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Breast cancer risk among postmenopausal women: Exploring existing interactions between BMI and reproductive factors (Fertile Years) in the Malmö Diet and Cancer Study

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Master Thesis

Abstract

Introduction:

Breast cancer remains a global public health priority, with increasing incidence and mortality among postmenopausal women. While high body mass index (BMI) and reproductive history are established risk factors, the interaction between BMI and cumulative reproductive exposure, measured as fertile years, has not been thoroughly investigated. This study investigated the independent and interactive effects of BMI and fertile years on postmenopausal breast cancer risk.

Methods:

Data from 6,628 postmenopausal women enrolled in the Malmö Diet and Cancer Study were analysed. BMI (kg/m²) was measured at baseline, and fertile years were estimated by subtracting the duration of pregnancy, breastfeeding, and miscarriage from the interval between menarche and menopause. Cox proportional hazards models estimated hazard ratios (HRs) for breast cancer risk. Interaction effects were evaluated on both multiplicative and additive scales using indices such as Relative Excess Risk due to Interaction (RERI), Attributable Proportion (AP), and Synergy Index (SI).

Results:

Over approximately 29,000 person-years of follow-up, 625 breast cancer cases were identified (9.4%), yielding an incidence rate of 3.3 per 1,000 person-years. Independent associations between higher BMI and longer fertile years with breast cancer were observed, but not statistically significant. No significant multiplicative interaction was detected. However, a statistically significant additive interaction was found: RERI = 0.86 (95% CI: 0.14–1.58, $p = 0.018$) and AP = 0.39 (95% CI: 0.13–0.66, $p = 0.003$), indicating that 39% of the joint effect could be attributed to interaction.

Conclusion:

This study provides novel evidence of a significant additive interaction between BMI and fertile years in postmenopausal breast cancer risk. These findings highlight the importance of assessing BMI and fertile years jointly in breast cancer risk evaluation. Future studies should explore underlying biological mechanisms and validate these results in diverse populations to inform targeted prevention strategies and improve the treatment options.

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Abbreviations

AP	Attributable Proportion Due to Interaction
BC	Breast Cancer
BMI	Body Mass Index
CI	Confidence Interval
Fertile years	Accumulated Time with Menstruation
IQR	Interquartile Range
OR	Odds Ratio
RERI	Relative Excess Risk Due to Interaction
SD	Standard Deviation
SI	Synergy Index

1.0 Introduction

1.1 Public Health Significance

Breast cancer (BC) remains a major global public health challenge. In 2020, over two million cases were diagnosed, resulting in approximately 670,000 deaths worldwide. According to the World Health Organization (WHO), BC was among the most prevalent cancers as of 2022. It accounts for over 20% of all new cancer cases in women and is the leading cause of cancer-related deaths among women globally (Azamjah, Soltan-Zadeh, & Zayeri, 2019; Arnold et al., 2022). In Sweden, BC incidence continues to rise, with 8,619 women diagnosed in 2021, an increase of 3.9% compared to pre-pandemic levels (Socialstyrelsen, 2022). While improved screening may partially explain this rise, modifiable risk factors such as obesity and reproductive history play substantial roles in driving disease burden (Liu et al., 2018; Coughlin, 2019).

1.2 Obesity and Postmenopausal BC Risk

Obesity, commonly measured using body mass index (BMI), is a well-established modifiable risk factor for postmenopausal BC. A large meta-analysis by Liu et al. (2018), a meta-analysis on 12 prospective cohort studies comprising 22,728,674 participants, found a robust association between higher BMI and increased BC risk in women. Body composition metrics such as BMI and waist-to-hip ratio (WHR) both emerged as significant predictors. Adipose tissue functions as an extragonadal source of estrogen through the aromatization of androgens, thereby increasing systemic estrogen levels and contributing to the development of estrogen receptor-positive tumors (Calle & Kaaks, 2004). Obesity may also drive carcinogenesis via chronic inflammation, insulin resistance, and the secretion of adipokines and pro-inflammatory cytokines (Engin, 2017).

