

Supplementary Online Content

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eMethods. Study Collaboration and Analysis

eTable 1. Study Characteristics and Numbers of Premenopausal Women With Information on BMI by Cohort Study

eTable 2. Relative Risk of Premenopausal Breast Cancer for All Participants and Those With Information on BMI at Ages 18-24 Years

eTable 3. Relative Risk of Premenopausal Breast Cancer by Age at BMI and Invasiveness of Breast Cancer

eTable 4. Characteristics of Breast Cancer Cases by Most Recent BMI Category Before Diagnosis

eTable 5. Relative Risk of Premenopausal Breast Cancer Associated With BMI Category by Age at BMI and Estrogen or Progesterone Receptor Status of Breast Cancer

eTable 6. Relative Risk of Premenopausal Breast Cancer per 5.0-U Difference in BMI by Age at BMI and Other Breast Cancer Risk Factors

eTable 7. Relative Risk of Premenopausal Breast Cancer Associated With BMI Category by Age at BMI

eTable 8. Relative Risk of Premenopausal Breast Cancer Associated With BMI Category at Ages 18 to 24 Years, Excluding Participants Contributing to Each Successive Cohort

eTable 9. Relative Risk of Premenopausal Breast Cancer Associated With BMI Category at Ages 45 to 54 Years, Excluding Participants Contributing to Each Successive Cohort

eFigure 1. Relative Risk of Premenopausal Breast Cancer Associated With BMI by Age at BMI

eFigure 2. Relative Risk of Premenopausal Breast Cancer Associated With BMI at Ages 18 to 24 Years by Combined ER/PR Status of Breast Cancer

eFigure 3. Forest Plot of Study-Specific Hazard Ratios of Premenopausal Breast Cancer by BMI Category and Age Category

eFigure 4. Relative Risk of Premenopausal Breast Cancer per 5-U Difference in BMI by Age at BMI and Attained Age During Follow-up

eFigure 5. Relative Risk of Premenopausal Breast Cancer per 5-U Difference in BMI by Age at BMI and Combined Estrogen and Progesterone Receptor Status of Breast Cancer

eFigure 6. Relative Risk of Premenopausal Breast Cancer per 5-U Difference in BMI at Ages 18 to 24 Years by Selected Other Breast Cancer Risk Factors

This supplementary material has been provided by the authors to give readers additional information about their work.

Body-mass index, age and premenopausal breast cancer risk: A prospective analysis of 758,592 women

Supplementary methods and results

Table of contents

eMethods	3
eResults	
eTable 1: Study characteristics and numbers of premenopausal women with information on BMI, by cohort study	6
eTable 2: Relative risk of premenopausal breast cancer in relation to BMI category, by age at BMI, for all subjects and subjects with information on BMI at age 18-24 years.	7
eTable 3: Relative risk of premenopausal breast cancer in relation to BMI, by age at BMI and invasiveness of breast cancer	9
eTable 4: Characteristics of breast cancer cases, by most recent BMI category prior to diagnosis	10
eTable 5: Relative risk of premenopausal breast cancer in relation to BMI category, by age at BMI and oestrogen or progesterone receptor status of breast cancer	12
eTable 6: Relative risk of premenopausal breast cancer per 5 kg/m ² difference in BMI, by age at BMI and other breast cancer risk factors	13
eTable 7: Relative risk of premenopausal breast cancer in relation to BMI category, by age at BMI. For (1) all subjects included in main analysis (2) breast cancer with known ER, PR and HER2 status as endpoint (3) excluding subjects with weight assessed less than three years postpartum (4) strictly known premenopausal time only (5) excluding first two years of follow-up.	16
eTable 8: Relative risk of premenopausal breast cancer in relation to BMI category at age 18-24 years, excluding subjects contributing to each successive cohort.	19
eTable 9: Relative risk of premenopausal breast cancer in relation to BMI category at age 45-54 years, excluding subjects contributing to each successive cohort.	20
eFigure 1: Relative risk of premenopausal breast cancer in relation to BMI relative to the reference category of 20 kg/m ² , by age at BMI	21
eFigure 2: Relative risk of premenopausal breast cancer in relation to BMI at ages 18-24 years relative to the reference category of 20 kg/m ² , by combined ER/PR status of breast cancer	22
eFigure 3a: Forest plot of study-specific hazard ratios of premenopausal breast cancer by BMI category, relative to BMI 18.5-24.9 kg/m ² , at age 18-24 years.	23
eFigure 3b: Forest plot of study-specific hazard ratios of premenopausal breast cancer by BMI category, relative to BMI 18.5-24.9 kg/m ² , at age 25-34 years.	24
eFigure 3c: Forest plot of study-specific hazard ratios of premenopausal breast cancer by BMI category, relative to BMI 18.5-24.9 kg/m ² , at age 35-44 years.	25
eFigure 3d: Forest plot of study-specific hazard ratios of premenopausal breast cancer by BMI category, relative to BMI 18.5-24.9 kg/m ² , at age 45-54 years.	26

eFigure 4: Relative risk of premenopausal breast cancer per 5 kg/m ² difference in BMI, by age at BMI and attained age during follow-up	27
eFigure 5: Relative risk of premenopausal breast cancer per 5 kg/m ² difference in BMI, by age at BMI and combined oestrogen and progesterone receptor status of breast cancer	28
eFigure 6: Relative risk of premenopausal breast cancer per 5 kg/m ² difference in BMI at age 18-24 years, by selected other breast cancer risk factors	29
eReferences	30

eMethods

Cohort abbreviations

BWHS: Black Women's Health Study

CLUE2: Campaign against Cancer and Heart Disease

CSDLH: Canadian Study of Diet, Lifestyle, and Health

CTS: California Teachers Study

E3N: Etude Epidémiologique auprès de femmes de la Mutuelle Générale de l'Education Nationale

EPIC: European Prospective Study into Cancer and Nutrition

GS: Generations Study

HUNT2: Helseundersøkelsen i Nord-Trøndelag

MCC: Melbourne Collaborative Cohort Study

NHS: Nurses' Health Study

NHS2: Nurses' Health Study 2

NOWAC: Norwegian Women and Cancer Study

NYUWHS: New York University Women's Health Study

RERF: Radiation Effects Research Foundation Lifespan Study

SCHS: Singapore Chinese Health Study

SIS: Sister Study

SMC: Swedish Mammography Cohort

USRT: United States Radiologic Technologist Cohort

SWLHS: Sweden Women's Lifestyle and Health Study.

The collaboration

Full details of the Premenopausal Breast Cancer Collaborative Group have been published elsewhere.¹ Individual-level data were pooled from 19 prospective cohorts with ≥ 100 breast cancer cases diagnosed before age 55 years, with the collaboration facilitated by the National Cancer Institute Cohort Consortium. Data were harmonised to a common template for 1-16 questionnaire rounds per study; all studies had at least two rounds except for the European Prospective Investigation into Cancer and Nutrition (EPIC) study, the Canadian Study of Diet, Lifestyle and Health (CSDLH), and HUNT2 for which only the baseline questionnaire was available. One study (CSDLH) provided data for a case-cohort subset; all the others provided data for the full cohort. Seventeen studies provided information on incident invasive and *in-situ* breast cancer and two (HUNT2 and Canadian Study of Diet, Lifestyle, and Health, CLDLH) on invasive breast cancer only. The pooled dataset was used to construct a dataset to investigate the endpoint of premenopausal breast cancer.

Derivation of age at menopause and premenopausal follow-up time

All cohorts collected information on menopausal status of participants at one or more questionnaire rounds. Participants were asked whether they had had any menstrual periods during the previous 6 or 12 months, depending on study, and/or whether they believed their periods had stopped permanently. Participants were asked about the age at their last period and the reason their periods stopped. We used this information to construct premenopausal follow-up time for analysis. Age at menopause was computed for each participant based on (i) reported age at menopause or, if age was missing, (ii) age first known postmenopausal if under age 50, (iii) age last known premenopausal if over age 50 or (iv) age 50 if no information was provided. When a hysterectomy was reported as reason for the menopause follow-up was censored at the reported age of the procedure. Since women with breast cancer often become postmenopausal due to their treatment and breast cancers diagnosed in the year of their menopause could be considered aetiologically premenopausal, we lagged reported menopausal ages (subjects under i) for all women by +1 year, i.e. the year during which they reported that they had become postmenopausal was analysed as premenopausal follow-up time. As a sensitivity analysis, we repeated the main analyses including only known premenopausal follow-up time up to the age at reported menopause (subjects under i) or, if age at menopause was missing, the age at the last questionnaire when the participant reported she was premenopausal (ii and iii).

Computation of BMI at various ages

We used data on current weight at the time of questionnaire completion and on recalled weight at ages before questionnaire completion, to construct variables for weight within the age ranges 18-24, 25-34, 35-44, 45-54 years. None of the studies had information to calculate BMI at ages younger than 18 years. Most weights at ages 18-24 years were retrospectively reported (most often for ages 18-21) but a minority were concurrently reported by subjects who were recruited at ages 18-24 years. At ages 25-34, 35-44 and 45-54, the majority of weights were concurrently reported. When weights were assessed on multiple occasions within an age category we used the earliest concurrent weight or otherwise the retrospectively reported weight relative to the youngest age within the age group. We recoded the following extreme values to missing based on visual inspection of histograms and percentile distributions: height (<130 or >195 cm), weight (<30 , >200 kg), BMI (<15 , >49 kg/m²) and weights that arose from BMI values outside this range. In pooled analyses, BMI was categorised according to World Health Organization definitions² as severe/moderate thinness (<17 kg/m²), mild thinness (17-18.5 kg/m²), normal range (18.5-22.9 and 23.0-24.9 kg/m²), overweight (25-27.4 and 27.5-29.9 kg/m²), obese Class I (30-32.4 and 32.5-34.9 kg/m²) and obese Class II/III (≥ 35 kg/m²). Where numbers in the extreme categories were small or to obtain study-specific, stratum-specific or tumour type-specific estimates we combined categories to obtain stable estimates. For each age-specific BMI investigated, studies with less than 10 cases among subjects with known BMI were excluded from the model to improve convergence.

Clinicopathological surrogate definition of breast cancer intrinsic subtypes

Immunohistochemistry data on estrogen (ER) and progesterone receptor (PR) status, as well as data on Human epidermal growth factor receptor-2 (HER2) oncogene expression was collected from the centres. Given the absence of data on the proliferation marker KI-67, we adapted clinicopathological surrogate definitions of luminal A and luminal B-like intrinsic breast cancer subtypes proposed by the St Gallen Expert Consensus.³ We classified all ER+PR+HER2- breast cancer as luminal A-like, ER+PR-HER2- and ER-PR+HER2- as luminal B-like HER2 negative, [ER+/PR+]HER2+ to luminal B-like HER2 positive, ER+PR- and ER-PR+ with HER2 status unknown as luminal B unclassified, ER+ or PR+ with other markers unknown as unclassified luminal, ER-PR-HER2- as triple-negative, ER-PR-HER2+ as HER2 enriched, ER- with PR unknown or PR- with ER unknown regardless of HER2 status as unclassified.

Statistical methods

Analyses were conducted using Stata 14.2 software⁴. BMI was analysed separately as a categorical and as a continuous variable (per 5 kg/m²), assuming a log-linear dose-response relationship, the validity of which was checked using 5-knot restricted cubic spline models.⁵ Hazard ratios (HR) as estimates of relative risk of breast cancer were obtained from Cox proportional hazards models⁶ with attained age as the underlying time-scale. All analyses were conducted using Stata 14.2 software⁴. Pooled analyses were adjusted for attained age (implicit in the Cox model) and cohort (including country within EPIC). In multivariable-adjusted models we additionally adjusted for year of birth (<1930, 1930-9, 1940-9, 1950-9, 1960-9, 1970-9, to ≥1980), age at menarche (7-11, 12-13, ≥14 years, not known), age at first birth (<25, 25-34, ≥35 years, not known or not applicable), time since last birth (<5, 5-9, 10-14, 15-19, 20-24, 25-29, ≥30 years, not known or not applicable), parity (0, 1, 2, ≥3, parous but not known) and family history of breast cancer (yes, no, not known). Hazard ratios for breast cancer with respect to BMI were near-identical in age- and cohort-adjusted models compared with models additionally (fully) adjusted for other breast cancer risk factors. Fully adjusted models are therefore presented in the main paper. In models additionally adjusted for BMI at age 18-24, BMI at this age was coded as <18.5, 18.5-22.9, 23.0-24.9, 25.0-27.4, 27.5-29.9, ≥30 kg/m²). Height was included as a continuous variable in models additionally adjusted for adult height. Covariate information was time-updated, where possible, with information from follow-up questionnaires for all pregnancy-related variables and family history of breast cancer. Subjects with missing covariate values were included in the analyses by fitting a category for the missing value. In order to include the case-cohort study (CSDLH) in the pooled data set, we included Barlow weights⁷ for CSDLH corresponding to a sampling fraction of 5.0 percent as an off-set in the model. We also applied Barlow weights with a sampling fraction of (effectively) 1.0 to all other cohorts using the `stcasecoh` command in Stata 14.2 software⁴, which did not affect the results for those cohorts, but facilitated ease of obtaining results from a single pooled dataset.

