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Title: The association of adolescent to midlife weight change with age at natural menopause: a population study of 263,586 women in Norway.

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Abstract

Age at menopause varies considerably among women and is linked to health after menopause. Body mass index is associated with age at natural menopause, but the influence of weight change remains unclear. Thus, we studied associations of adolescent to midlife weight change with age at natural menopause. We performed a retrospective population-based cohort study of 263,586 women aged 50-69 years attending BreastScreen Norway (2006-2015). The associations were estimated as hazard ratios (HRs) for having reached menopause using Cox proportional hazard models. We included nine categories of weight change based on recalls of adolescent weight compared to peers and quartiles of midlife weight in kilograms. We adjusted for year and country of birth, education, number of childbirths, height, smoking, and exercise. Women with the largest estimated weight loss had highest hazard of reaching menopause (adjusted HR 1.11, 95% CI: 1.06-1.17) compared to women with estimated stable average weight. Conversely, women with the largest estimated weight gain had lower hazard (adjusted HR 0.96, 95% CI: 0.93-0.99). Women with estimated stable high weight had lowest hazard of reaching menopause (adjusted HR 0.93, 95% CI: 0.90-0.95). Our findings suggest that changes in body weight across the life course may influence the timing of menopause.

Keywords: Body-weight trajectory, body weight changes, cohort study, lifestyle, menopause, weight gain, weight loss

Menopause is defined as the cessation of menstrual periods for at least 12 consecutive months (1) and marks the end of a woman's reproductive period. Median age at natural menopause in Western populations is approximately 50-52 years (2,3). However, age at natural menopause varies considerably and occurs in most women between the ages of 40 and 60 years (4). Early menopause increases the risk of cardiovascular disease, stroke, type 2 diabetes, osteoporosis, bone fractures, and early death (5–7). Whereas late menopause is associated with increased risk of hormone sensitive cancers, such as breast, endometrial, and ovarian cancers (8–10).

Menopause occurs when few follicles remain in the ovaries (11), but we know little about why some women reach menopause early and others late. We know that genetic factors explain approximately 50 percent of the variation in age at menopause (12), and that sociodemographic factors, reproductive factors, and lifestyle factors, such as smoking and body mass index (BMI), play roles (4,13–16). Low BMI has been associated with earlier menopause in most studies (17–19). Conversely, high BMI and high body weight have been associated with later menopause (19–25). The association of high BMI with later menopause is, however, not consistent across studies. A study of 5,288 women in Europe reported that BMI >30 kg/m^2 was associated with earlier menopause (26), whereas a prospective study of 78,759 women in the USA reported a J-shaped association of BMI with the risk of early menopause (27).

It has been suggested that not only weight in itself, but weight change across the life course may influence age at menopause (28). However, the evidence is scarce and inconclusive. For instance, weight loss has been associated with earlier menopause (27), whereas episodic weight loss of more than 5 kg has been associated with later menopause (29). Weight gain has also been associated with later menopause (21,22,29), however, other studies report no association of weight change with age at menopause (25,28,30).

Valid knowledge about how weight change across the life course influences age at menopause may contribute to our understanding of ovarian ageing. In a cohort of 263,586 women in Norway, aged 50-69 years, we aimed to study the associations of adolescent to midlife weight change with age at natural menopause.

Materials and methods

Study design, recruitment, and data collection

We performed a retrospective population-based cohort study using self-administered data from women who participated in the Norwegian breast cancer screening program (BreastScreen Norway) during the years 2006-2015. The screening program is administered by the Cancer Registry of Norway and offers biennial mammographic examination to all women in Norway aged 50-69 years (31). The attendance rate during our study period was 84% (31), and women with low education and immigrant background were less likely to participate (32). All women attending the screening program during the years 2006-2015 were invited to fill in two self-administered questionnaires (31,33). The first questionnaire collected information about sociodemographic characteristics, reproductive history, and lifestyles prior to the age of 50 years. The second questionnaire collected data about menstruation, systemic menopausal hormone therapy, surgery on the uterus and ovaries, and current lifestyles.