1.3 Reproductive Factors and Cumulative Hormonal Exposure

Reproductive history influences cumulative lifetime exposure to endogenous estrogens. Early menarche, late menopause, nulliparity, and shorter durations of breastfeeding are linked to prolonged hormonal exposure and increased BC risk (Khalis et al., 2018; Coughlin, 2019). The total number of fertile years, calculated as the time between menarche and menopause, serves as a useful proxy for cumulative estrogen exposure. This aggregate measure may better

capture risk than individual reproductive factors alone (Chavez-MacGregor et al., 2008; Cole et al., 2021).

1.4 Rationale for Interaction Analysis and Knowledge Gap

Taken together, obesity and reproductive history are established risk factors for postmenopausal breast cancer. However, these exposures may not only operate independently but also interact in ways that modify their combined effect on risk. In epidemiology, additive interaction examines whether the joint effect of two exposures exceeds the sum of their individual effects, offering insight into public health impact. Besides, multiplicative interaction assesses whether the combined effect surpasses the product of their individual effects, shedding light on potential biological synergy. Despite substantial evidence for the individual roles of obesity and cumulative hormonal exposure, their potential interaction remains underexplored in BC research. Previous studies in other chronic diseases, such as type 2 diabetes and hypertension, and their interaction effects on cardio-cerebrovascular diseases have shown that co-occurring risk factors can produce synergistic effects far greater than expected from their independent contributions (Wang, Yang, and Fu, 2021). In recent years, there has been a growing interest in interactions between exposures. The processes underlying disease and other health outcomes are often inherently complex, and interactions between exposures represent one manifestation of this complexity (Richardson & Kaufman, 2009; VanderWeele & Knol, 2014).

Yet, interaction studies examining BMI and fertile years in breast cancer are limited, despite strong theoretical rationale and clinical relevance. Although detailed biological mechanisms are beyond the scope of this study, clarifying the epidemiological interaction between adiposity and hormonal exposure can provide essential groundwork for targeted prevention strategies. This study aims to fill this gap by investigating additive and multiplicative interactions between BMI and fertile years in a large cohort of postmenopausal women from the Malmö Diet and Cancer Study (MDCS). The MDCS is a population-based prospective cohort designed to investigate the role of diet and lifestyle in chronic disease development.

1.5 Research Question

How do body mass index (BMI) and fertile years, individually and jointly, influence the risk of postmenopausal breast cancer among women in the Malmö Diet and Cancer Study cohort? Specifically, to what extent do these factors interact on additive and multiplicative scales to modify risk?

1.6 Aim

This study aims to investigate the independent and joint effects of BMI and cumulative reproductive exposure (fertile years) on postmenopausal breast cancer risk in the Malmö Diet and Cancer Study cohort, with a focus on quantifying interactions on both additive and multiplicative scales. The goal is to clarify how these risk factors may synergistically influence BC development.

2. Methods

2.1 Study Design

This study used data from the Malmö Diet and Cancer Study (MDCS), a population-based prospective cohort study conducted in Malmö, Sweden. The cohort recruited men and women aged 45–73 years between 1991 and 1996. For this study analysis, 6,628 postmenopausal women with complete data on body mass index (BMI), reproductive history, and relevant covariates were included. Body weight and height were measured at baseline, and BMI was calculated as weight in kilograms divided by height in meters squared (kg/m^2). Reproductive factors included age at menarche, age at menopause, number of pregnancies (parity), age at first birth, breastfeeding duration, and number of miscarriages or abortions. Covariates comprised smoking status (current, former, or never), alcohol consumption, physical activity level, educational level, use of oral contraceptives, and use of hormone replacement therapy (HRT). Postmenopausal status was defined as the absence of menstrual cycles for 12 months or more. Women with a prior diagnosis of breast cancer at baseline or missing key variables were excluded. Participants were followed from the date of menopause until breast cancer

diagnosis, death, emigration, or the end of follow-up, with a mean follow-up of 29.5 years (SD 9.3) (Berglund et al., 1993).