Sensitivity analyses

In sensitivity analyses, we repeated the analyses (i) for BMI at ages 25 onwards adjusting for BMI at age 18-24 years (Figure 1) (ii) for BMI at ages 25 onwards restricted to individuals for whom BMI at ages 18-24 was also available (eTable 2) (iii) excluding subjects whose weight was recalled or reported less than three years postpartum (eTable 7) (iv) restricting follow-up to person-time that was known to be, rather than assumed to be, premenopausal (eTable 7) (v) excluding the first two years of follow-up (eTable 7) (vi) restricting the endpoint to breast cancer with information on all of ER, PR and HER2 status (eTable 7) (vii) excluding one cohort at the time (eTable 8) (viii) additional adjustment for adult height (not shown) (vix) comparing with and without adjustment for polycystic ovary syndrome (PCOS), for centres with data on PCOS (not shown).

eTable 1: Study characteristics and numbers of premenopausal women with information on BMI, by cohort study

Cohort	Country	Number of Subjects	Age at entry, median years	Age at entry, min years	Follow-up, median years	Number of Cases	BMI age 18-24 years		BMI age 25-34 years		BMI age 35-44 years		BMI age 45-54 years	
							Median BMI	Number of Subjects	Median BMI	Number of Subjects	Median BMI	Number of Subjects	Median BMI	Number of Subjects
BWHS	USA	45091	35.2	20.4	12	828	20.9	44482	25.3	21447	27.1	35361	28.4	25553
CLUE2	USA	4119	36.5	18.5	10.5	64	21	4110	23.3	1722	24.4	2879	25.6	2111
CSDLH (a)	Canada	1105	42.5	23.1	6.4	213	20.5	1099	22	156	22.9	552	23.2	381
CTS	USA	45708	41.2	22.2	8.8	641	20.8	45327	22.3	12107	23	23370	23.6	18184
E3N	France	58215	44.7	38.6	6.4	1245	-	0 (c)	-	0 (c)	21.4	30674	22	54722
EPIC (b)	Europe	94967	40.8	19.9	8.2	942	21.1	49045	22.2	15535	23.7	47837	24.8	27553
GS	UK	60916	38.4	18	6.4	655	21.6	59751	22.7	34825	23.8	47284	24.5	23865
HUNT2	Norway	16889	36.5	20.5	12	117	23.5	2090	24.1	5282	24.5	6423	25.3	3094
MCC	Australia	8097	45.4	31.1	4.6	86	20.8	7985	-	0 (c)	24.2	3720	24.9	6448
NHS	USA	94945	40.6	29.5	13.4	2334	20.9	76550	21.9	21372	22.5	65826	23.8	88173
NHS2	USA	83620	36.8	24.8	14.2	2515	20.6	82703	22.4	28926	23.2	82528	25.1	68850
NOWAC	Norway	75740	42.5	31.5	6.5	797	20.4	72012	22	3991	22.3	45472	23.5	44139
NYUWHS	USA	6649	43.5	31.5	7.5	241	-	0 (c)	22.1	85	22.9	4259	23.9	4544
RERF	Japan	11430	40.1	24.3	9.9	64	20.2	126	20.5	7599	21.5	6822	22.2	4721
SCHS	Singapore	9978	47.5	43.5	3.5	38	-	0 (c)	-	0 (c)	23.1	133	23.1	9857
SIS	USA	15314	46.3	35	4.5	397	-	0 (c)	-	0 (c)	23.4	15261	25.8	12844
SMC	Sweden	26110	44.8	38.4	6.7	332	20.1	15622	-	0 (c)	22.8	13572	23.6	15681
USRTC	USA	52682	34.4	22.2	12.2	911	20.6	40519	21.5	27083	22.9	42389	24.4	21376
WLHS	Sweden	47017	39.6	29.2	10.7	662	20.2	44319	22.2	12445	22.9	28834	23.8	17873
All		758592	40.6	18	9.3	13082	20.8	545740	22.3	192575	23.1	503196	24.0	449969

Abbreviations: BMI: Body-mass index; BWHS: Black Women's Health Study; CLUE2: Campaign against Cancer and Heart Disease; CSDLH: Canadian Study of Diet, Lifestyle, and Health; CTS: California Teachers Study; E3N: Etude Epidémiologique auprès de femmes de la Mutuelle Générale de l'Education Nationale; EPIC: European Prospective Study into Cancer and Nutrition; GS: Breast Cancer Now Generations Study; HUNT2: Helseundersøkelsen i Nord-Trøndelag; MCC: Melbourne Collaborative Cohort Study; NHS: Nurses' Health Study; NHS2: Nurses' Health Study 2; NOWAC: Norwegian Women and Cancer Study; NYUWHS: New York University Women's Health Study; RERF: Radiation Effects Research Foundation Lifespan Study; SCHS: Singapore Chinese Health Study; SIS: Sister Study; SMC: Swedish Mammography Cohort; USRTC: United States Radiologic Technologist Cohort; WLHS: Sweden Women's Lifestyle and Health Study. References for details of each cohort have previously been published ¹ (a) case-cohort selected from a cohort of 28000 women recruited under age 55 (b) EPIC includes cohorts from 8 European countries (c) Data not collected at these age groups for these studies

eTable 2: Relative risk of premenopausal breast cancer in relation to BMI category, by age at BMI, for all subjects and subjects with information on BMI at age 18-24 years.

Age at BMI	BMI category, kg/m ²	All subjects		Subjects with BMI at age 18-24 years		
		Multivariable-adjusted		Multivariable-adjusted		Multivariable-adjusted plus BMI at age 18-24 years
		No. of cases	HR (95% CI) (a)	No. of cases	HR (95% CI) (a)	HR (95% CI) (b)
BMI at age 18-24 years						
	15.0-16.9	328	1.15 (1.03-1.29)	328	1.15 (1.03-1.29)	
	17.0-18.4	1169	1.09 (1.02-1.16)	1169	1.09 (1.02-1.16)	
	18.5-22.9	6364	1.00 (ref)	6364	1.00 (ref)	
	23.0-24.9	864	0.80 (0.75-0.86)	864	0.80 (0.75-0.86)	
	25.0-27.4	418	0.73 (0.66-0.81)	418	0.73 (0.66-0.81)	
	27.5-29.9	141	0.68 (0.58-0.81)	141	0.68 (0.58-0.81)	
	30.0-32.4	81	0.73 (0.58-0.90)	81	0.73 (0.58-0.90)	
	32.5-34.9	25	0.47 (0.32-0.70)	25	0.47 (0.32-0.70)	
	35.0-49.9	15	0.27 (0.16-0.45)	15	0.27 (0.16-0.45)	
	Trend per 5 kg/m ² (c)	7908	0.77 (0.73-0.80)	7908	0.77 (0.73-0.80)	
BMI at age 25-34 years						
	15.0-18.4	221	1.22 (1.06-1.40)	187	1.21 (1.04-1.41)	1.16 (0.99-1.36)
	18.5-22.9	2222	1.00 (ref)	1963	1.00 (ref)	1.00 (ref)
	23.0-24.9	607	0.91 (0.83-0.99)	546	0.91 (0.83-1.00)	0.94 (0.86-1.04)
	25.0-27.4	403	0.82 (0.74-0.91)	364	0.81 (0.72-0.90)	0.87 (0.77-0.97)
	27.5-29.9	176	0.76 (0.65-0.88)	165	0.77 (0.66-0.91)	0.86 (0.73-1.02)
	30.0-32.4	101	0.67 (0.54-0.81)	93	0.66 (0.54-0.82)	0.77 (0.62-0.96)
	32.5-34.9	58	0.63 (0.49-0.82)	56	0.65 (0.50-0.85)	0.79 (0.60-1.04)
	35.0-37.4	38	0.67 (0.48-0.92)	37	0.68 (0.49-0.95)	0.87 (0.62-1.23)
	37.5-39.9	24	0.64 (0.42-0.95)	23	0.63 (0.42-0.95)	0.84 (0.55-1.29)
	40.0-49.9	25	0.49 (0.33-0.74)	24	0.49 (0.33-0.74)	0.72 (0.46-1.11)
	Trend per 5 kg/m ² (c)	3654	0.85 (0.82-0.89)	3271	0.85 (0.82-0.89)	0.92 (0.88-0.97)
BMI at age 35-44 years						
	15.0-18.4	318	1.05 (0.94-1.18)	215	1.10 (0.96-1.26)	1.05 (0.92-1.21)
	18.5-22.9	5340	1.00 (ref)	3845	1.00 (ref)	1.00 (ref)

eTable 2: continued

Age at BMI	BMI category, kg/m ²	All subjects		Subjects with BMI at age 18-24 years		
		Multivariable-adjusted		Multivariable-adjusted		Multivariable-adjusted plus BMI at age 18-24 years
		No. of cases	HR (95% CI) (a)	No. of cases	HR (95% CI) (a)	HR (95% CI) (b)
	23.0-24.9	1882	0.91 (0.86-0.96)	1392	0.91 (0.85-0.97)	0.94 (0.88-1.00)
	25.0-27.4	1264	0.82 (0.77-0.88)	977	0.84 (0.78-0.90)	0.88 (0.82-0.95)
	27.5-29.9	636	0.81 (0.74-0.88)	498	0.82 (0.75-0.90)	0.89 (0.81-0.98)
	30.0-32.4	417	0.81 (0.73-0.90)	334	0.82 (0.74-0.92)	0.93 (0.82-1.04)
	32.5-34.9	214	0.70 (0.61-0.80)	174	0.71 (0.61-0.83)	0.82 (0.70-0.96)
	35.0-37.4	123	0.63 (0.53-0.75)	111	0.69 (0.57-0.84)	0.83 (0.69-1.01)
	37.5-39.9	74	0.60 (0.48-0.76)	65	0.64 (0.50-0.82)	0.79 (0.62-1.02)
	40.0-49.9	81	0.49 (0.39-0.61)	73	0.52 (0.41-0.65)	0.68 (0.53-0.87)
	Trend per 5 kg/m ² (c)	10031	0.87 (0.85-0.89)	7469	0.88 (0.86-0.90)	0.93 (0.91-0.96)
BMI at age 45-54 years						
	15.0-18.4	120	1.04 (0.87-1.25)	63	1.12 (0.87-1.44)	1.11 (0.86-1.43)
	18.5-22.9	2484	1.00 (ref)	1535	1.00 (ref)	1.00 (ref)
	23.0-24.9	1127	0.94 (0.87-1.01)	788	0.94 (0.87-1.03)	0.96 (0.88-1.05)
	25.0-27.4	859	0.85 (0.79-0.92)	644	0.87 (0.79-0.95)	0.89 (0.81-0.98)
	27.5-29.9	430	0.77 (0.69-0.85)	338	0.80 (0.71-0.90)	0.84 (0.74-0.94)
	30.0-32.4	302	0.80 (0.71-0.90)	234	0.79 (0.69-0.91)	0.85 (0.74-0.98)
	32.5-34.9	160	0.72 (0.61-0.84)	123	0.69 (0.57-0.83)	0.76 (0.63-0.92)
	35.0-37.4	112	0.76 (0.63-0.92)	83	0.71 (0.57-0.89)	0.80 (0.63-1.00)
	37.5-39.9	62	0.66 (0.52-0.86)	54	0.71 (0.54-0.93)	0.81 (0.61-1.07)
	40.0-49.9	70	0.56 (0.44-0.71)	60	0.57 (0.44-0.74)	0.68 (0.52-0.90)
	Trend per 5 kg/m ² (c)	5606	0.88 (0.86-0.91)	3859	0.88 (0.85-0.91)	0.91 (0.88-0.95)

Abbreviations: BMI, Body-mass Index; CI, confidence interval; HR, hazard ratio

- (a) HRs adjusted for attained age, cohort, year of birth, age at menarche, age at first birth, number of births, time since last birth and family history of breast cancer
(b) Additionally adjusted for BMI at age 18-24 years
(c) Linear trend per 5 unit difference fitted across BMI values from 18.5 to 49.9 kg/m²

eTable 3: Relative risk of premenopausal breast cancer in relation to BMI, by age at BMI and invasiveness of breast cancer

Age at BMI and invasiveness of breast cancer	No. of cases	Body-mass index category, kg/m ²				Trend per 5 kg/m ² BMI (b)	
		<18.5	18.5-24.9	25.0-29.9	≥ 30.0	HR (95% CI) (a)	P trend
BMI at age 18-24 years							
Invasive	7738	1.14 (1.07-1.21)	1.00 (ref)	0.75 (0.68-0.82)	0.55 (0.45-0.68)	0.77 (0.74-0.81)	<0.001
In-situ	1582	1.11 (0.96-1.27)	1.00 (ref)	0.71 (0.57-0.88)	0.61 (0.39-0.93)	0.71 (0.64-0.80)	<0.001
				P int=0.92		P int=0.20	
BMI at age 25-34 years							
Invasive	3109	1.25 (1.07-1.46)	1.00 (ref)	0.88 (0.79-0.97)	0.71 (0.61-0.82)	0.88 (0.84-0.92)	<0.001
In-situ	707	1.23 (0.90-1.68)	1.00 (ref)	0.59 (0.47-0.75)	0.47 (0.33-0.68)	0.76 (0.69-0.85)	<0.001
				P int=0.006		P int=0.02	
BMI at age 35-44 years							
Invasive	8486	0.99 (0.87-1.13)	1.00 (ref)	0.86 (0.82-0.91)	0.74 (0.68-0.80)	0.88 (0.86-0.90)	<0.001
In-situ	1775	1.54 (1.23-1.93)	1.00 (ref)	0.73 (0.64-0.83)	0.62 (0.51-0.74)	0.81 (0.76-0.86)	<0.001
				P int=<0.001		P int=0.01	
BMI at age 45-54 years							
Invasive	4676	1.01 (0.82-1.24)	1.00 (ref)	0.85 (0.79-0.91)	0.74 (0.68-0.82)	0.88 (0.85-0.91)	<0.001
In-situ	1010	1.35 (0.92-1.99)	1.00 (ref)	0.81 (0.69-0.94)	0.75 (0.62-0.91)	0.88 (0.82-0.94)	<0.001
				P int=0.51		P int=0.93	

