6)	9415 (22.7)	12952 (25.3)	3859 (27.8)	972 (29.8)
Moderately inactive	100295 (32.6)	43034 (32.5)	21287 (32.8)	13573 (32.7)	16860 (32.9)	4489 (32.3)	1052 (32.2)
Moderately active	70977 (23.1)	32177 (24.3)	14749 (22.7)	9440 (22.7)	11100 (21.7)	2854 (20.5)	657 (20.1)
Active	62152 (20.2)	28031 (21.1)	13074 (20.2)	8365 (20.2)	9619 (18.8)	2519 (18.1)	544 (16.7)
Missing information	6700 (2.2)	3994 (3.0)	1120 (1.7)	707 (1.7)	665 (1.3)	175 (1.3)	39 (1.2)
<b>Education: N (%)</b>							
None	9377 (3.1)	3182 (2.4)	2255 (3.5)	1123 (2.7)	2100 (4.1)	560 (4.0)	157 (4.8)
Primary school completed	90254 (29.4)	31658 (23.9)	20359 (31.4)	13613 (32.8)	18220 (35.6)	5172 (37.2)	1232 (37.7)
Technical/professional school	77398 (25.2)	32758 (24.7)	15956 (24.6)	11061 (26.7)	13259 (25.9)	3588 (25.8)	776 (23.8)
Secondary school	53830 (17.5)	27531 (20.8)	11073 (17.1)	6263 (15.1)	6836 (13.4)	1719 (12.4)	408 (12.5)
Longer education (incl. University degree)	67606 (22.0)	33387 (25.2)	13330 (20.5)	8324 (20.1)	9457 (18.5)	2518 (18.1)	590 (18.1)
Missing information	8853 (2.9)	4074 (3.1)	1899 (2.9)	1116 (2.7)	1324 (2.6)	339 (2.4)	101 (3.1)
<b>Antihypertensive treatment: N (%)</b>							
No treatment	227336 (74.0)	110105 (83.0)	50113 (77.2)	28744 (69.3)	30577 (59.7)	6477 (46.6)	1320 (40.4)
Treated	37017 (12.0)	5988 (4.5)	6453 (9.9)	6278 (15.1)	12212 (23.9)	4847 (34.9)	1239 (38.0)
Missing information	42965 (14.0)	16497 (12.4)	8306 (12.8)	6478 (15.6)	8407 (16.4)	2572 (18.5)	705 (21.6)