2.2 Eligibility and Exclusion Criteria

The initial sample included 18,326 women enrolled in MDCS. Women with missing data on age at menopause (n = 4,560) were excluded. Participants were classified as postmenopausal if they had experienced 12 consecutive months of amenorrhea (absence of menstruation) not attributable to pregnancy, lactation, or other medical conditions, in accordance with the World Health Organization (WHO) and the American College of Obstetricians and Gynecologists (ACOG) definitions of natural menopause (WHO., 2022). Women meeting this criterion at baseline were included in the postmenopausal subgroup for the present analysis. Premenopausal status was defined based on menstruation history, and then excluded (n = 6,931). Additionally, 207 individuals diagnosed with breast cancer before menopause were excluded. The final analytical sample comprised 6,628 postmenopausal women. The flow of participant inclusion and exclusion is presented in Figure 1

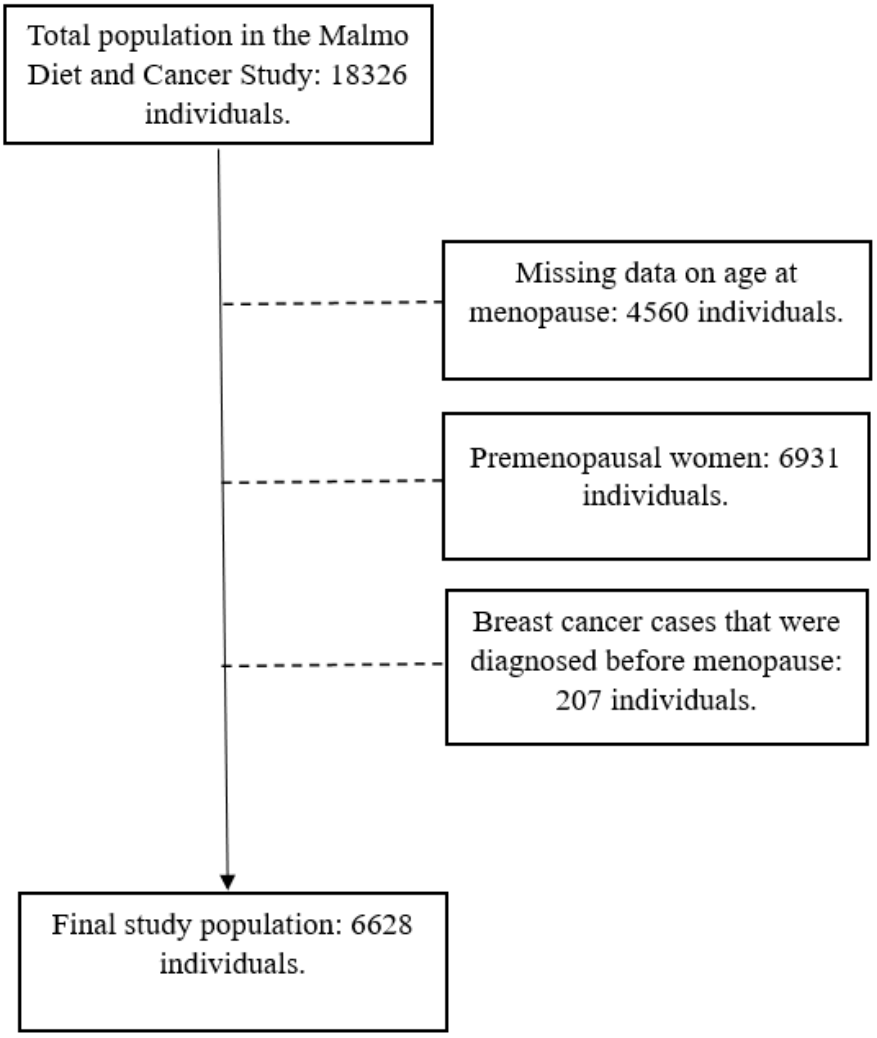

Figure 1

Flow diagram of the study population.