Abbreviations: BMI, Body-mass Index; CI, confidence interval; HR, hazard ratio

(a) HRs adjusted for attained age, cohort, year of birth, age at menarche, age at first birth, number of births, time since last birth and family history of breast cancer

(b) Linear trend per 5 unit difference fitted across BMI values from 18.5 to 49.9 kg/m²

eTable 4: Characteristics of breast cancer cases, by most recent BMI category prior to diagnosis

	Most recent body-mass index (kg/m ²) (a)												All cases	
	<18.5		18.5-24.9		25.0-29.9		30.0-34.9		≥35					
	N or mean	%	N or mean	%	N or mean	%	N or mean	%	N or mean	%	N or mean	%		
Mean interval between age at BMI and diagnosis, years	3.4		3.0		2.4		2.1		2.0		2.8			
Age at diagnosis, years														
<40	48	14.9	810	9.7	220	7.6	74	7.1	39	7.6	1191	9.1		
40-44	91	28.2	1962	23.6	655	22.8	243	23.3	127	24.9	3078	23.5		
45-49	146	45.2	3995	48.0	1355	47.1	472	45.3	237	46.4	6205	47.4		
50-54	38	11.8	1564	18.8	646	22.5	252	24.2	108	21.1	2608	19.9		
Race/ethnicity														
Caucasian	193	84.6	5350	90.0	1890	82.5	695	76.0	309	66.0	8437	85.7		
Black	13	5.7	337	5.7	323	14.1	192	21.0	141	30.1	1006	10.2		
Asian	18	7.9	168	2.8	39	1.7	9	1.0	1	0.2	235	2.4		
Other	4	1.8	88	1.5	39	1.7	19	2.1	17	3.6	167	1.7		
Not known	95		2388		585		126		43		3237			
Ever had mammography for screening (b)														
No	63	28.0	1442	25.7	379	20.3	119	18.1	57	16.4	2060	23.7		
Yes	162	72.0	4169	74.3	1489	79.7	540	81.9	290	83.6	6650	76.3		
Not known	98		2720		1008		382		164		4372			
Invasiveness														
In situ	70	21.7	1385	16.7	440	15.5	156	15.2	87	17.5	2138	16.5		
Invasive	252	78.3	6904	83.3	2401	84.5	868	84.8	411	82.5	10836	83.5		
Not known	1		42		35		17		13		108			
ER status														
Positive	115	71.4	3532	75.2	1352	74.0	537	73.2	263	72.9	5799	74.6		
Negative	46	28.6	1163	24.8	475	26.0	197	26.8	98	27.1	1979	25.4		
Borderline/not known	162		3636		1049		307		150		5304			
Combined ER and PR status														
ER+PR+	95	63.3	2744	63.2	1086	63.9	437	63.6	208	61.7	4570	63.3		
ER+PR-	11	7.3	487	11.2	162	9.5	60	8.7	36	10.7	756	10.5		
ER-PR+	39	26.0	836	19.3	365	21.5	158	23.0	86	25.5	1484	20.6		
ER-PR-	5	3.3	274	6.3	86	5.1	32	4.7	7	2.1	404	5.6		
Unclassified	173		3990		1177		354		174		5868			

eTable 4:continued

	Most recent body-mass index (kg/m ²) (a)											
	<18.5		18.5-24.9		25.0-29.9		30.0-34.9		≥35		All cases	
	N or mean	%	N or mean	%	N or mean	%	N or mean	%	N or mean	%	N or mean	%
Clinicopathological surrogate definition of intrinsic tumour subtype (c)												
Luminal A-like	40	25.0	1201	25.8	514	28.4	206	28.2	97	27.2	2058	26.7
Luminal B-like HER2-	8	5.0	240	5.2	82	4.5	35	4.8	17	4.8	382	5.0
Luminal B-like HER2+	14	8.8	287	6.2	131	7.2	62	8.5	22	6.2	516	6.7
Luminal B-like, unclassified	7	4.4	444	9.5	135	7.5	41	5.6	21	5.9	648	8.4
HER2-enriched	3	1.9	121	2.6	54	3.0	19	2.6	10	2.8	207	2.7
Triple-negative	10	6.3	269	5.8	116	6.4	53	7.3	35	9.8	483	6.3
Unclassified luminal	52	32.5	1644	35.3	584	32.2	228	31.2	113	31.7	2621	34.0
Unclassified non-luminal	26	16.3	446	9.6	195	10.8	86	11.8	41	11.5	794	10.3
Unclassified	163		3679		1065		311		155		5373	
All cases of breast cancer	323	100.0	8331	100.0	2876	100.0	1041	100.0	511	100.0	13082	100.0

Abbreviations: ER, oestrogen-receptor; HER2, Human Epidermal Growth Factor Receptor-2; PR, progesterone-receptor

(a) Most recently assessed BMI prior to diagnosis

(b) Most recent mammographic screening status prior to diagnosis

(c) Luminal A-like: ER+PR+HER2-

Luminal B-like, all: All ER+ and/or PR+ tumours that are not ER+PR+HER2- with subtypes Luminal B-like, HER2-: ER+PR-HER2- and ER-PR+HER2- and Luminal B-like, HER2+: [ER+ and/or PR+] and HER2+

Non-luminal, all: ER-PR- regardless of HER2 status with subtypes HER2-enriched: ER-PR-HER2+ and Triple-negative: ER-PR-HER2-

eTable 5: Relative risk of premenopausal breast cancer in relation to BMI category, by age at BMI and oestrogen or progesterone receptor status of breast cancer

Age at BMI and hormone-receptor status	No. of cases	Body-mass index category, kg/m ²				Trend per 5 kg/m ² (b)	
		<18.5	18.5-24.9	25.0-29.9	≥30.0	HR (95% CI) (a)	P trend
BMI age 18-24 years							
Oestrogen-receptor							
ER+	4436	1.15 (1.06-1.25)	1.00 (ref)	0.75 (0.66-0.84)	0.55 (0.43-0.72)	0.76 (0.71-0.81)	<0.001
ER-	1478	1.18 (1.02-1.35)	1.00 (ref)	0.79 (0.65-0.97)	0.45 (0.28-0.72)	0.81 (0.74-0.90)	<0.001
Progesterone-receptor				P int=0.82(c)		P int=0.25(c)	
PR+	3710	1.12 (1.03-1.23)	1.00 (ref)	0.74 (0.64-0.84)	0.47 (0.35-0.63)	0.74 (0.70-0.80)	<0.001
PR-	1723	1.20 (1.05-1.37)	1.00 (ref)	0.77 (0.63-0.93)	0.58 (0.40-0.86)	0.80 (0.73-0.88)	<0.001
BMI age 25-34 years				P int=0.70(c)		P int=0.21(c)	
Oestrogen-receptor							
ER+	1884	1.37 (1.13-1.65)	1.00 (ref)	0.81 (0.71-0.92)	0.64 (0.53-0.77)	0.85 (0.80-0.90)	<0.001
ER-	613	1.03 (0.70-1.52)	1.00 (ref)	0.89 (0.72-1.10)	0.80 (0.60-1.06)	0.90 (0.83-0.99)	0.025
Progesterone-receptor				P int=0.24(c)		P int=0.26(c)	
PR+	1626	1.30 (1.05-1.61)	1.00 (ref)	0.83 (0.72-0.95)	0.58 (0.47-0.71)	0.83 (0.78-0.88)	<0.001
PR-	719	1.25 (0.90-1.75)	1.00 (ref)	0.86 (0.70-1.05)	0.90 (0.70-1.16)	0.94 (0.86-1.02)	0.122
BMI age 35-44 years				P int=0.06(c)		P int=0.02(c)	
Oestrogen-receptor							
ER+	4904	1.02 (0.86-1.21)	1.00 (ref)	0.83 (0.77-0.90)	0.71 (0.64-0.78)	0.87 (0.84-0.90)	<0.001
ER-	1588	1.06 (0.78-1.43)	1.00 (ref)	0.96 (0.85-1.09)	0.81 (0.68-0.95)	0.92 (0.87-0.97)	0.001
Progesterone-receptor				P int=0.20(c)		P int=0.07(c)	
PR+	4213	1.04 (0.87-1.25)	1.00 (ref)	0.84 (0.77-0.91)	0.71 (0.64-0.79)	0.86 (0.83-0.89)	<0.001
PR-	1830	1.05 (0.80-1.39)	1.00 (ref)	0.91 (0.81-1.02)	0.79 (0.68-0.92)	0.91 (0.86-0.95)	<0.001
BMI age 45-54 years				P int=0.52(c)		P int=0.08(c)	

Oestrogen-receptor							
ER+	3016	0.76 (0.56-1.02)	1.00 (ref)	0.86 (0.79-0.94)	0.77 (0.69-0.86)	0.90 (0.86-0.93)	<0.001
ER-	867	1.28 (0.83-1.98)	1.00 (ref)	0.81 (0.69-0.96)	0.75 (0.61-0.91)	0.90 (0.84-0.97)	0.004
Progesterone-receptor							
PR+	2589	0.83 (0.61-1.13)	1.00 (ref)	0.86 (0.78-0.95)	0.79 (0.70-0.89)	0.91 (0.87-0.95)	<0.001
PR-	1064	1.07 (0.70-1.63)	1.00 (ref)	0.80 (0.69-0.93)	0.71 (0.59-0.86)	0.87 (0.82-0.93)	<0.001
				P int=0.22(c)		P int=0.84(c)	
				P int=0.49(c)		P int=0.26(c)	

Abbreviations: BMI, Body-mass Index; CI, confidence interval; ER, oestrogen-receptor; HR, hazard ratio; PR, progesterone-receptor

(a) HRs adjusted for attained age, cohort, year of birth, age at menarche, age at first birth, number of births, time since last birth and family history of breast cancer

(b) Linear trend per 5 unit difference fitted across BMI values from 18.5 to 49.9 kg/m²

(c) Tests for heterogeneity in effect by ER or PR status obtained from an Augmentation model.⁸

eTable 6: Relative risk of premenopausal breast cancer per 5 kg/m² difference in BMI, by age at BMI and other breast cancer risk factors

Variable (a)	Age at BMI, years							
	BMI at age 18-24 years		BMI at age 25-34 years		BMI at age 35-44 years		BMI at age 45-54 years	
	No. of cases	HR (95% CI) (b)	No. of cases	HR (95% CI) (b)	No. of cases	HR (95% CI) (b)	No. of cases	HR (95% CI) (b)
Adult height, cms								
<160	1378	0.79 (0.71-0.87)	666	0.86 (0.78-0.95)	1881	0.88 (0.84-0.93)	1101	0.88 (0.82-0.94)
160-169	4378	0.76 (0.71-0.80)	1901	0.85 (0.81-0.90)	5509	0.86 (0.83-0.89)	3156	0.87 (0.84-0.90)
≥170	2152	0.79 (0.72-0.85) P int=0.65	1087	0.85 (0.79-0.92) P int=0.98	2641	0.89 (0.85-0.93) P int=0.46	1349	0.92 (0.87-0.97) P int=0.26
Age at menarche, years								
<12	1806	0.78 (0.72-0.84)	846	0.90 (0.84-0.97)	2187	0.88 (0.85-0.92)	1209	0.92 (0.87-0.97)
12-13	4386	0.77 (0.72-0.81)	2067	0.83 (0.78-0.88)	5461	0.87 (0.84-0.90)	3098	0.87 (0.83-0.90)
≥14	1562	0.75 (0.67-0.84) P int=0.89	671	0.84 (0.75-0.94) P int=0.17	2111	0.84 (0.79-0.89) P int=0.41	1180	0.89 (0.83-0.96) P int=0.20
Ever having had a birth								
No	1200	0.72 (0.66-0.79)	638	0.79 (0.73-0.87)	1436	0.84 (0.80-0.89)	698	0.85 (0.79-0.91)
Yes	6461	0.78 (0.74-0.82) P int=0.16	2823	0.88 (0.84-0.93) P int=0.03	8180	0.88 (0.85-0.90) P int=0.15	4734	0.89 (0.86-0.92) P int=0.18
Age at first birth, years (parous)								
<25	2472	0.77 (0.71-0.83)	885	0.89 (0.82-0.96)	3285	0.86 (0.82-0.90)	2040	0.90 (0.86-0.94)
25-34	3550	0.78 (0.73-0.83)	1758	0.87 (0.82-0.93)	4333	0.88 (0.85-0.92)	2396	0.88 (0.84-0.92)
≥35	383	0.81 (0.67-0.97) P int=0.89	161	0.84 (0.68-1.03) P int=0.84	522	0.91 (0.82-1.00) P int=0.45	283	0.93 (0.83-1.05) P int=0.63
Number of births (parous)								
1	1160	0.82 (0.74-0.90)	603	0.82 (0.74-0.91)	1504	0.87 (0.82-0.92)	787	0.92 (0.86-0.99)
2	3061	0.79 (0.74-0.86)	1355	0.90 (0.84-0.97)	3893	0.89 (0.85-0.92)	2152	0.91 (0.87-0.96)
≥3	2191	0.72 (0.65-0.79) P int=0.12	816	0.86 (0.78-0.95) P int=0.26	2676	0.86 (0.82-0.90) P int=0.63	1763	0.85 (0.81-0.90) P int=0.09
Time since last birth, years (parous)								
<5	298	0.89 (0.72-1.09)	269	0.89 (0.77-1.04)	281	0.86 (0.75-0.99)	21	1.19 (0.81-1.74)
5-9	814	0.84 (0.74-0.96)	486	0.86 (0.76-0.96)	1036	0.90 (0.83-0.96)	224	0.88 (0.76-1.02)
10-14	1431	0.75 (0.68-0.84)	719	0.86 (0.78-0.95)	1868	0.88 (0.84-0.93)	729	0.87 (0.80-0.94)