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<b>Reproductive factors (women)</b>	<b>Total</b>	<b>&lt; 80 mmHg</b>	<b>80-84 mmHg</b>	<b>85-89 mmHg</b>	<b>90-99 mmHg</b>	<b>100-109 mmHg</b>	<b>≥ 110 mmHg</b>
<b>Age at first menstrual period: N (%)</b>							
< 12 years	27085 (13.9)	13479 (14.0)	5358 (13.7)	3341 (13.9)	3709 (13.6)	973 (14.5)	225 (15.6)
≥ 12 and < 15 years	125828 (64.6)	62216 (64.6)	25302 (64.8)	15521 (64.8)	17646 (64.9)	4225 (62.9)	918 (63.7)
≥ 15 years	32391 (16.6)	15202 (15.8)	6700 (17.2)	4100 (17.1)	4843 (17.8)	1285 (19.1)	261 (18.1)
Missing information	9423 (4.8)	5455 (5.7)	1699 (4.3)	994 (4.1)	1001 (3.7)	237 (3.5)	37 (2.6)
<b>Age at first full term pregnancy: N (%)</b>							
≤ 21 years	36839 (18.9)	16461 (17.1)	7737 (19.8)	4927 (20.6)	5914 (21.7)	1486 (22.1)	314 (21.8)
> 21 and ≤ 30 years	106230 (54.6)	51245 (53.2)	21671 (55.5)	13514 (56.4)	15248 (56.1)	3752 (55.8)	800 (55.5)
> 30 years	15709 (8.1)	8160 (8.5)	3046 (7.8)	1798 (7.5)	2053 (7.5)	536 (8.0)	116 (8.0)
Missing information	35949 (18.5)	20486 (21.3)	6605 (16.9)	3717 (15.5)	3984 (14.6)	946 (14.1)	211 (14.6)
<b>Number of full-term pregnancies: N (%)</b>							
None	25571 (13.1)	14179 (14.7)	4822 (12.3)	2708 (11.3)	2966 (10.9)	733 (10.9)	163 (11.3)
One	28796 (14.8)	13454 (14.0)	5985 (15.3)	3708 (15.5)	4341 (16.0)	1089 (16.2)	219 (15.2)
Two	75357 (38.7)	36127 (37.5)	15607 (40.0)	9564 (39.9)	10861 (39.9)	2652 (39.5)	546 (37.9)
Three	33031 (17.0)	15360 (15.9)	6857 (17.6)	4320 (18.0)	5001 (18.4)	1213 (18.1)	280 (19.4)
Four or more	14897 (7.7)	6462 (6.7)	3007 (7.7)	2045 (8.5)	2540 (9.3)	674 (10.0)	169 (11.7)
Missing information	17075 (8.8)	10770 (11.2)	2781 (7.1)	1611 (6.7)	1490 (5.5)	359 (5.3)	64 (4.4)
<b>Menopausal status: N (%)</b>							
Pre-menopausal	58190 (29.9)	37077 (38.5)	10288 (26.3)	5117 (21.4)	4575 (16.8)	930 (13.8)	203 (14.1)
Post-menopausal	96806 (49.7)	40368 (41.9)	20574 (52.7)	13749 (57.4)	16786 (61.7)	4392 (65.4)	937 (65.0)
Peri-menopausal or unknown	33371 (17.1)	16206 (16.8)	6856 (17.6)	4236 (17.7)	4731 (17.4)	1107 (16.5)	235 (16.3)
Surgical post-menopausal	6360 (3.3)	2701 (2.8)	1341 (3.4)	854 (3.6)	1107 (4.1)	291 (4.3)	66 (4.6)
<b>Age at menopause: N (%)</b>							
< 40 years	4301 (2.2)	1857 (1.9)	952 (2.4)	543 (2.3)	728 (2.7)	178 (2.6)	43 (3.0)
≥ 40 and ≤ 46 years	18912 (9.7)	7770 (8.1)	4087 (10.5)	2617 (10.9)	3331 (12.2)	915 (13.6)	192 (13.3)
> 46 and ≤ 50 years	31996 (16.4)	12971 (13.5)	6878 (17.6)	4602 (19.2)	5723 (21.0)	1515 (22.5)	307 (21.3)
> 50 and ≤ 56 years	29427 (15.1)	11645 (12.1)	6290 (16.1)	4350 (18.2)	5449 (20.0)	1395 (20.8)	298 (20.7)
> 56 years	1997 (1.0)	740 (0.8)	438 (1.1)	296 (1.2)	377 (1.4)	112 (1.7)	34 (2.4)
Missing information or not applicable	108094 (55.5)	61369 (63.7)	20414 (52.3)	11548 (48.2)	11591 (42.6)	2605 (38.8)	567 (39.3)
<b>Oral contraceptive use: N (%)</b>							
Never	82568 (42.4)	35792 (37.1)	17637 (45.2)	10976 (45.8)	13796 (50.7)	3544 (52.7)	823 (57.1)
Former	91622 (47.1)	48163 (50.0)	17767 (45.5)	10943 (45.7)	11444 (42.1)	2758 (41.0)	547 (38.0)
Current	10050 (5.2)	5938 (6.2)	1853 (4.7)	1034 (4.3)	986 (3.6)	213 (3.2)	26 (1.8)
Missing information	10487 (5.4)	6459 (6.7)	1802 (4.6)	1003 (4.2)	973 (3.6)	205 (3.1)	45 (3.1)
<b>Hormone replacement therapy: N (%)</b>							
Never	129049 (66.3)	66219 (68.7)	25508 (65.3)	15027 (62.7)	17067 (62.7)	4232 (63.0)	996 (69.1)
Former	16259 (8.3)	7398 (7.7)	3453 (8.8)	2211 (9.2)	2451 (9.0)	621 (9.2)	125 (8.7)
Current	30133 (15.5)	14950 (15.5)	6120 (15.7)	3918 (16.4)	4049 (14.9)	919 (13.7)	177 (12.3)
Missing information	19286 (9.9)	7785 (8.1)	3978 (10.2)	2800 (11.7)	3632 (13.4)	948 (14.1)	143 (9.9)