Study sample

Of the 759,294 women who were invited to BreastScreen Norway during the years 2006-2015 (31), 554,206 women answered at least one questionnaire, and 394,206 women answered both (Figure 1). We excluded women who had missing or implausible values (<15 or >71 years) on age at menopause (n=35,572) or never had experienced a menstrual period (n=157). We also

excluded women who had undergone removal of the uterus (n=1,969) and/or both ovaries (n=1,047) but had not reported their age at such surgery. Finally, we excluded 93,899 women with missing information about weight at age 15 (n=77,999) and/or weight at the time of data collection (n=25,122). Thus, 263,586 women were included in our study sample (approximately 35% of all women aged 50-69 years in Norway during our study period). They were born during the years 1936-1966.

Main study factors

Our outcome variable was age at natural menopause (in years). Age at menopause was based on the responses to the questions: "Are you still having menstrual periods" (yes/yes, but irregularly/no), and "If you no longer have menstrual periods, how old were you at your final menstrual period?". Women who answered "yes, but irregularly" were considered as being premenopausal. We defined age at natural menopause as the reported age at the final menstrual period. The questionnaire did not include a specific question about time since the final menstrual period. Thus, we could not use the standard definition of menopause (cessation of menstrual periods for at least 12 consecutive months) (1).

Our main exposure variable was weight change from adolescence (age 15 years) to midlife (age 50-69 years). In the first questionnaire, the participants rated their weight at age 15 years compared to that of peers (much below average, somewhat below average, average, somewhat above average, much above average). In the second questionnaire, the participants reported their current weight (in kilograms). We categorized adolescent weight into three groups: low weight ("much" and "somewhat" below average), average weight, and high weight ("much" and "somewhat" above average). Midlife weight was categorized into three groups as follows: low weight (<63 kg/138.9 lbs, first quartile of the weight distribution of the study sample), average weight (63-79 kg/138.9-174.2 lbs, second and third quartile), and high

weight (>79 kg/174.2 lbs, fourth quartile). Based on this information, we firstly defined three exclusive groups of adolescent to midlife weight change: stable weight (reference), lost weight, and gained weight. Thereafter, we defined nine exclusive sub-groups of adolescent to midlife weight change: stable low, stable average (reference), stable high, average to low, high to average, high to low, average to high, low to average, and low to high weight.

Covariates

We performed a literature search and identified, by using directed acyclic graphs, year of birth, country of birth, educational level, number of childbirths, smoking habits, and exercise as possible confounding factors of the association of weight with age at menopause (4,14,16,22,34–39). We also adjusted for self-reported height to account for the dependency of weight on height. Year of birth and height (in centimeters) were included in the data analyses as continuous variables, whereas the other study factors were included as categorical variables: country of birth (Norway, Europe, outside Europe), educational level (<high school, high school, ≤4 years of university, >4 years of university), number of childbirths (0, 1, 2, ≥3), smoking habits (never-smoker, former smoker, smoker), and regular exercise at high intensity (no exercise, 0-1, 2-3, 4-5, ≥6 hours per week).

Statistical methods

Since some women had not yet reached menopause at the time of data collection, we used a time to event approach to estimate median age at menopause with interquartile range (IQR). The associations of adolescent to midlife weight change with age at natural menopause were estimated as hazard ratios (HR) by using the Cox proportional hazard model. The follow-up time was from birth (age 0 years) until age at natural menopause or age at data collection if menopause had not occurred (censoring). Women who had undergone removal of the uterus

(6.2%), both ovaries (0.6%), or had undergone both surgeries (2.9%), were censored at their attained age at surgery. The proportional hazards assumption was evaluated by the Schoenfeld residuals and by inspection of the log-log plots. Firstly, we included weight change in three categories (stable weight, lost weight, gained weight). We present HRs with adjustment for year of birth, and HRs with further adjustment for country of birth, educational level, number of childbirths, height, smoking habits, and exercise. In an additional analysis, we estimated HRs with further adjustment for ever-use of oral contraceptives (yes/no) and alcohol consumption (mean grams per week) at the age of 20-49 years. We repeated the main analyses by using the nine exclusive sub-groups of adolescent to midlife weight change as the exposure variable. All data analyses were performed by applying the statistical software package Stata/SE version 17.0 (StataCorp, College Station, TX, U.S.A.). The significance level was 5% for all analyses.