eTable 6: continued

Variable (a)	Age at BMI, years							
	BMI at age 18-24 years		BMI at age 25-34 years		BMI at age 35-44 years		BMI at age 45-54 years	
	No. of cas es	HR (95% CI) (b)	No. of cas es	HR (95% CI) (b)	No. of cas es	HR (95% CI) (b)	No. of cas es	HR (95% CI) (b)
15-19	171				230		144	
	5	0.76 (0.69-0.84)	662	0.87 (0.79-0.96)	7	0.87 (0.83-0.92)	6	0.89 (0.84-0.94)
≥20	169				223		213	
Ever used oral contracep tion	1	0.77 (0.70-0.85) P int=0.66	499	0.91 (0.81-1.01) P int=0.99	1	0.86 (0.81-0.90) P int=0.85	1	0.90 (0.86-0.95) P int=0.43
No	126				202		204	
	7	0.68 (0.61-0.76)	384	0.85 (0.75-0.97)	6	0.81 (0.77-0.86)	4	0.85 (0.81-0.90)
Yes	604		297		716		331	
Ever diagnosis with infertility	5	0.79 (0.75-0.83) P int=0.02	9	0.86 (0.82-0.90) P int=0.84	1	0.88 (0.86-0.91) P int=0.009	9	0.90 (0.87-0.94) P int=0.08
No	352		176		422		175	
	5	0.78 (0.73-0.83)	7	0.84 (0.79-0.90)	0	0.89 (0.86-0.92)	2	0.92 (0.88-0.96)
Yes	813		415		108		573	
Ever diagnosis with PCOS		0.74 (0.65-0.85) P int=0.52		0.86 (0.76-0.96) P int=0.82	9	0.85 (0.80-0.91) P int=0.30		0.90 (0.83-0.98) P int=0.63
No	101				125			
	5	0.78 (0.69-0.90)	417	0.81 (0.71-0.94)	3	0.88 (0.82-0.94)	561	0.92 (0.84-1.01)
Yes	217		110		262		143	
Ever had a mammogr am		0.67 (0.53-0.86) P int=0.28		0.72 (0.58-0.91) P int=0.39		0.78 (0.69-0.89) P int=0.12		0.84 (0.73-0.98) P int=0.30

Family history of breast cancer	No	132 2 370	0.84 (0.75-0.93)	647 137	0.91 (0.83-1.00)	138 9 539	0.89 (0.83-0.95)	421 354	0.91 (0.81-1.02)
	Yes	6	0.76 (0.71-0.81) P int=0.12	8	0.83 (0.77-0.88) P int=0.08	3	0.87 (0.84-0.89) P int=0.52	9	0.88 (0.85-0.92) P int=0.67
Attained education level	No	588 9 161	0.75 (0.72-0.79)	274 9	0.86 (0.82-0.90)	680 0 231	0.87 (0.84-0.89)	381 4 144	0.88 (0.85-0.91)
	Yes	0	0.80 (0.73-0.87) P int=0.32	768	0.83 (0.75-0.91) P int=0.45	2	0.89 (0.85-0.93) P int=0.34	6	0.90 (0.86-0.95) P int=0.41
Primary and lower		325	0.84 (0.66-1.05)	35	0.90 (0.61-1.32)	318	0.76 (0.64-0.89)	226	0.82 (0.68-0.99)
High School		485	0.80 (0.67-0.96)	204	0.84 (0.72-0.99)	522	0.88 (0.80-0.97)	203	0.84 (0.72-0.98)
Some college		132	0.81 (0.73-0.90)	831	0.89 (0.82-0.96)	168	0.86 (0.82-0.91)	563	0.90 (0.83-0.98)
University		482 1	0.75 (0.71-0.79) P int=0.51	228 8	0.85 (0.80-0.90) P int=0.82	550 2	0.88 (0.85-0.91) P int=0.30	334 3	0.88 (0.85-0.92) P int=0.72

eTable 6: continued

Variable (a)	Age at BMI, years							
	BMI at age 18-24 years		BMI at age 25-34 years		BMI at age 35-44 years		BMI at age 45-54 years	
	No. of cases	HR (95% CI) (b)	No. of cases	HR (95% CI) (b)	No. of cases	HR (95% CI) (b)	No. of cases	HR (95% CI) (b)
Ethnicity								
Caucasian	5922	0.73 (0.70-0.77)	2836	0.83 (0.79-0.88)	6708	0.86 (0.84-0.89)	3780	0.88 (0.85-0.91)
Black	709	0.84 (0.76-0.93)	460	0.90 (0.83-0.98)	820	0.90 (0.85-0.95)	282	0.91 (0.83-1.01)
Asian	79	0.69 (0.40-1.18) P int=0.08	93	0.89 (0.61-1.31) P int=0.29	124	1.02 (0.77-1.36) P int=0.30	90	0.80 (0.57-1.12) P int=0.68
Continent								
North-America	5603	0.76 (0.72-0.80)	2960	0.86 (0.82-0.90)	6669	0.88 (0.86-0.90)	3658	0.89 (0.86-0.92)

Europe	2236	0.80 (0.73-0.88)	657	0.81 (0.72-0.90)	3279	0.84 (0.80-0.89)	1857	0.85 (0.79-0.91)
Asia			37	1.79 (0.95-3.40)	38	0.75 (0.39-1.44)	37	0.71 (0.39-1.28)
Australia	69	0.65 (0.38-1.12)	2960	0.86 (0.82-0.90)	45	0.68 (0.45-1.02)	54	1.06 (0.79-1.40)
		P int=0.48		P int=0.07		P int=0.25		P int=0.33
Year of birth								
<1940	976	0.75 (0.66-0.85)	22	1.55 (0.66-3.66)	1012	0.85 (0.78-0.92)	1083	0.84 (0.78-0.91)
1940-1949	1770	0.72 (0.65-0.79)	777	0.83 (0.74-0.92)	2912	0.83 (0.79-0.88)	2410	0.86 (0.82-0.90)
1950-1959	3623	0.78 (0.73-0.83)	1461	0.86 (0.80-0.92)	4563	0.88 (0.85-0.91)	1703	0.90 (0.86-0.95)
≥1960	1539	0.80 (0.73-0.87)	1394	0.85 (0.80-0.91)	1544	0.90 (0.85-0.94)	410	0.94 (0.87-1.03)
		P int=0.41		P int=0.58		P int=0.20		P int=0.11

Abbreviations: BMI, Body-mass Index; CI, confidence interval; HR, hazard ratio; PCOS, polycystic ovary syndrome

- (a) Stratifying variables are time-updated, where possible, for reproductive variables, oral contraceptive use, infertility, PCOS, screening mammogram and family history of breast cancer.
- (b) Hazard ratio represents linear trend per 5 kg/m² difference fitted across BMI values from 18.5 to 49.9 kg/m² and are adjusted for attained age, cohort, year of birth, age at menarche, age at first birth, number of births, time since last birth and family history of breast cancer.

eTable 7: Relative risk of premenopausal breast cancer in relation to BMI category, by age at BMI. For (1) all subjects included in main analysis (2) breast cancer with known ER, PR and HER2 status as endpoint (3) excluding subjects with weight assessed less than three years postpartum (4) strictly known premenopausal time only (5) excluding first two years of follow-up.

Age at BMI and BMI category, kg/m ²	All subjects		Cases with information on all of ER, PR and HER2 status only		Excluding subjects with weights recalled or reported <3 years postpartum		Analyses restricted to strictly known premenopausal time only		Analyses excluding first two years of follow-up	
	No. of cases	HR (95% CI) (a)	No. of cases	HR (95% CI) (a)	No. of cases	HR (95% CI) (a)	No. of cases	HR (95% CI) (a)	No. of cases	HR (95% CI) (a)
BMI at age 18-24 years										
15.0-16.9	328	1.15 (1.03-1.29)	87	1.09 (0.88-1.35)	293	1.12 (1.00-1.26)	184	1.20 (1.04-1.40)	283	1.15 (1.02-1.30)
17.0-18.4	1169	1.09 (1.02-1.16)	342	1.08 (0.96-1.21)	1068	1.08 (1.01-1.15)	636	1.08 (1.00-1.18)	998	1.07 (1.00-1.15)
18.5-22.9	6364	1.00 (ref)	2046	1.00 (ref)	5924	1.00 (ref)	3701	1.00 (ref)	5529	1.00 (ref)
23.0-24.9	864	0.80 (0.75-0.86)	277	0.78 (0.69-0.88)	793	0.80 (0.74-0.86)	470	0.77 (0.70-0.85)	758	0.81 (0.75-0.88)
25.0-27.4	418	0.73 (0.66-0.81)	137	0.71 (0.60-0.84)	384	0.73 (0.66-0.81)	251	0.75 (0.66-0.85)	367	0.73 (0.66-0.81)
27.5-29.9	141	0.68 (0.58-0.81)	54	0.76 (0.58-0.99)	127	0.67 (0.56-0.80)	78	0.63 (0.51-0.79)	128	0.70 (0.58-0.83)
30.0-32.4	81	0.73 (0.58-0.90)	21	0.55 (0.36-0.84)	72	0.70 (0.56-0.89)	44	0.67 (0.50-0.90)	74	0.74 (0.59-0.93)
32.5-34.9	25	0.47 (0.32-0.70)	7	0.40 (0.19-0.84)	23	0.48 (0.32-0.72)	11	0.39 (0.22-0.71)	19	0.40 (0.25-0.62)
35.0-49.9	15	0.27 (0.16-0.45)	6	0.35 (0.16-0.77)	15	0.30 (0.18-0.50)	7	0.26 (0.12-0.55)	13	0.26 (0.15-0.45)
Trend per 5 kg/m ² (b)	7908	0.77 (0.73-0.80)	2548	0.75 (0.69-0.81)	7338	0.76 (0.73-0.80)	4562	0.74 (0.70-0.78)	6888	0.77 (0.73-0.80)
BMI at age 25-34 years										
15.0-18.4	221	1.22 (1.06-1.40)	85	1.25 (1.00-1.56)	151	1.29 (1.09-1.53)	132	1.22 (1.02-1.46)	203	1.20 (1.04-1.38)
18.5-22.9	2222	1.00 (ref)	834	1.00 (ref)	1405	1.00 (ref)	1359	1.00 (ref)	2130	1.00 (ref)

23.0-24.9	607	0.91 (0.83-0.99)	213	0.87 (0.74-1.01)	412	0.99 (0.89-1.11)	347	0.92 (0.82-1.03)	575	0.90 (0.82-0.99)
25.0-27.4	403	0.82 (0.74-0.91)	138	0.79 (0.66-0.95)	259	0.84 (0.74-0.97)	216	0.82 (0.71-0.95)	390	0.83 (0.74-0.92)
27.5-29.9	176	0.76 (0.65-0.88)	66	0.83 (0.64-1.06)	127	0.86 (0.71-1.03)	97	0.85 (0.69-1.05)	167	0.75 (0.64-0.88)
30.0-32.4	101	0.67 (0.54-0.81)	34	0.66 (0.47-0.93)	71	0.70 (0.55-0.88)	49	0.64 (0.48-0.85)	99	0.68 (0.56-0.84)
32.5-34.9	58	0.63 (0.49-0.82)	21	0.70 (0.45-1.08)	39	0.61 (0.44-0.84)	28	0.65 (0.45-0.95)	56	0.64 (0.49-0.83)
35.0-37.4	38	0.67 (0.48-0.92)	11	0.59 (0.33-1.08)	29	0.72 (0.50-1.05)	17	0.63 (0.39-1.01)	37	0.68 (0.49-0.94)
37.5-39.9	24	0.64 (0.42-0.95)	4	0.35 (0.13-0.95)	13	0.49 (0.28-0.84)	6	0.38 (0.17-0.85)	23	0.63 (0.42-0.96)
40.0-49.9	25	0.49 (0.33-0.74)	9	0.66 (0.34-1.27)	17	0.43 (0.27-0.70)	9	0.46 (0.24-0.89)	24	0.49 (0.33-0.74)

eTable 7: continued

Age at BMI and BMI category, kg/m ²	All subjects		Cases with information on all of ER, PR and HER2 status only		Excluding subjects with weights recalled or reported <3 years postpartum		Analyses restricted to strictly known premenopausal time only		Analyses excluding first two years of follow-up only	
	No. of cases	HR (95% CI) (a)	No. of cases	HR (95% CI) (a)	No. of cases	HR (95% CI) (a)	No. of cases	HR (95% CI) (a)	No. of cases	HR (95% CI) (a)
Trend per 5 kg/m ² (b)	3654	0.85 (0.82-0.89)	1330	0.85 (0.80-0.92)	2372	0.85 (0.81-0.90)	2128	0.85 (0.80-0.90)	3501	0.85 (0.82-0.89)
BMI at age 35-44 years										
15.0-18.4	318	1.05 (0.94-1.18)	91	1.14 (0.92-1.40)	256	1.06 (0.93-1.20)	234	1.13 (0.99-1.29)	283	1.06 (0.94-1.20)
18.5-22.9	5340	1.00 (ref)	1556	1.00 (ref)	4441	1.00 (ref)	3595	1.00 (ref)	4724	1.00 (ref)
23.0-24.9	1882	0.91 (0.86-0.96)	576	0.93 (0.85-1.03)	1583	0.91 (0.86-0.97)	1129	0.90 (0.84-0.96)	1683	0.93 (0.88-0.98)
25.0-27.4	1264	0.82 (0.77-0.88)	389	0.84 (0.75-0.94)	1073	0.83 (0.77-0.89)	741	0.84 (0.78-0.91)	1127	0.83 (0.78-0.89)
27.5-29.9	636	0.81 (0.74-0.88)	211	0.86 (0.74-0.99)	563	0.84 (0.77-0.92)	358	0.82 (0.73-0.91)	551	0.79 (0.72-0.87)