N - number of individuals; (%) - percentage from total number in blood pressure category (for reproductive factors in women only); SD - standard deviation

**Supplementary Table 5 Summary of statistical analyses**

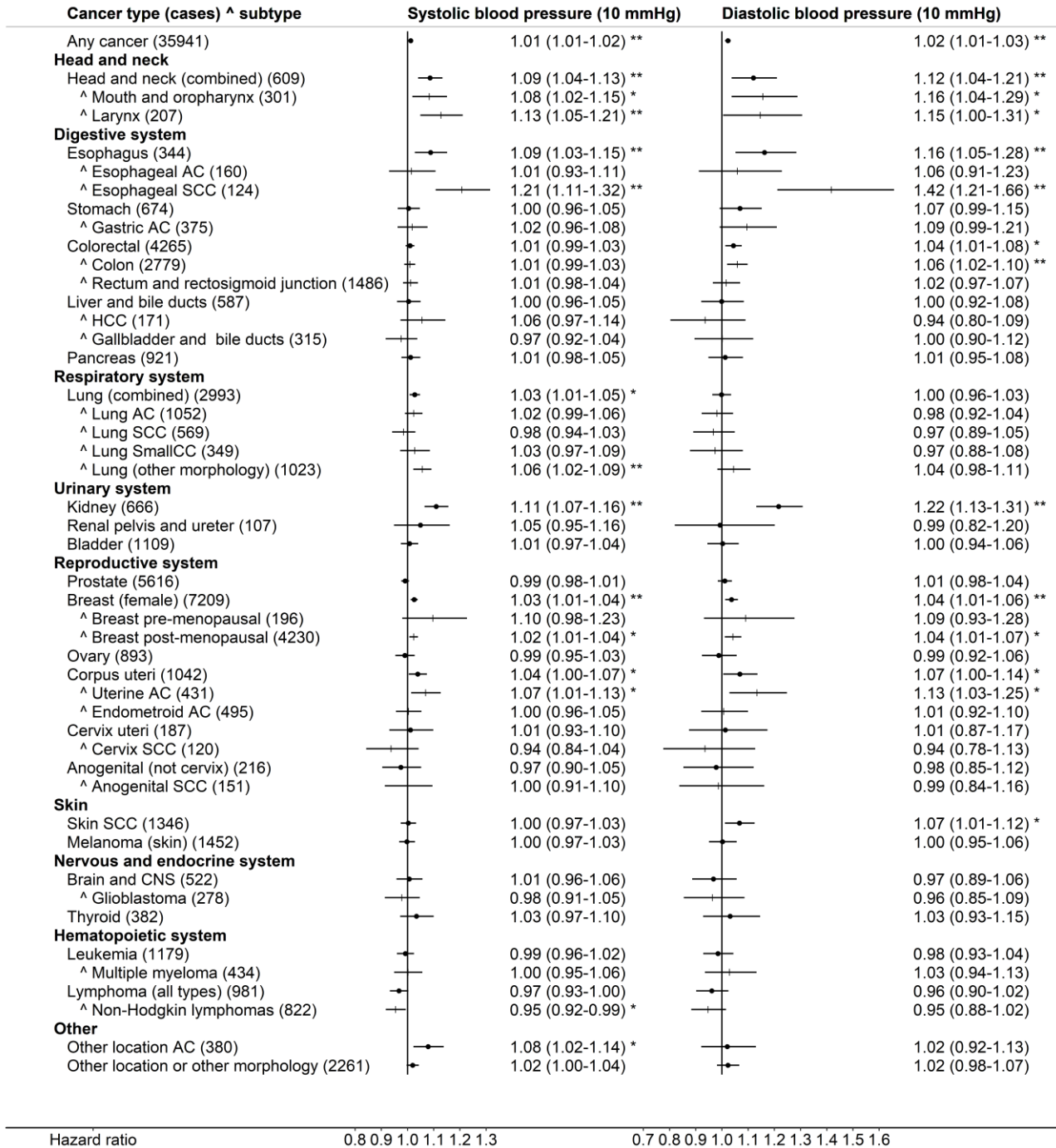
*see separate file: ST5\_HT\_CA\_EPIC.pdf or ST5\_HT\_CA\_EPIC.xls (same data, different format)*