To investigate the consistency of our findings, we firstly compared the characteristics of women included in the study sample with the characteristics of women excluded due to missing information about weight change. Secondly, we imputed values for missing information about weight change and covariates by using multiple imputation by chained equations (40). The imputation model was based on the available information on all study factors. The number of imputations was 30, which was checked using the Monte Carlo error, and the degrees of freedom were adjusted for the large study sample. Thirdly, we repeated the main analyses after exclusion of women who had ever used systemic menopausal hormone therapy or a hormonal intrauterine device since such treatments during perimenopause may lead to lack of recognition of natural menopause (41). We also repeated the main analysis after exclusion of the women who reported their final menstrual period within one year prior to data collection (2.7%).

Ethical considerations

The study was approved by the Regional Committee for Medical and Health Research Ethics in Norway (reference no. 226831 REK South-East D). All women received written information about the questionnaire study along with the invitation to BreastScreen Norway. Women agreed to participate by returning the questionnaires.

Results

At the time of data collection (midlife), the mean age of the women was 56.3 years (SD 5.7 years), and 64.0% had experienced natural menopause (Table 1). A total of 20.9% rated their weight at 15 years (adolescent) as below average, and 10.9% rated their weight above average compared to peers. Mean self-reported weight at midlife was 71.4 kg/157.4 lbs (SD 13.2 kg/29.1 lbs). We estimated 21.9% of the women to have lost weight from adolescence to midlife and 28.5% to have gained weight.

Estimated median recalled age at menopause was 52 years (IQR 49-54 years) among women with stable adolescent to midlife weight, 51 years (IQR 49-54 years) among women who lost weight, and 52 years (ICR 49-54 years) among women who gained weight (Table 2). Compared to women with stable weight (reference), the birth year adjusted HRs of reaching menopause was 1.08 (95% CI: 1.07-1.10) for women who lost weight and 0.97 (95% CI: 0.96-0.98) for women who gained weight. After further adjustments for country of birth, educational level, number of childbirths, height, smoking habits, and exercise, the corresponding HRs of reaching menopause remained virtually unchanged (adjusted HRs 1.06, 95% CI: 1.05-1.08 and 0.97, 95% CI: 0.96-0.98, respectively) (Table 2). Additional adjustments for oral contraceptive use and alcohol consumption did not change the HR estimates notably (Table S1).

The association of the nine exclusive sub-groups of weight change with age at menopause is presented in Table 2 and Figure 2. In the fully adjusted model, women with the largest weight loss (high to low weight) had the highest hazard of reaching menopause compared to women with stable average weight (reference) (adjusted HR 1.11, 95% CI: 1.06-1.17). A weight loss from average to low weight was also associated with a higher hazard of reaching menopause (adjusted HR 1.08, 95% CI: 1.06-1.10). Conversely, a weight gain from low or average to high weight was associated with a lower hazard of reaching menopause compared to the reference group (adjusted HRs 0.96, 95% CI: 0.93-0.99 and 0.95, 95% CI: 93-0.96, respectively). Women with a stable high weight from adolescence to midlife had the lowest hazard of reaching menopause (adjusted HR 0.93, 95% CI: 0.90-0.95).