30.0-32.4	417	0.81 (0.73-0.90)	135	0.85 (0.71-1.01)	364	0.83 (0.75-0.93)	225	0.81 (0.70-0.92)	375	0.82 (0.74-0.91)
32.5-34.9	214	0.70 (0.61-0.80)	78	0.81 (0.64-1.02)	186	0.70 (0.60-0.81)	110	0.66 (0.55-0.80)	188	0.69 (0.59-0.79)
35.0-37.4	123	0.63 (0.53-0.75)	41	0.65 (0.48-0.89)	106	0.62 (0.51-0.75)	61	0.57 (0.45-0.74)	110	0.63 (0.52-0.76)
37.5-39.9	74	0.60 (0.48-0.76)	20	0.53 (0.34-0.82)	63	0.59 (0.46-0.76)	31	0.49 (0.34-0.70)	61	0.55 (0.43-0.71)
40.0-49.9	81	0.49 (0.39-0.61)	20	0.39 (0.25-0.60)	73	0.50 (0.39-0.63)	36	0.43 (0.31-0.59)	79	0.52 (0.42-0.66)
Trend per 5 kg/m ² (b)	1003 1	0.87 (0.85-0.89)	3026	0.88 (0.85-0.92)	8452	0.87 (0.85-0.89)	6286	0.86 (0.83-0.89)	8898	0.87 (0.85-0.89)
BMI at age 45-54 years										
15.0-18.4	120	1.04 (0.87-1.25)	23	0.92 (0.60-1.39)	120	1.08 (0.90-1.30)	102	1.06 (0.87-1.29)	103	1.10 (0.90-1.34)
18.5-22.9	2484	1.00 (ref)	668	1.00 (ref)	2436	1.00 (ref)	2063	1.00 (ref)	2037	1.00 (ref)
23.0-24.9	1127	0.94 (0.87-1.01)	366	1.01 (0.89-1.14)	1104	0.93 (0.87-1.00)	869	0.91 (0.84-0.99)	933	0.95 (0.88-1.03)
25.0-27.4	859	0.85 (0.79-0.92)	303	0.91 (0.79-1.04)	844	0.85 (0.79-0.92)	649	0.84 (0.77-0.92)	710	0.86 (0.78-0.93)
27.5-29.9	430	0.77 (0.69-0.85)	176	0.89 (0.76-1.06)	429	0.78 (0.70-0.86)	331	0.78 (0.70-0.88)	348	0.75 (0.67-0.84)
30.0-32.4	302	0.80 (0.71-0.90)	117	0.84 (0.69-1.02)	302	0.81 (0.71-0.91)	221	0.77 (0.67-0.89)	260	0.81 (0.71-0.92)
32.5-34.9	160	0.72 (0.61-0.84)	68	0.79 (0.61-1.02)	159	0.72 (0.61-0.85)	113	0.68 (0.56-0.82)	136	0.70 (0.59-0.84)
35.0-37.4	112	0.76 (0.63-0.92)	58	0.98 (0.74-1.28)	112	0.76 (0.63-0.93)	86	0.77 (0.62-0.96)	96	0.74 (0.60-0.91)
37.5-39.9	62	0.66 (0.52-0.86)	21	0.56 (0.36-0.86)	62	0.67 (0.52-0.87)	42	0.60 (0.44-0.82)	57	0.69 (0.53-0.89)
40.0-49.9	70	0.56 (0.44-0.71)	33	0.65 (0.46-0.92)	69	0.55 (0.43-0.71)	48	0.52 (0.39-0.69)	61	0.54 (0.42-0.70)

eTable 7: continued

Age at BMI and BMI	All subjects		Cases with information on all of ER, PR and HER2 status only		Excluding subjects with weights recalled or reported <3 years postpartum		Analyses restricted to strictly known premenopausal time only		Analyses excluding first two years of follow-up	
	No. of	HR (95% CI) (a)	No. of	HR (95% CI) (a)	No. of	HR (95% CI) (a)	No. of	HR (95% CI) (a)	No. of cases	HR (95% CI) (a)

category, kg/m ²	case s		case s		case s		case s		case s	
Trend per 5 kg/m ² (b)	5606	0.88 (0.86- 0.91)	1810	0.92 (0.87- 0.96)	5517	0.88 (0.86- 0.91)	4422	0.88 (0.85- 0.91)	4638	0.88 (0.85- 0.91)

Abbreviations: BMI, Body-mass Index; HR, hazard ratio; CI, confidence interval; HER2, human epidermal growth factor receptor-2; ER, oestrogen-receptor; PR, progesterone-receptor

- (a) HRs adjusted for attained age, cohort, year of birth, age at menarche, age at first birth, number of births, time since last birth and family history of breast cancer
- (b) Linear trend per 5 unit difference fitted across BMI values from 18.5 to 49.9 kg/m²

eTable 8: Relative risk of premenopausal breast cancer in relation to BMI category at age 18-24 years, excluding subjects contributing to each successive cohort.

Excluded cohort	No. of cases	Body-mass index category, kg/m ²					Trend per 5 kg/m ² (b)	P trend
		<18.5	18.5-24.9	25.0-29.9	30.0-34.9	≥ 35.0		
		HR (95% CI)(a)	HR (95% CI)	HR (95% CI)(a)	HR (95% CI)(a)	HR (95% CI)(a)		
No exclusions	9405	1.13 (1.07-1.20)	1.00 (ref)	0.74 (0.68-0.81)	0.66 (0.55-0.81)	0.28 (0.17-0.47)	0.77 (0.73-0.80)	<0.001
BWHS	8585	1.11 (1.05-1.18)	1.00 (ref)	0.76 (0.69-0.83)	0.64 (0.51-0.79)	0.23 (0.12-0.44)	0.75 (0.72-0.79)	<0.001
CLUE2	9341	1.13 (1.07-1.20)	1.00 (ref)	0.74 (0.68-0.81)	0.67 (0.56-0.82)	0.29 (0.17-0.47)	0.77 (0.73-0.80)	<0.001
CSDLH	9192	1.14 (1.07-1.20)	1.00 (ref)	0.74 (0.68-0.81)	0.66 (0.54-0.80)	0.28 (0.17-0.47)	0.77 (0.73-0.80)	<0.001
CTS	8769	1.13 (1.07-1.20)	1.00 (ref)	0.74 (0.68-0.81)	0.67 (0.55-0.82)	0.30 (0.17-0.50)	0.77 (0.74-0.81)	<0.001
E3N (c)	-	-	-	-	-	-	-	-
EPIC	8993	1.14 (1.08-1.21)	1.00 (ref)	0.74 (0.68-0.81)	0.66 (0.54-0.80)	0.29 (0.17-0.48)	0.76 (0.73-0.80)	<0.001
GS	8764	1.13 (1.07-1.20)	1.00 (ref)	0.73 (0.67-0.80)	0.65 (0.53-0.80)	0.30 (0.18-0.49)	0.76 (0.73-0.80)	<0.001
HUNT2 (d)	-	-	-	-	-	-	-	-
MCC	9322	1.13 (1.07-1.20)	1.00 (ref)	0.74 (0.68-0.81)	0.67 (0.55-0.81)	0.28 (0.17-0.47)	0.77 (0.73-0.80)	<0.001
NHS	7428	1.12 (1.05-1.19)	1.00 (ref)	0.76 (0.69-0.84)	0.65 (0.53-0.81)	0.26 (0.15-0.45)	0.79 (0.75-0.83)	<0.001
NHS2	6912	1.14 (1.07-1.22)	1.00 (ref)	0.72 (0.65-0.80)	0.71 (0.57-0.89)	0.30 (0.17-0.55)	0.76 (0.72-0.80)	<0.001
NOWAC	8638	1.14 (1.08-1.21)	1.00 (ref)	0.73 (0.67-0.80)	0.65 (0.53-0.79)	0.29 (0.17-0.48)	0.76 (0.73-0.80)	<0.001
NYUWHS (c)	-	-	-	-	-	-	-	-
RERF (d)	-	-	-	-	-	-	-	-
SCHS (c)	-	-	-	-	-	-	-	-
SIS (c)	-	-	-	-	-	-	-	-
SMC	9195	1.14 (1.07-1.20)	1.00 (ref)	0.74 (0.68-0.81)	0.66 (0.55-0.80)	0.28 (0.17-0.47)	0.76 (0.73-0.80)	<0.001
USRTC	8948	1.13 (1.07-1.20)	1.00 (ref)	0.74 (0.68-0.81)	0.69 (0.56-0.83)	0.28 (0.16-0.47)	0.77 (0.73-0.80)	<0.001
WLHS	8773	1.13 (1.07-1.20)	1.00 (ref)	0.74 (0.68-0.81)	0.67 (0.56-0.82)	0.29 (0.17-0.48)	0.77 (0.73-0.80)	<0.001

Abbreviations: BMI, Body-mass Index; CI, confidence interval; HR, hazard ratio; for cohort abbreviations see page 3.

(a) HRs adjusted for attained age, cohort, year of birth, age at menarche, age at first birth, number of births, time since last birth and family history of breast cancer

(b) Linear trend per 5 unit difference fitted across BMI values from 18.5 to 49.9 kg/m²

(c) BMI data at age 18-24 years not collected for these cohorts

(d) Insufficient number of cases with BMI at age 18-24 years for these cohorts

eTable 9: Relative risk of premenopausal breast cancer in relation to BMI category at age 45-54 years, excluding subjects contributing to each successive cohort.

Abbreviations: BMI, Body-mass Index; CI, confidence interval; HR, hazard ratio; for cohort abbreviations see page 3.