**SUPPLEMENTARY FIGURES**

**Supplementary Figure 1 Forest plot of hazard ratios for sub-group analyses of continuous systolic and diastolic blood pressure**

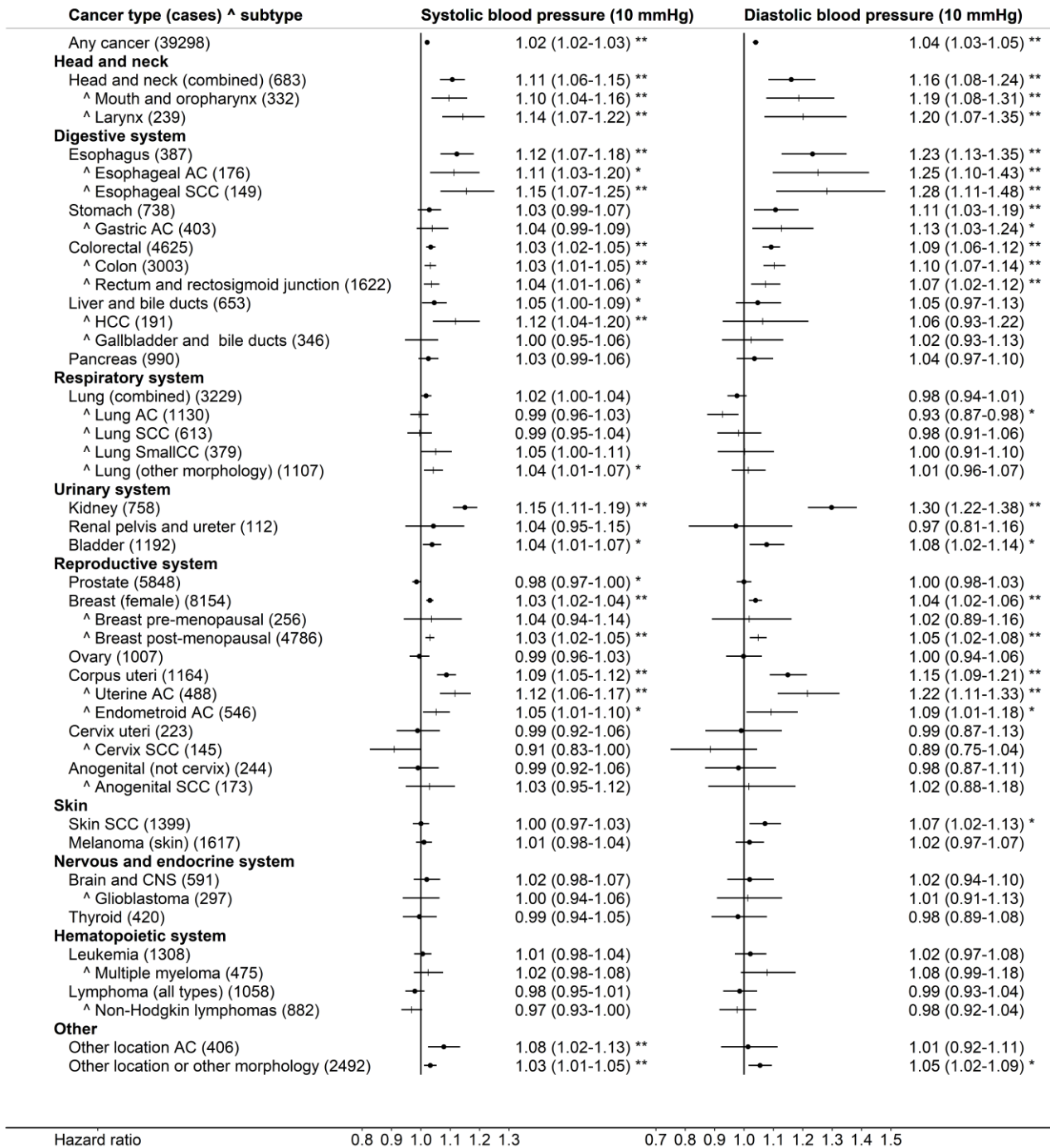
Subgroup analyses by sex (A,B), body mass index (C,D), age at recruitment (E,F), smoking status (G,H), alcohol intake (I,J) and antihypertensive treatment (yes/no) (K,L).