Supplementary analyses

The women with missing information about weight change, and therefore not included in the data analyses, were older, less likely to be born in Norway, had lower education, a higher number of childbirths, and were more often smokers than women in our study sample (Table S2). They were also younger at menopause (median age 51 years versus 52 years, $P < 0.001$). The multiple imputation procedure imputed values for all women excluded due to missing information about weight change and covariates (Table S3). The maximum Monte Carlo error was 0.0015. The HRs estimated by the imputation model (n=357,485) were similar to the HRs estimated in the complete case analyses (n=205,243). Also in separate analyses of never-users of systemic menopausal hormone therapy (n=156,924), of never-users of a hormonal intrauterine device (n=159,210), and in a subsample in which women with final menstrual period within one year prior to data collection were excluded (n=199,424), the results were similar to those in the main data analyses (Table S4).

Discussion

Summary of findings

In this population study of 263,586 women in Norway, estimated weight loss from adolescence to midlife was associated with earlier menopause compared to having a stable weight. We also found that estimated weight gain or having a stable high weight were associated with later menopause.

Strengths and limitations

To our knowledge, this study is the largest yet to explore the association of weight change with age at natural menopause. The large sample size provided statistical power for estimating the risk of reaching menopause according to nine exclusive sub-groups of weight change. Our study had, however, limitations to consider. Possibly, our study sample did not represent women in general. We aimed to include all women aged 50 to 69 years in Norway by using data from BreastScreen Norway. Of women in the target group, approximately 84% attended the screening program at least once during our study period (2006-2015) (31). Non-participants in BreastScreen Norway were older, had lower education and income, were more likely to be immigrants, and less likely to be married compared to participants (42). After exclusion of women who did not answer both questionnaires or lacked information about age at menopause and weight change, our study sample represented approximately 35% of all women in Norway aged 50 to 69 years during the study period. Missing information about weight change was a major cause of exclusion, and women for whom such information was missing were older, less likely to be born in Norway, had lower education, a higher number of childbirths, and were more often smokers. Most of these factors are known to be associated with age at menopause, but in different directions. We used multiple imputation to replace missing data about weight change and covariates, and we found almost identical HR estimates

as in the complete case analyses, suggesting generalizable associations. Although our estimated median age at menopause may be biased by skewed selection of the study sample and therefore not generalizable, our estimated association of weight change with age at natural menopause may have external validity (43). Our data did not include detailed information about race or ethnicity. Women born in Norway during the years 1936-1966 were predominantly Caucasian, and only 5.6% of the women in our study were born outside Norway. Thus, our study sample does not reflect the ethnic diversity of women around the world or in Norway today. Additionally, the exclusion of women with missing data limits the representativeness of our study sample.

Age at menopause was based on self-reports at age 50-69 years. Research has shown that women are fairly accurate in reporting their age at menopause (44,45), but the accuracy decreases by time since menopause (46,47). The use of menopausal hormone therapy or hormonal intrauterine devices may have caused imprecise reporting of age at natural menopause (41). We therefore excluded women who had had such treatment in additional analyses, and the HR estimates remained almost unchanged. In our study, 2.7% of the women reported their final menstrual period within one year prior to data collection, and their menstrual periods could possibly have reoccurred. We excluded these women in an additional analysis, but such exclusion did not change our results.

Misclassifications of women according to weight change from adolescence to midlife may have occurred. We categorized weight change based on self-reports of weight at age 15 compared to peers and weight in kilograms at data collection. Recalled body size at age 10 and also clothing size at age 20 have been shown to be correlated with actual body size at young age (45). In general, self-reports of body weight underestimate actual weight (48), possibly leading to underestimation of midlife weight and weight gain in our study. It is well known that women tend to gain weight around menopause (49). Current weight was reported

in kilograms at the age of 50-69 years (at data collection), and 64% had reached menopause at data collection. Since many women gain weight during their peri- and postmenopausal years, midlife weight and weight gain could also have been overestimated, particularly for the postmenopausal women. In addition, some women's weight change may have been misclassified due to differences in the measurements of adolescent and midlife weight. Weight was not measured at either time, but self-reported as weight compared to peers in adolescence and in kilograms at data collection. Any misclassification of weight change is likely to underestimate rather than overestimate the associations.