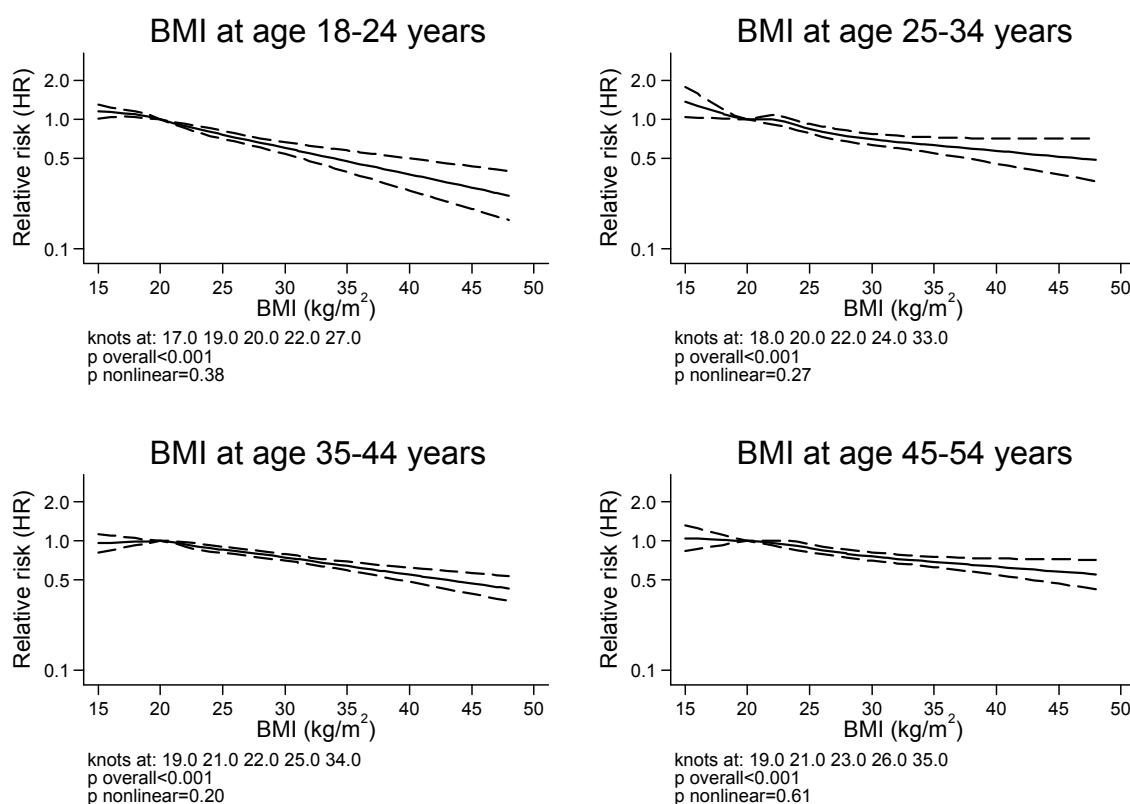
Excluded cohort	No. of cases	Body-mass index category, kg/m ²					Trend per 5 kg/m ² (b)	P trend
		<18.5	18.5-24.9	25.0-29.9	30.0-34.9	≥ 35.0		
		HR (95% CI) (a)	HR (95% CI)	HR (95% CI) (a)	HR (95% CI) (a)	HR (95% CI) (a)		
No exclusions	5726	1.06 (0.88-1.27)	1.00 (ref)	0.84 (0.79-0.90)	0.79 (0.71-0.87)	0.68 (0.60-0.78)	0.88 (0.86-0.91)	<0.001
BWHS	5515	1.06 (0.89-1.28)	1.00 (ref)	0.85 (0.80-0.91)	0.78 (0.70-0.87)	0.69 (0.60-0.80)	0.88 (0.86-0.91)	<0.001
CLUE2	5704	1.06 (0.89-1.28)	1.00 (ref)	0.84 (0.79-0.90)	0.78 (0.71-0.86)	0.69 (0.60-0.79)	0.88 (0.86-0.91)	<0.001
CSDLH	5707	1.06 (0.88-1.27)	1.00 (ref)	0.85 (0.79-0.90)	0.78 (0.71-0.87)	0.68 (0.60-0.78)	0.88 (0.86-0.91)	<0.001
CTS	5593	1.07 (0.89-1.29)	1.00 (ref)	0.84 (0.79-0.90)	0.78 (0.70-0.86)	0.68 (0.60-0.78)	0.88 (0.85-0.91)	<0.001
E3N	4719	1.03 (0.82-1.30)	1.00 (ref)	0.84 (0.78-0.90)	0.79 (0.71-0.87)	0.67 (0.59-0.77)	0.88 (0.85-0.91)	<0.001
EPIC	5596	1.08 (0.90-1.29)	1.00 (ref)	0.84 (0.79-0.90)	0.79 (0.71-0.87)	0.68 (0.59-0.78)	0.89 (0.86-0.91)	<0.001
GS	5481	1.06 (0.89-1.28)	1.00 (ref)	0.84 (0.78-0.90)	0.78 (0.71-0.87)	0.68 (0.59-0.77)	0.88 (0.85-0.91)	<0.001
HUNT2	5707	1.06 (0.89-1.28)	1.00 (ref)	0.85 (0.79-0.90)	0.78 (0.71-0.87)	0.68 (0.60-0.78)	0.88 (0.86-0.91)	<0.001
MCC	5672	1.07 (0.89-1.28)	1.00 (ref)	0.84 (0.79-0.90)	0.78 (0.71-0.87)	0.68 (0.59-0.77)	0.88 (0.85-0.91)	<0.001
NHS	4159	1.04 (0.85-1.29)	1.00 (ref)	0.86 (0.80-0.93)	0.83 (0.74-0.93)	0.71 (0.61-0.83)	0.90 (0.87-0.93)	<0.001
NHS2	4431	1.02 (0.84-1.25)	1.00 (ref)	0.82 (0.77-0.89)	0.78 (0.69-0.88)	0.66 (0.56-0.78)	0.87 (0.84-0.90)	<0.001
NOWAC	5494	1.07 (0.89-1.28)	1.00 (ref)	0.84 (0.78-0.90)	0.79 (0.72-0.87)	0.68 (0.60-0.78)	0.88 (0.86-0.91)	<0.001
NYUWHS	5619	1.06 (0.88-1.27)	1.00 (ref)	0.85 (0.79-0.91)	0.78 (0.71-0.87)	0.69 (0.61-0.79)	0.89 (0.86-0.91)	<0.001
RERF (c)	-	-	-	-	-	-	-	-
SCHS	5689	1.08 (0.90-1.30)	1.00 (ref)	0.85 (0.79-0.90)	0.79 (0.71-0.87)	0.68 (0.60-0.78)	0.88 (0.86-0.91)	<0.001
SIS	5458	1.08 (0.89-1.29)	1.00 (ref)	0.84 (0.79-0.90)	0.77 (0.69-0.85)	0.68 (0.59-0.78)	0.88 (0.85-0.91)	<0.001
SMC	5582	1.06 (0.89-1.28)	1.00 (ref)	0.85 (0.80-0.91)	0.79 (0.71-0.87)	0.69 (0.60-0.79)	0.89 (0.86-0.91)	<0.001
USRTC	5627	1.03 (0.86-1.25)	1.00 (ref)	0.83 (0.78-0.89)	0.78 (0.71-0.86)	0.68 (0.59-0.77)	0.88 (0.85-0.91)	<0.001
WLHS	5589	1.07 (0.89-1.29)	1.00 (ref)	0.85 (0.79-0.90)	0.79 (0.71-0.87)	0.68 (0.59-0.78)	0.88 (0.86-0.91)	<0.001

(a) HRs adjusted for attained age, cohort, year of birth, age at menarche, age at first birth, number of births, time since last birth and family history of breast cancer

(b) Linear trend per 5 unit difference fitted across BMI values from 18.5 to 49.9 kg/m²

(c) Insufficient number of cases with BMI at age 45-54 years for this cohort

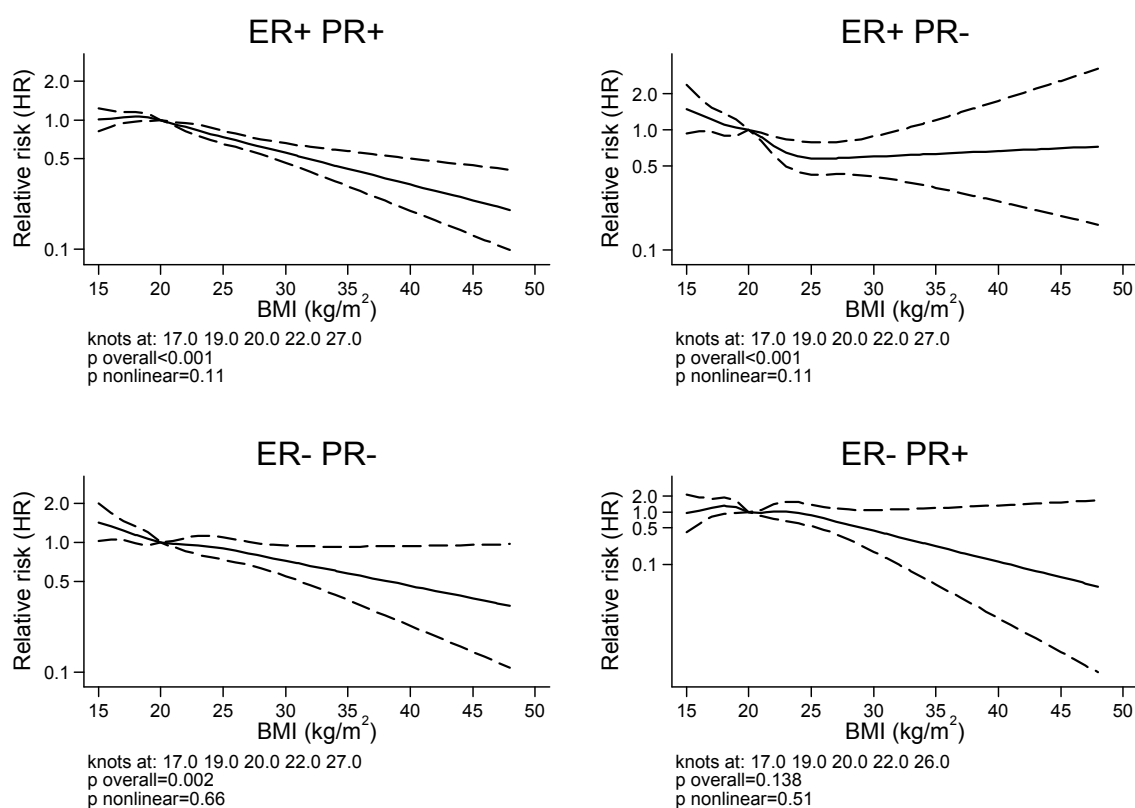
eFigure 1: Relative risk of premenopausal breast cancer in relation to BMI relative to the reference category of 20 kg/m², by age at BMI



Abbreviations: BMI, Body-mass Index; HR, hazard ratio

HRs obtained from 5-knot restricted cubic spline model adjusted for attained age, cohort, year of birth, age at menarche, age at first birth, number of births, time since last birth and family history of breast cancer. Knot locations are based on Harrell's recommended percentiles⁵ as specified in Stata⁴, corresponding to the 5th, 25th, 50th, 75% and 95% percentile distribution. Solid line represents hazard ratio relative to the reference group of 20 kg/m², dashed line represents 95% confidence interval of hazard ratio.

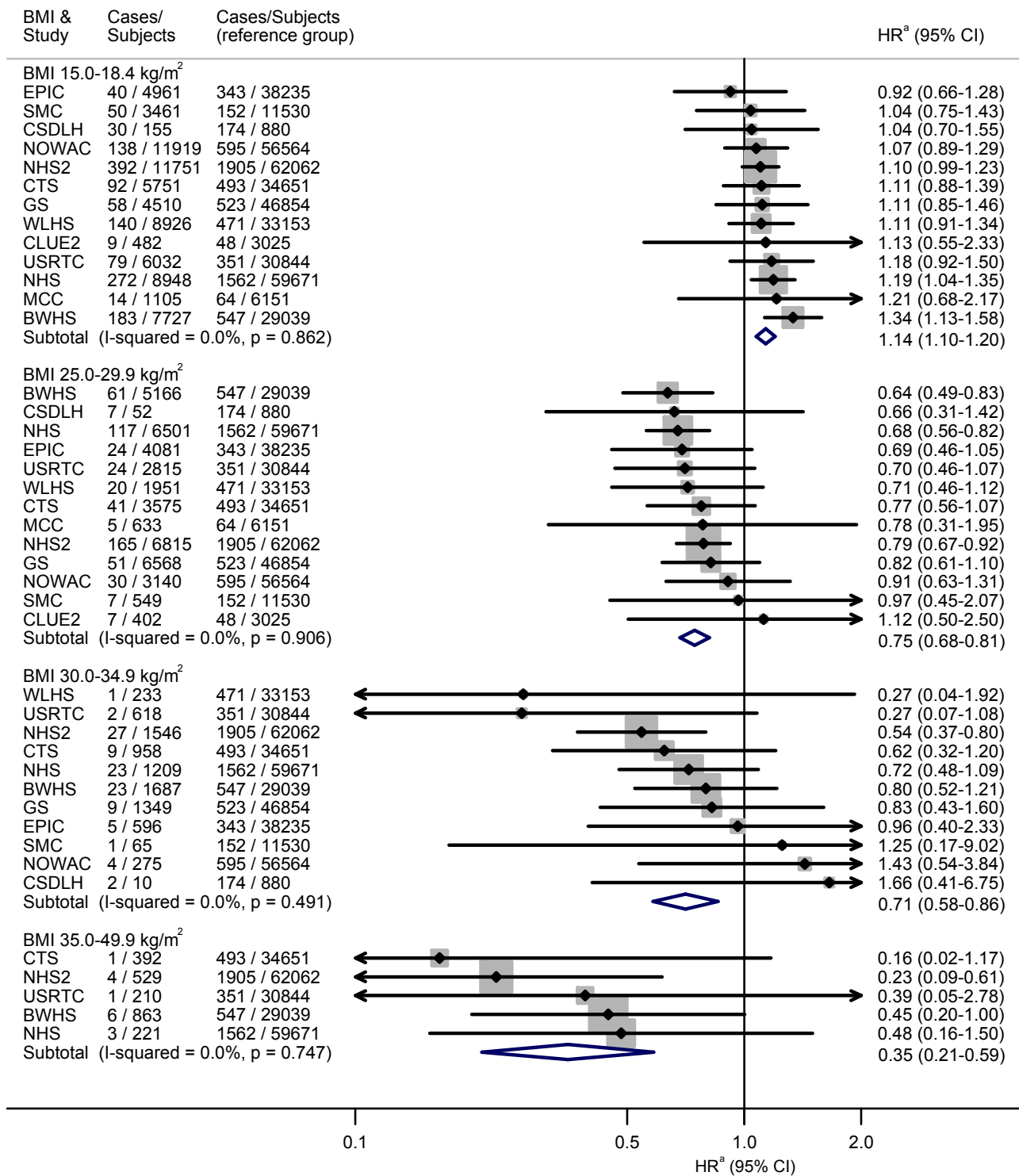
eFigure 2: Relative risk of premenopausal breast cancer in relation to BMI at ages 18-24 years relative to the reference category of 20 kg/m², by combined ER/PR status of breast cancer



Abbreviations: BMI, Body-mass Index; ER, oestrogen-receptor; HR, hazard ratio; PR, progesterone-receptor

HRs obtained from 5-knot restricted cubic spline model adjusted for attained age, cohort, year of birth, age at menarche, age at first birth, number of births, time since last birth and family history of breast cancer. Knot locations are based on Harrell's recommended percentiles⁵ as specified in Stata⁴, corresponding to the 5th, 25th, 50th, 75th and 95th percentile distribution. Solid line represents hazard ratio relative to the reference group of 20 kg/m², dashed line represents 95% confidence interval of hazard ratio. Note the different Y-axis for the ER-PR+ category.