*See separate file: SF1\_HT\_CA\_EPIC.pdf*



### Supplementary Figure 2 Sensitivity analysis – first two years of follow-up excluded

**Hazard ratios** – estimates (95% confidence intervals) (per 10mmHg higher blood pressure) derived from Cox proportional hazards models, stratified by study centre and age at recruitment (5-year categories) and adjusted for potential confounders and risk factors (Supplementary Table 2); **AC** – adenocarcinoma; **CNS** – central nervous system; **HCC** – hepatocellular carcinoma; **SCC** – squamous cell carcinoma; **SmallCC** – small cell carcinoma; **Vertical order** – determined by the hazard ratio estimates for systolic blood pressure (SBP) of the main anatomical locations (**dot** symbols), each followed by the relevant specific locations or morphologies marked with **^** (+ symbols) for the main analysis (as per Figure 2) (other locations, not included in those specified, are shown last).



### Supplementary Figure 3 Sensitivity analysis – crude (unadjusted) hazard ratio estimates

**Hazard ratios** – unadjusted (crude) estimates (95% confidence intervals) (per 10mmHg higher blood pressure) derived from Cox proportional hazards models, stratified by study centre and age at recruitment (5-year categories); **AC** – adenocarcinoma; **CNS** – central nervous system; **HCC** – hepatocellular carcinoma; **SCC** – squamous cell carcinoma; **SmallCC** – small cell carcinoma; **Vertical order** – determined by the hazard ratio estimates for systolic blood pressure (SBP) of the main anatomical locations (**dot** symbols), each followed by the relevant specific locations or morphologies marked with ^ (+ symbols) for the main analysis adjusted for potential confounders and risk factors (as per Figure 2) (other locations, not included in those specified, are shown last).

**SUPPLEMENTARY RESULTS AND DISCUSSION**

Literature reports are often controversial for cancers, for which we found no association with blood pressure (BP) within the main analyses.

***Malignant melanoma***

We found no association of BP with the risk of malignant melanoma of the skin, with a reasonably large number of cases (n=1617) (Figure 2).

However, reports from the Me-Can support a positive association for malignant melanoma: for men (n=1015): HR=1.22 (1.08-1.39) per SD higher mid-BP (mean of systolic BP (SBP) and diastolic BP (DBP)), as well as in women (n=713): HR=1.15 (1.03-1.28) [1], with similar findings per 10mmHg higher mid-BP [2].

***Cancers of the liver, gallbladder and bile ducts***

We found some suggestion for a positive association of systolic blood pressure (SBP) with hepatocellular cancer (HCC) only in a small number of never smokers (n=49): hazard ratio HR=1.15 (95% confidence interval 0.99-1.33) and not with HCC in the total cohort (n=191) or with cancers of the gallbladder and bile ducts (n=346) (Figure 2).

Our latter observation is supported by results from the Metabolic Syndrome and Cancer study (Me-Can), for which Borena et al. found no association of mid-BP (mean of SBP and diastolic blood pressure (DBP)) with the risk of cancer of the gallbladder [3]. However, Me-Can findings for liver are less consistent. Whilst Borena et al., considering jointly HCC and intrahepatic cholangiocarcinoma, reported a borderline higher risk only when comparing the highest with the lowest quintile of mid-BP: HR=2.08 (0.95-4.73), but not per SD higher mid-BP [4], whilst Stocks et al. found a positive association, considering separately men women: men (n=188): HR=1.19 (0.97-1.47), women (n=67): HR=1.43 (1.05=1.94) [2].

***Pancreas***

For pancreatic cancer, we found evidence for association only at BMI $\leq$ 25kg/m<sup>2</sup> (n=428): HR=1.07 (1.02-1.12) for SBP and borderline for DBP=1.08 (0.98-1.19) (Supplemental Figure 1), but not in the total cohort (n=990) (Figure 2).

Published results are, to some extent, controversial. For the Me-Can project Johansen et al. [5] and later Stocks et al. reported a positive association of mid-BP and pancreatic cancer, in men (n=503): HR=1.14 (1.00-1.31) per 10mmHg and in women (n=295): HR=1.27 (1.09-1.48) [2]. At the same time, an Italian case-control study (n=326) was suggestive of a negative association in individuals with treated hypertension [6].