We made adjustment for self-reported height at data collection to control for differences in weight that may be attributed to differences in height. We assumed that self-reported height at data collection represents height at age 15 and midlife height. These assumptions may not be true since some adolescents gain height after age 15 (50), and some women lose height after menopause (51). Exclusion of height as study factor in the multivariable model, however, did not change our results (data not shown). All presented HR estimates were adjusted for year of birth, since women's weight and age at menopause have changed over time. Also the other factors included in the multivariable model were known to be associated with both weight and age at menopause, such as country of birth as a proxy for race/ethnicity, educational level, number of childbirths, smoking habits, and exercise. These adjustments, and further adjustments for oral contraceptive use and alcohol consumption, did not alter the estimated associations notably. Unfortunately, our data did not include information about changes in health status. Having a stable low weight or an adolescent to midlife weight loss could be a result of poor health (52), and poor health is linked to earlier menopause (5–7). Poor health could therefore explain, at least in part, the associations of low weight and weight loss with earlier menopause.

Comparison with other studies

To our knowledge, no previous studies have investigated the association of weight change from adolescence to midlife with age at menopause. However, some have studied weight change from early adulthood (18 to 35 years) to midlife (21,22,27,29). These studies reported that weight loss was associated with earlier menopause, or that weight gain was associated with later menopause. In a prospective study of 78,759 women in the USA, women who lost >9 kg between the ages of 18 and 35 years were at increased risk of early menopause compared to women who gained 2-7 kg (27). In contrast, a retrospective study of 1,106 women in Turkey found that episodic weight loss of >5 kg was associated with later menopause (29). Episodic weight loss is prevalent in overweight women. Thus, overweight could possibly be the underlying explanation of the results in the Turkish study. A retrospective study of 50,678 women in the United Kingdom studied weight change in five categories between the ages of 20 and 40 years and reported that weight gain was associated with later menopause (22). Also in a prospective study of 33,054 women in China, weight gain between the ages of 20 and 50 years was associated with later menopause (21). In contrast, a smaller prospective cohort study of 1,583 women from the United Kingdom found no association of weight change between the ages of 20 and 36 years with age at menopause (30). Also other studies based on rather small study samples, reported no association (25,28).

Interpretation

Menopause occurs when few follicles remain in the ovaries (11,53). Thus, our study suggests that changes in body weight across the life course may influence the rate of atresia of the ovarian follicles. Anti-Müllerian hormone levels are used as a marker of the ovarian reserve (54). A recent literature review concluded that Anti-Müllerian hormone levels decrease after weight loss in obese women with or without polycystic ovary syndrome, particularly after

bariatric surgery (55). Thus, weight loss could possibly accelerate ovarian follicle atresia and thereby expedite menopause.

Women with chronic disease may be prone to lose weight, and they are also at increased risk of early menopause (52,56). Certain medical treatment, such as chemotherapy and radiotherapy, are associated with early menopause (57). Thus, chronic disease could possibly be an underlying mechanism of the earlier menopause among women in our study with stable low weight or weight loss.

A direct effect of low weight or weight loss on ovarian follicle atresia, and thereby age at menopause, is plausible. Adipose tissue functions as an endocrine organ and synthesizes hormones such as estrogens (58). In women with abundant adipose tissue and thereby high estrogen levels, the menstrual cycle with recruitment of ovarian follicles may be suppressed (59). It is conceivable that suppression of ovarian follicle recruitment decreases the rate of follicle atresia. Although this "oocyte sparing" theory is speculative (60), anovulatory cycles caused by abundant fatty tissue could possibly delay menopause. Women with polycystic ovarian syndrome often have overweight and rare ovulations, and polycystic ovarian syndrome is associated with high Anti-Müllerian hormone levels and prolonged fertility (61).

Conclusions

In our study, women who lost weight from adolescence to midlife had earlier menopause, while women who gained weight had later menopause compared to women who remained at a stable weight. Maintaining a stable average weight across the life course may mitigate the risks of disease associated with early and late menopause.