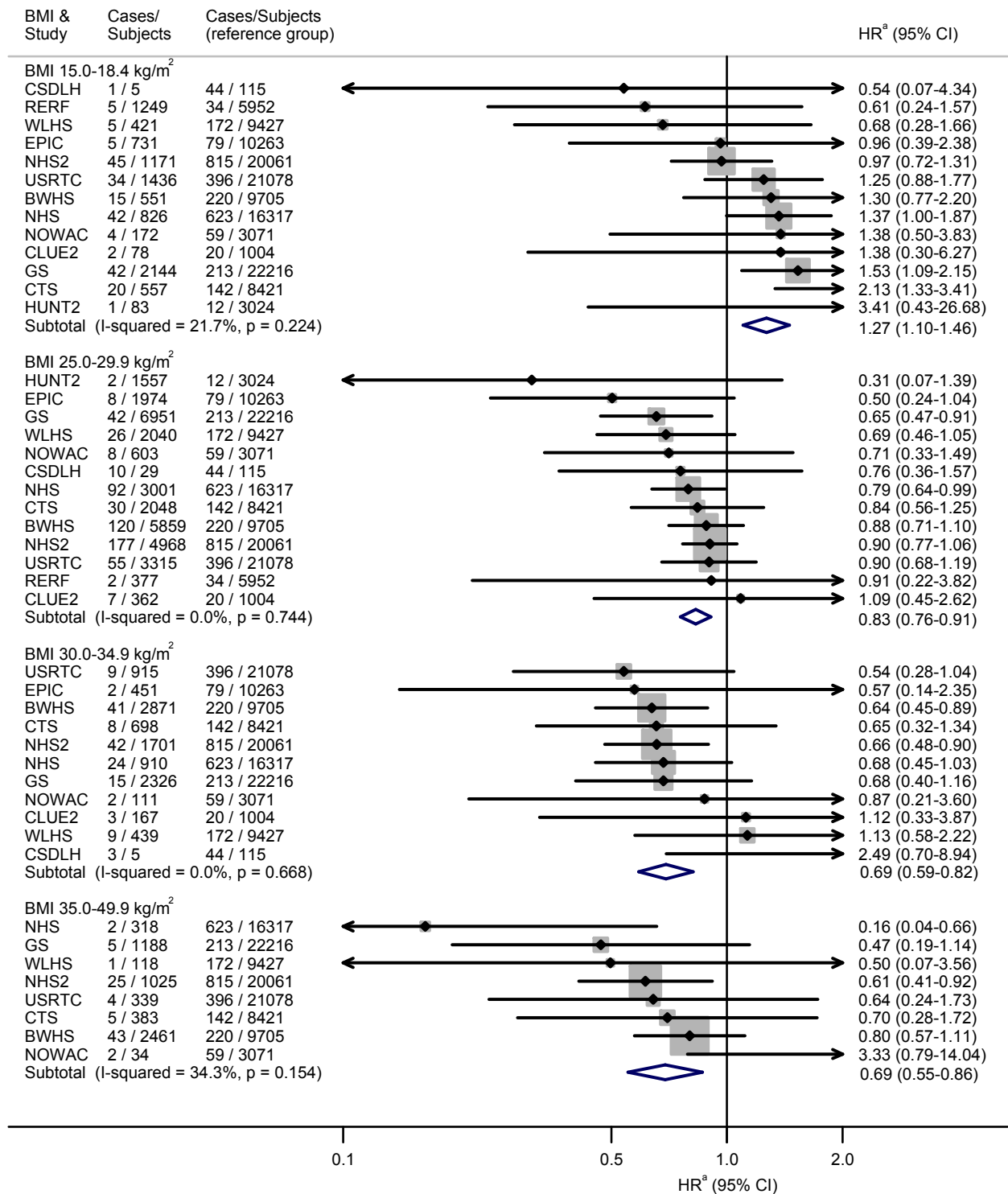
eFigure 3a: Forest plot of study-specific hazard ratios of premenopausal breast cancer by BMI category, relative to BMI 18.5-24.9 kg/m², at age 18-24 years.



Abbreviations: BMI, Body-mass Index; CI, confidence interval; HR, hazard ratio; for cohort abbreviations see page 3.

^aHRs adjusted for attained age, year of birth, age at menarche, age at first birth, number of births, time since last birth and family history of breast cancer.

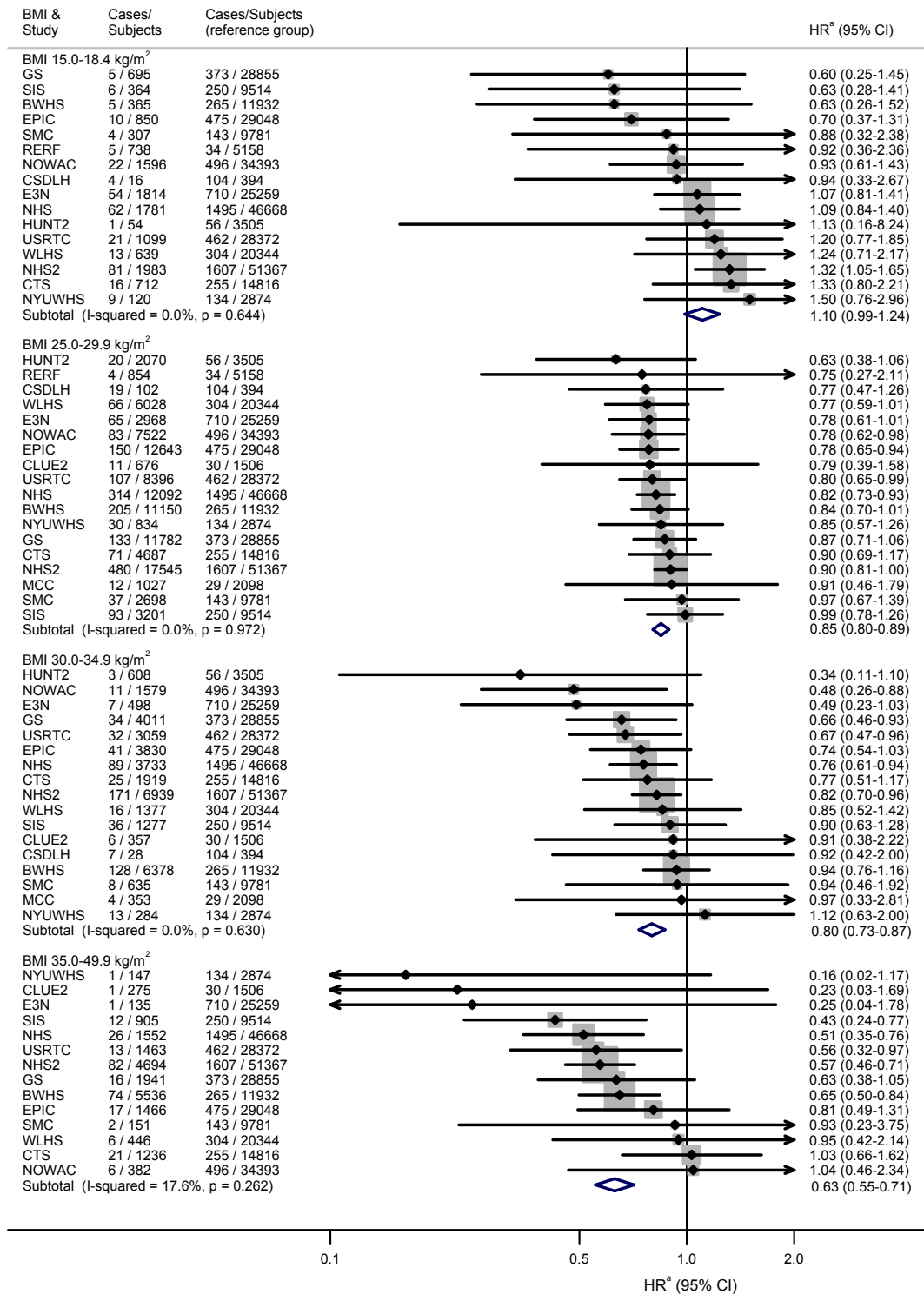
eFigure 3b: Forest plot of study-specific hazard ratios of premenopausal breast cancer by BMI category, relative to BMI 18.5-24.9 kg/m², at age 25-34 years.



Abbreviations: BMI, Body-mass Index; CI, confidence interval; HR, hazard ratio; for cohort abbreviations see page 3.

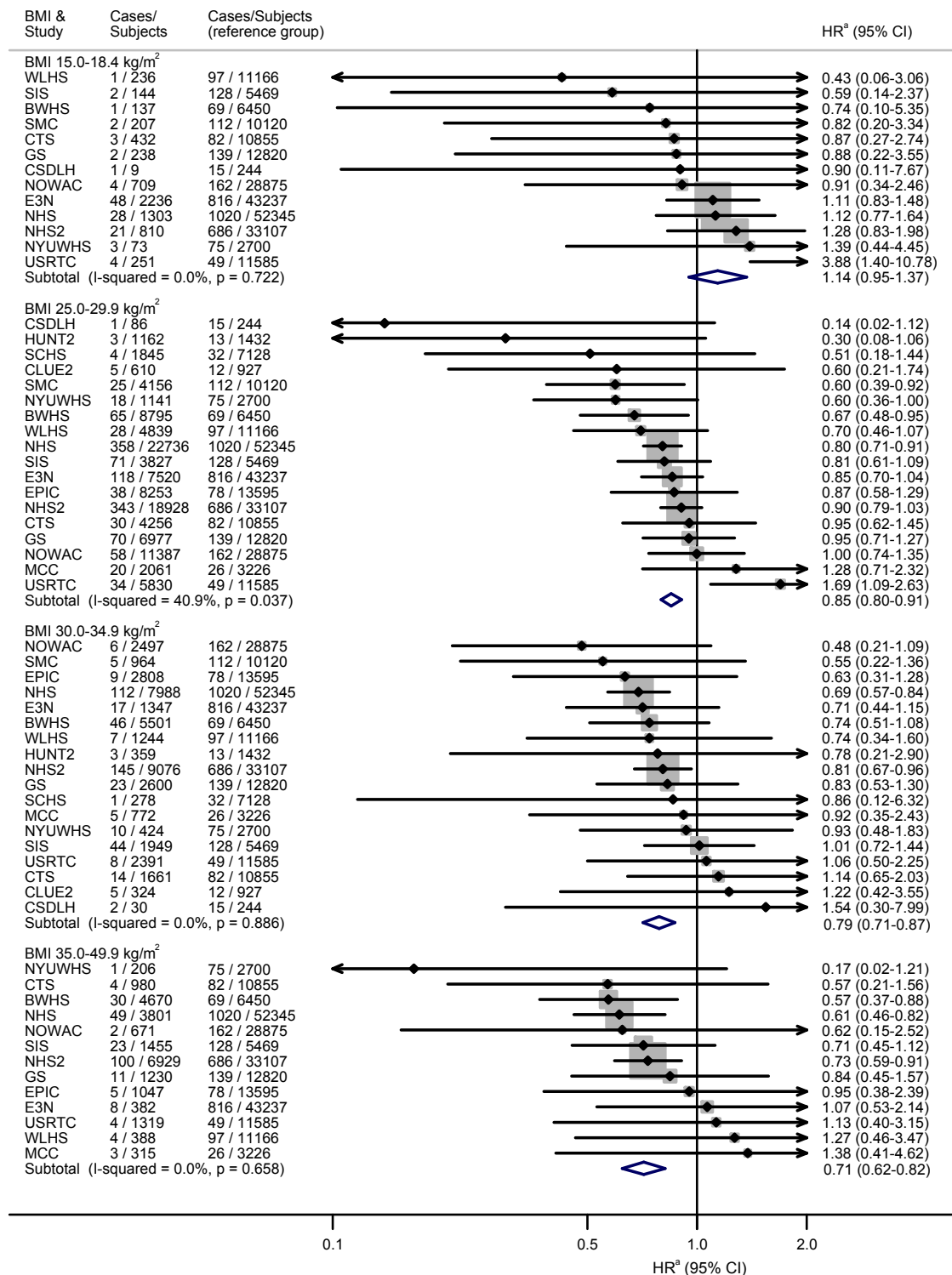
^aHRs adjusted for attained age, year of birth, age at menarche, age at first birth, number of births, time since last birth and family history of breast cancer.

eFigure 3c: Forest plot of study-specific hazard ratios of premenopausal breast cancer by BMI category, relative to BMI 18.5-24.9 kg/m², at age 35-44 years.