2.3 Data Collection and Variable Definitions

At the Malmö Diet and Cancer Study (MDCS), anthropometric and reproductive data were collected at baseline using standardized questionnaires and physical examinations. Dietary intake was assessed using a self-administered food-frequency questionnaire, validated in European cohorts (Kroke et al., 1999). For this analysis, BMI was calculated as weight in kilograms divided by height in meters squared (kg/m²) and categorized as underweight (<18.5), normal weight (18.5–24.9), overweight (25–29.9), and obese (≥30). Reproductive exposure was assessed through questionnaires. Fertile years is a variable that represents cumulative hormone exposure time and was calculated as the time from first menstruation to menopause, with deductions for breastfeeding, miscarriages, and pregnancy duration. Fertile years were analyzed as a continuous variable and categorized into 30–34.9 years, 35–39.9 years, and ≥40 years. Age at menarche and age at menopause were self-reported. Other covariates included baseline age, hormone replacement therapy use (yes/no; available for 2,340 women), contraceptive use, educational level (low/elementary, middle school, high school, university), physical activity score measured in MET-minutes per week per activity and season, and smoking status (never, ex-smoker, current).

2.4 Outcome Assessment

Incident postmenopausal breast cancer cases were identified through linkage with the Swedish Cancer Registry. Follow-up time was defined as the time from menopause to the earliest of breast cancer diagnosis, death, emigration, or study end. Person-years of follow-up were calculated for each participant for time-to-event analyses.

2.5 Statistical Analysis

Baseline characteristics were summarized by BMI categories using means (SD) for continuous variables and frequencies (%) for categorical variables (Table 1). Incidence rates per 1,000 person-years were calculated for BMI and fertile years categories (Table 2). Cox proportional hazards regression models were used to estimate crude and adjusted hazard ratios with 95% confidence intervals for the associations of BMI and fertile years with postmenopausal breast cancer risk (Table 3). Adjusted models included baseline age, contraceptive use, hormone replacement therapy, educational level, physical activity, and smoking status. Proportional hazards assumptions were verified using Schoenfeld residuals.

The interaction between BMI and fertile years was assessed on multiplicative and additive scales. Multiplicative interaction was evaluated by including a product term between BMI and fertile years in Cox models (Table 4). Additive interaction was quantified using Relative Excess Risk due to Interaction (RERI), Attributable Proportion (AP), and Synergy Index (SI) (Table 5). For additive interaction analyses, BMI and fertile years were dichotomized as <25 versus ≥25 kg/m² and <40 versus ≥40 years, respectively. All statistical analyses were conducted using Stata version 18. A p-value <0.05 was considered statistically significant.

2.6 Ethical Considerations

The MDCS cohort study was approved by the Regional Ethical Review Board in Lund, Sweden. All participants provided informed consent at baseline. Data were handled according to relevant privacy and research ethics regulations, and only de-identified data were used for the current analysis.

3.0 Results

3.1 Baseline Characteristics

A total of 6,628 postmenopausal women were included in the analysis. At baseline, the mean age was 61.7 years (SD = 5.94), and the mean body mass index (BMI) was 25.8 kg/m² (SD = 4.27), with 52.2% of participants classified as overweight or obese. The mean age at menarche was 10.1 years (SD = 2.0), and the mean age at menopause was 52.3 years (SD = 2.2). The average follow-up time from menopause until diagnosis of breast cancer or censoring was 29.5 years (SD = 9.3). The mean number of fertile years, defined as the duration between menarche and menopause, adjusted for time lost to pregnancy, breastfeeding, and miscarriage, was 36.3 years (SD = 3.2). Most participants (58.8%) had 35–39.9 fertile years. Regarding education, 75.4% had completed elementary education at most. Among the 2,340 women with available data, 32.3% reported using hormone replacement therapy (HRT). Contraceptive use was reported by 37.8% of the cohort, with a mean usage duration of 10.4 years (SD = 7.4). In total, 625 participants (9.4%) were diagnosed with breast cancer during follow-up. The proportion of cases was 11.4% among overweight and 8.9% among obese individuals (Table 1).