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Table 1. Characteristics of the study sample; 263 586 women in the BreastScreen Norway, born during the years 1936-1966.

	Number	Percent
Age at data collection, years (mean, SD)	56.3	5.7
Natural menopause	168,645	64.0
Surgery on the uterus or ovaries prior to menopause		
Removal of the uterus	16,381	6.2
Removal of both ovaries	1476	0.6
Removal of the uterus and both ovaries	7747	2.9
Ever use of systemic menopausal hormone therapy	80,727	30.6
Ever use of hormonal intrauterine device	56,870	23.9
Missing information	*25,921*	
Adolescent weight		
Low weight	55,278	20.9
Average weight	179,690	68.2
High weight	28,618	10.9
Midlife weight		
Low weight (<25th percentile)	65,405	24.8
Average weight (25-75th percentile)	137,531	52.2
High weight (>75th percentile)	60,650	23
Self-reported weight at data collection, kg (mean, SD)	71.4	13.2
Self-reported height at data collection, cm (mean, SD)	166.4	5.8
Missing information	*4152*	
Country of birth		
Norway	247,659	94.4
Other European countries	10,220	3.9
North America	1255	0.5
South America	476	0.2
Asia	2259	0.9
Africa	340	0.1
Oceania	80	<0.1
Missing information	*1297*	

Number of childbirths		
0	23,039	9.6
1	27,065	11.2
2	102,921	42.7
≥3	88,064	36.5
Missing information	*22,497*	
Educational level		
< High school	55,436	21.2
High school	108,529	41.6
≤ 4 years of college/university	59,408	22.7
> 4 years of college/university	37,821	14.5
Missing information	*2391*	
Smoking habits		
Never-smoker	106,111	41.2
Former smoker	86,023	33.4
Smoker	65,320	25.4
Missing information	*6132*	
Exercise at high intensity per week		
No exercise	72,688	31.4
0-1 hour	63,037	27.2
2-3 hours	67,623	29.2
4-5 hours	19,124	8.3
≥ 6 hours	9012	3.9
Missing information	*32,102*	

SD, Standard deviation

Table 2. Median and mean age at menopause, and hazard ratios of reaching menopause according to adolescent to midlife weight change among 263,586 women in BreastScreen Norway, born during the years 1936–1966.

		No. women	Median	IQR	Mean	95% CI	Adjusted HR[a]	95 % CI	Adjusted HR[b]	95 % CI
Adolescent to midlife weight change (3 categories)										
Stable weight		130,638	52	49-54	51.28	51.25 - 51.31	Reference		Reference	
Lost weight		57,695	51	49-54	50.94	50.89 - 50.98	1.08	1.07 - 1.10	1.06	1.05 - 1.08
Gained weight		75,253	52	49-54	51.37	51.33 - 51.41	0.97	0.96 - 0.98	0.97	0.96 - 0.98
Adolescent to midlife weight change (9 categories)										
Stable weight	Stable low	19,751	51	49-54	51.12	51.05 - 51.19	1.06	1.04 - 1.08	1.07	1.05 - 1.09
	Stable average	97,872	52	49-54	51.29	51.26 - 51.33	Reference		Reference	
	Stable high	13,015	52	49-54	51.47	51.38 - 51.57	0.95	0.93 - 0.98	0.93	0.90 - 0.95
Lost weight	Average to low	42,092	51	49-54	50.92	50.87 - 50.97	1.09	1.08 - 1.11	1.08	1.06 - 1.10
	High to average	12,041	51	49-54	51.07	50.98 - 51.16	1.05	1.03 - 1.08	1.03	1.00 - 1.06
	High to low	3,562	51	49-54	50.61	50.44 - 50.77	1.17	1.12 - 1.22	1.11	1.06 - 1.17
Gained weight	Average to high	39,726	52	49-54	51.41	51.35 - 51.46	0.96	0.95 - 0.98	0.95	0.93 - 0.96
	Low to average	27,618	52	49-54	51.33	51.26 - 51.39	0.99	0.98 - 1.01	1.00	0.98 - 1.02
	Low to high	7,909	52	49-54	51.34	51.22 - 51.47	0.96	0.93 - 0.99	0.96	0.93 - 0.99