### **Bladder**

We found no evidence for association of BP with bladder cancer, with a reasonably large number of samples (n=1,192) (Figure 2).

In contrast, Haggstrom et al. reported for the Me-Can study a positive association of mid-BP with the risk of bladder cancer in men (n=1587): HR=1.13 (1.03-1.25) per SD higher mid-BP and only with a trend when considering separately quintile of SBP and DBP, but not in women (n=327): HR=0.87 (0.69-1.09) [7], with similar results when Stock et al. considered mid-BP per 10mmHg higher levels. At the same time, Jiang et al. reported, for a population-based case-control study of hypertension in the US (n=1585), a negative association in individuals with untreated hypertension (n=104): odds ratio OR=0.65 (0.48-0.88) and especially pronounced in current smokers with untreated hypertension (n=46): OR=0.43 (0.27-0.71), but no evidence for association was found in individuals with hypertension who regularly used diuretics or other antihypertensive drugs [8].

### **Ovary**

We found no evidence for association of BP with ovarian cancer, with a reasonably large number of samples (n=1,007) (Figure 2).

Our results are compatible with the findings of Soler et al. from a large Italian case-control study, which did not support an association of hypertension with ovarian cancer (n=970) [9]. More recently Bjorge et al. reported for the Me-Can study results suggestive of a positive association of mid-BP with the risk of epithelial ovarian cancer only in women younger than 50 years (n=161): HR=1.30 (0.95-1.78) per SD higher mid-BP and not in older women (n=483) and also some stronger evidence for a positive association with the risk of endometrioid ovarian cancer (n=66): HR=1.63 (1.16-2.28) [10].

### **Thyroid**

Overall, there was no evidence for association of BP with the risk of thyroid cancer (n=420), except that there was some borderline positive association with DBP only at age≤53 years: HR=1.12 (0.98-1.28) (Supplemental Figure 1).

Whilst individual studies, similarly to our main results, could not support an association of high BP with thyroid cancer [9, 11], a Yin et al. in a recent meta-analysis, including 7 studies addressing hypertension, has reported a positive association : relative risk RR=1.14 (1.06-1.23) [12].

### **Brain and central nervous system (CNS)**

We found no evidence for association of BP with the risk of cancers of the brain and CNS (n=591) (Figure 2), except for a negative association of SBP with glioblastoma, observed only in men (n=153): HR=0.90 (0.82-0.99).

On the contrary, results from Me-Can support a positive association for brain & CNS cancer (n=1312) and more specifically for meningiomas (n=348): HR=1.41 (1.16-1.78) per SD higher SBP and

HR=1.43 (1.16-1.78) for DBP, but not for gliomas [13]. We did not consider meningiomas separately, as there were only 19 cases.

### ***Other locations***

Among AC morphology in other locations, the risk of AC in locations not included in the main anatomical sites was positively associated with higher SBP (n=406): HR=1.08 (1.03-1.14) per 10mmHg and, only in men, additionally with DBP (n=158): HR=1.16 (1.00-1.35).

### ***Adjustment for antihypertensive treatment***

Tobin et al. have argued that studies of quantitative traits for BP should incorporate adjustment for treatment effect, with the addition of some increment to the “observed” (measured) BP, in order to obtain an estimate of the “underlying” (maximal) blood pressure [14], because antihypertensive treatment would reduce BP. We did not consider this approach appropriate for our study on the grounds outlined below. First, Tobin’s methodology addresses investigations of the aetiology of hypertension, i.e. when hypertension is the outcome, in which context mainly “underlying” BP would be of interest. When hypertension is examined as exposure, as in our case relative to cancer as an outcome, “observed” BP may be of relevance if high BP is potentially causally linked to cancer, but “underlying” BP may also be relevant if hypertension and cancer share common mechanisms. Further, Tobin’s methodology is built upon nontrivial assumptions that the “observed” BP is equivalent to the “underlying” BP in untreated individuals and that the “underlying” BP in treated individuals is equal to or higher than the “observed” BP. We have already pointed out in the main manuscript that the main limitation of our study is that BP was measured in a single time point, which may not be representative of the longer-term BP levels. BP could be affected by the emotional state of the individual during the study visit and hypertensive individuals may be more prone to emotional influences, even when treated.

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