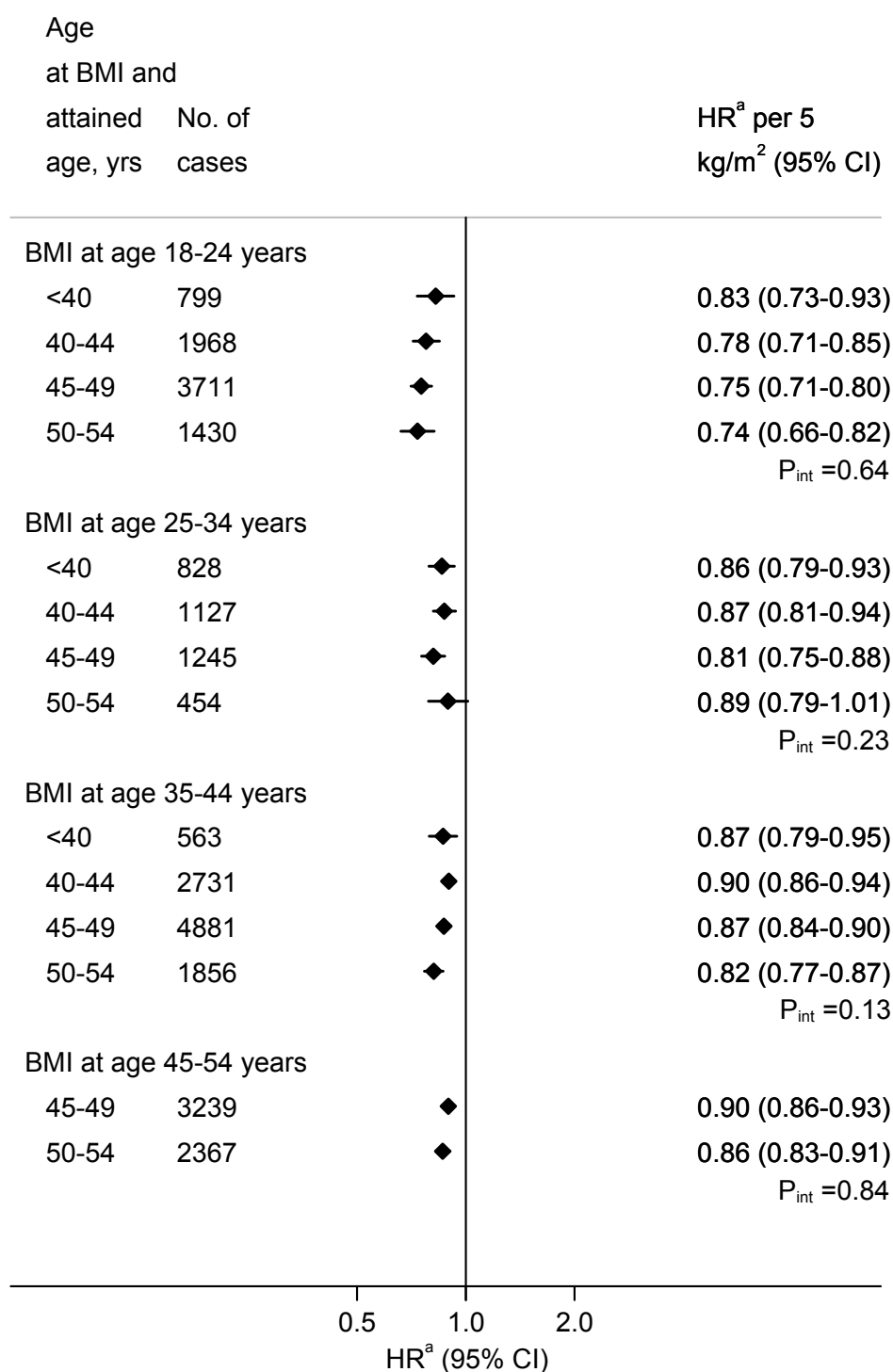
Abbreviations: BMI, Body-mass Index; CI, confidence interval; HR, hazard ratio; for cohort abbreviations see page 3.
^aHRs adjusted for attained age, year of birth, age at menarche, age at first birth, number of births, time since last birth and family history of breast cancer.

eFigure 3d: Forest plot of study-specific hazard ratios of premenopausal breast cancer by BMI category, relative to BMI 18.5-24.9 kg/m², at age 45-54 years.



Abbreviations: BMI, Body-mass Index; CI, confidence interval; HR, hazard ratio; for cohort abbreviations see page 3.
 ªHRs adjusted for attained age, year of birth, age at menarche, age at first birth, number of births, time since last birth and family history of breast cancer.

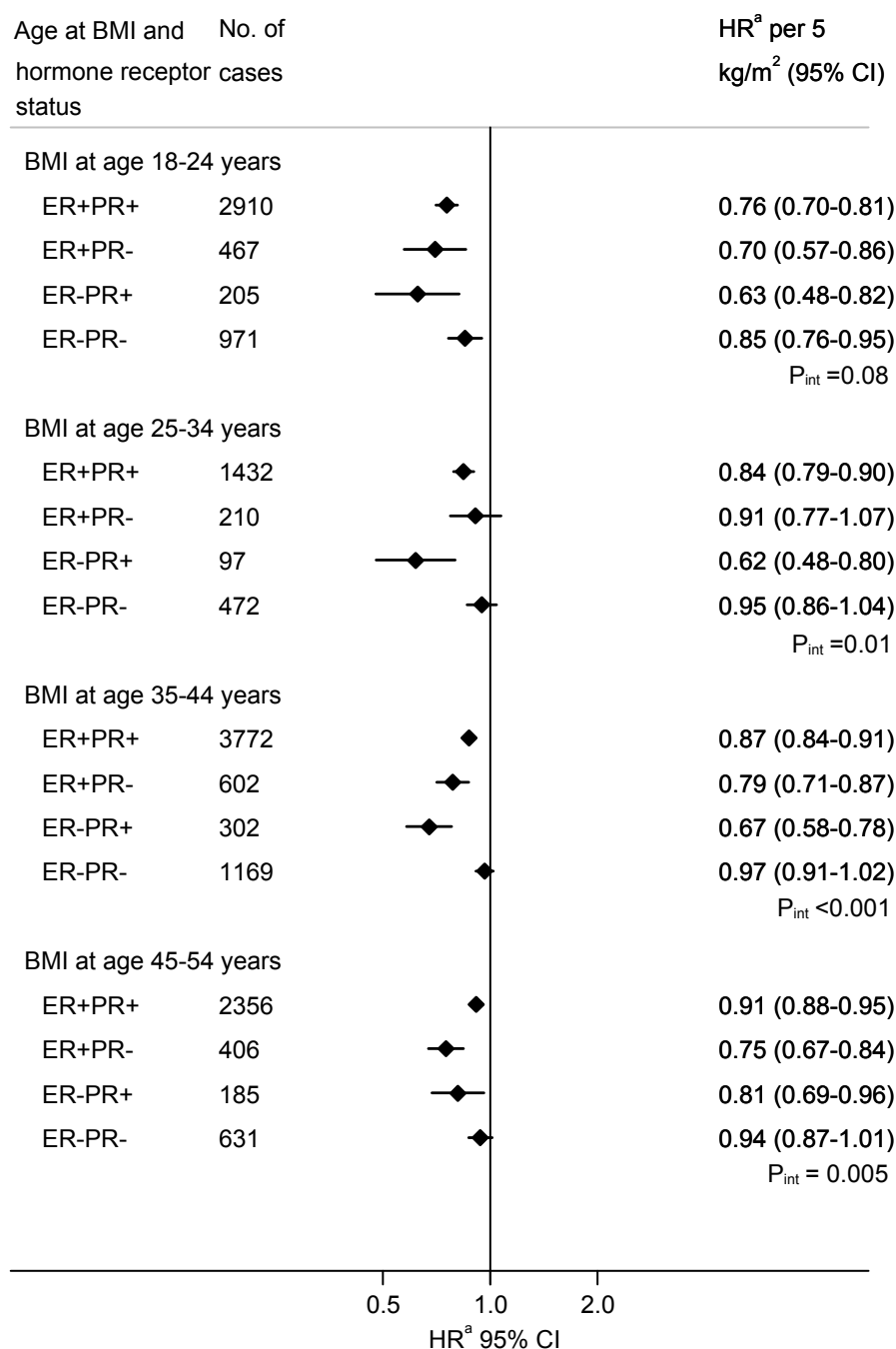
eFigure 4: Relative risk of premenopausal breast cancer per 5 kg/m² difference in BMI, by age at BMI and attained age during follow-up



Abbreviations: BMI, body-mass index; CI, confidence interval; HR, hazard ratio; P_{int}=p value for interaction

^aHRs represent linear trend per 5 kg/m² difference in BMI from 18.5 to 49.9 kg/m² and are adjusted for attained age, cohort and year of birth, age at menarche, age at first birth, number of births, time since last birth and family history of breast cancer

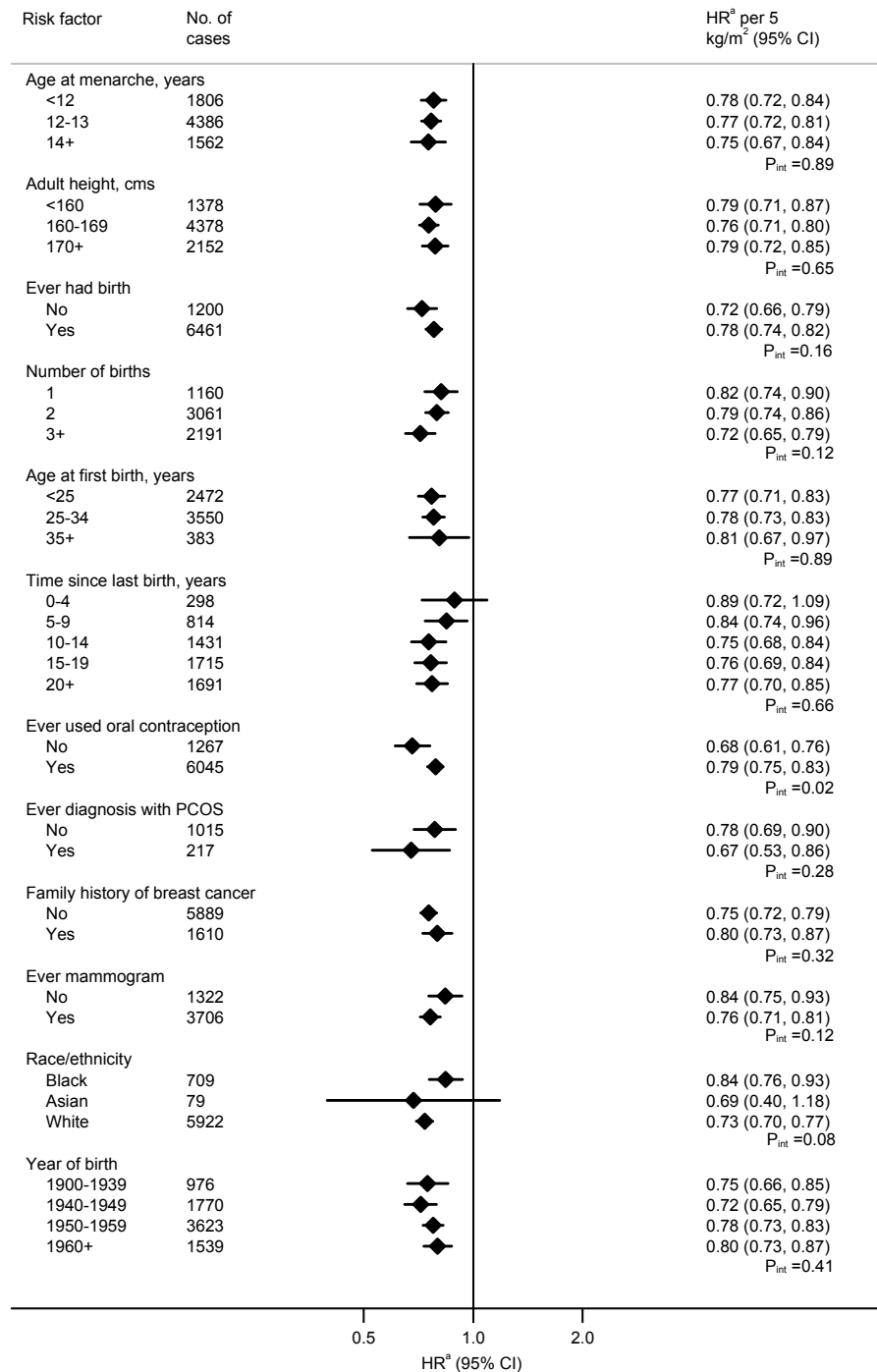
eFigure 5: Relative risk of premenopausal breast cancer per 5 kg/m² difference in BMI, by age at BMI and combined oestrogen and progesterone receptor status of breast cancer



Abbreviations: BMI, body-mass index; CI, confidence interval; ER, oestrogen-receptor; HR, hazard ratio; PR, progesterone-receptor; *P_{int}*=p value for interaction

^aHRs represent linear trend per 5 kg/m² difference in BMI from 18.5 to 49.9 kg/m² and are adjusted for attained age, cohort, year of birth, age at menarche, age at first birth, number of births, time since last birth and family history of breast cancer. Tests for heterogeneity in effect by combined ER/PR status was obtained from an Augmentation model including all four endpoints.⁸

eFigure 6: Relative risk of premenopausal breast cancer per 5 kg/m² difference in BMI at age 18-24 years, by selected other breast cancer risk factors



Abbreviations: BMI, body-mass index; CI, confidence interval; HR, hazard ratio; PCOS, polycystic ovary syndrome; P_{int}=p value for interaction

^aHRs represent linear trend per 5 kg/m² difference in BMI from 18.5 to 49.9 kg/m². HRs adjusted for attained age, cohort, year of birth, age at menarche, age at first birth, number of births, time since last birth and family history of breast cancer. Stratifying risk factors are time-updated, where data from follow-up questionnaires have been provided.

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