The associations were estimated as adjusted HRs using the Cox proportional hazard model. HR > 1.00 indicates earlier menopause compared to the reference group and HR < 1.00

indicates later menopause.
[a] Adjusted for year of birth.
[b] Adjusted for year of birth, country of birth, educational level, number of childbirths, height, smoking habits, and exercise. The study sample was restricted to women with information on all variables (n=205,243).
CI, confidence interval; *HR*, hazard ratio; *IQR*, interquartile range

Figure titles and legends

Figure 1.

Flow chart of the study sample; 263,586 women in BreastScreen Norway (2006-2015).

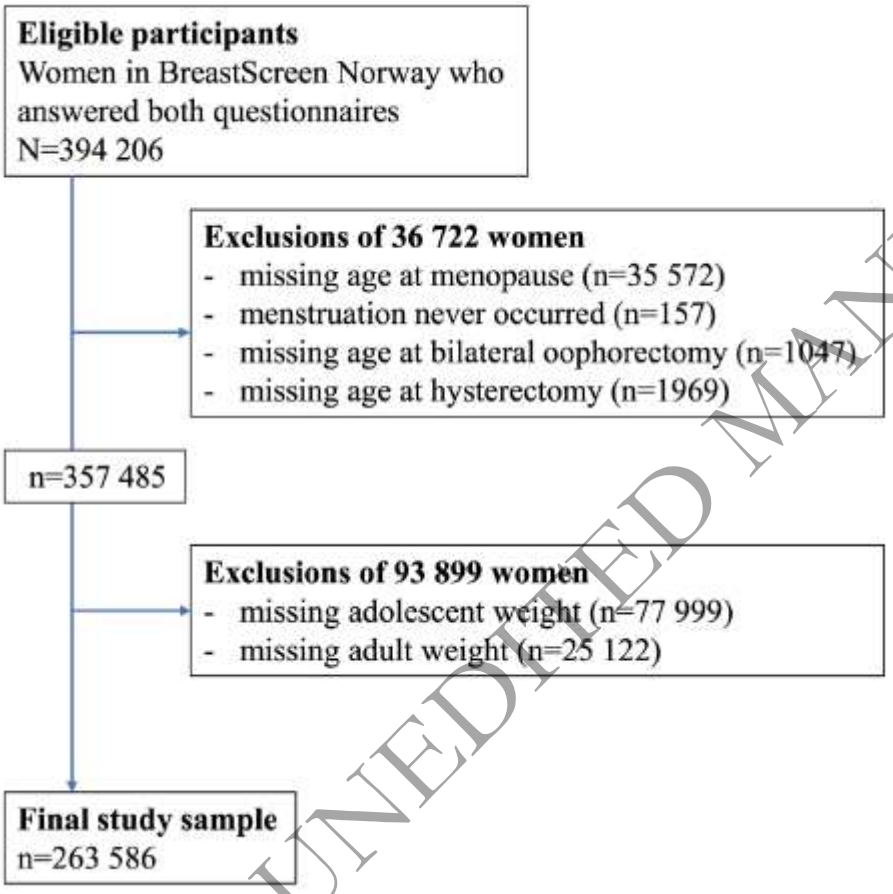

Figure 2.

Hazard ratios (HR) of the association of weight change with age at natural menopause with 95% confidence intervals among women in BreastScreen Norway, born 1936-1966. The HRs were estimated by applying the Cox proportional hazard model and adjusted for year of birth, country of birth, educational level, number of childbirths, height, smoking habits, and exercise. HR > 1.00 indicates earlier menopause compared to the reference group and HR < 1.00 indicates later menopause. The study sample was restricted to women with information on all variables (n=205,243).