3.2 Independent Associations of BMI and Fertile Years with Breast Cancer Risk

Breast cancer incidence rates (IRs) increased with higher BMI and longer accumulated time with menstruation. Among BMI categories, IRs rose from 2.9 per 1,000 person-years (95% CI: 2.5–3.3) in the normal-weight group to 4.0 (95% CI: 3.5–4.5) in the overweight group and 3.2 (95% CI: 2.6–3.9) in the obese group. Similarly, IRs increased from 3.3 (95% CI: 2.8–3.8) among those with 30–34.9 fertile years to 4.3 (95% CI: 3.4–5.3) among those with ≥40 fertile years (Table 2). In multivariable Cox regression models adjusted for age, education, physical activity, smoking status, contraceptive use, and HRT, overweight women had a significantly higher risk of breast cancer (HR: 1.43; 95% CI: 1.20–1.71; $p < 0.001$) compared to normal-weight women. The association for obesity was positive but not statistically significant (HR: 1.16; 95% CI: 0.91–1.47; $p = 0.22$). Regarding reproductive exposure, longer fertile years were associated with increased risk but did not reach statistical significance. Compared to those with 30–34.9 fertile years, the adjusted HR was 1.01 (95% CI: 0.84–1.20; $p = 0.90$) for 35–39.9 years and 1.30 (95% CI: 0.93–1.74; $p = 0.13$) for ≥40 years (Table 3).

3.3 Interaction Between BMI and Fertile Years

Multiplicative interaction analyses showed suggestive but statistically nonsignificant elevated risks. Overweight women with ≥40 fertile years had a higher risk of breast cancer (HR: 1.48; 95% CI: 0.94–2.34; $p = 0.089$), while those with fewer fertile years had a lower risk (HR: 0.90; 95% CI: 0.67–1.19; $p = 0.46$). Obese women with ≥40 fertile years also had an elevated, but not statistically significant, risk (HR: 1.80; 95% CI: 0.81–4.00; $p = 0.15$) (Table 4). The additive interaction results showed a statistically significant positive interaction between BMI and fertile years. The Relative Excess Risk due to Interaction (RERI) was 0.86 (95% CI: 0.14–1.58; $p = 0.018$), and the Attributable Proportion (AP) was 0.39 (95% CI: 0.13–0.66; $p = 0.003$), suggesting that 39% of the combined effect on breast cancer risk is attributable to the interaction. The synergy index (SI) was 3.76 (95% CI: 0.71–19.90; $p = 0.12$), indicating a possible synergistic effect, although not statistically significant (Table 5). These findings suggest that while the individual effects of BMI and reproductive exposure may be modest, their combination may pose a higher-than-expected risk under additive models. This has implications for identifying high-risk subgroups in public health prevention strategies.

4.0 Discussion

This study offers novel epidemiological evidence demonstrating an additive interaction between body mass index (BMI) and cumulative endogenous hormonal exposure**,** measured as fertile years, in influencing breast cancer (BC) risk among postmenopausal women in the MDCS population**.** While neither BMI nor fertile years alone showed statistically significant associations with BC risk, their joint effect exceeded the additive expectation**.** Specifically, the Relative Excess Risk due to Interaction (RERI) was 0.86 **(**95% CI: 0.14–1.58), and the Attributable Proportion (AP) of 0.39 (95% CI: 0.13–0.66; $p = 0.003$) suggests that nearly 40% of the risk among those exposed to both risk factors can be attributed to their interaction**.** These findings highlight the importance of modelling joint exposures in breast cancer epidemiology to uncover synergistic risk patterns that may remain undetected in conventional single-factor analyses.

The observed interaction is biologically plausible and supported by mechanistic evidence. In postmenopausal women, adipose tissue becomes the primary source of estrogen through the aromatase-driven conversion of androgens, particularly in those with elevated BMI (Calle & Kaaks, 2004). Concurrently, an extended reproductive lifespan results in prolonged exposure to endogenous estrogen, which enhances the activity of estrogen receptor signaling pathways associated with tumor development. The coexistence of these factors may synergistically increase oncogenic risk, particularly for estrogen receptor-positive tumors. Additionally, obesity creates a pro-inflammatory and insulin-resistant environment, which can further exacerbate processes that promote tumor growth (Engin, 2017). A publication by Munsell et al. in 2014 found that obesity elevates the risk of hormone receptor-positive breast cancer, underscoring the need to incorporate hormonal context into models of metabolic risk. This layered biological rationale strengthens the epidemiological observation of significant additive interactions. These findings build on existing literature investigating the dynamic interplay of risk factors in breast cancer.

Recently, Yang et al. (2022) identified an additive interaction between BMI and premenopausal status, underscoring the impact of hormonal conditions on metabolic cancer risk. This study advances this idea by exploring the interaction framework in postmenopausal women, thereby emphasizing the temporal and biological nuances of these interactions.

In addition to the primary factors of BMI and fertile years, several noteworthy patterns among covariates emerged in this analysis. A higher BMI was associated with lower educational attainment, which may indicate differences in lifestyle behaviors, health awareness, and access to screening services. Furthermore, physical activity levels showed an inverse relationship with BMI, aligning with its established protective role against breast cancer. Obese women also reported lower usage of hormone replacement therapy and a reduced prevalence of smoking compared to their normal-weight counterparts, both of which are significant considerations for breast cancer risk. Additionally, parity and the duration of breastfeeding tended to increase slightly with BMI, potentially confounding the observed associations. Collectively, these findings highlight that the connection between BMI and postmenopausal breast cancer exists within a broader socio-demographic and lifestyle context, which should be taken into account when interpreting results and guiding future research.

From a public health perspective, these results have direct implications for prevention strategies, clinical risk assessment, and policy development**.** Given that BMI is modifiable**,** weight management may be particularly beneficial for women with prolonged reproductive exposure, who may already be at elevated hormonal risk. Preventive strategies should prioritize this group for early interventions, ideally before or during the menopausal transition, to mitigate cumulative risk. Healthcare providers could consider both BMI and reproductive history in the BC risk assessments, as a more holistic approach may improve predictive accuracy and inform personalized prevention plans**.** Campaigns and educational programs should reinforce the dual importance of weight management and awareness of reproductive risk factors**,** particularly among postmenopausal women. Raising awareness may play a critical role in this context, particularly among highly educated populations, who tend to be more responsive to health information and preventive interventions (Cutler & Lleras-Muney, 2010).

This study also supports broader recommendations for health policy**.** Tailored interventions that integrate metabolic and reproductive risk profiles can enhance cost-effectiveness by targeting women with the highest attributable risk**.** Policymakers should adopt comprehensive prevention strategies that reflect the multifactorial nature of BC risk**,** including the additive interaction between BMI and fertile years. Integrating such considerations into national screening, education, and prevention programs may lead to more efficient resource allocation

and improved population-level outcomes. In addition to its practical implications, this research contributes to the advancement of scientific understanding of complex disease aetiology. Exploring interactions between biological and behavioural risk factors enhances our ability to identify subgroups at elevated risk and sheds light on potential mechanistic pathways. This aligns with the principles of precision public health, which advocates for context-specific, data-driven interventions. In this regard, the integration of joint exposure metrics into predictive models may represent a critical step toward improving risk stratification and developing targeted prevention strategies**.**

The methodological strengths of this study further support the validity of these findings. The Malmö Diet and Cancer Study (MDCS) offers a large, well-characterized cohort with extensive follow-up and validated cancer outcomes through national registries. Fertile years served as a biologically relevant measure of cumulative estrogen exposure**,** and the use of interaction indices such as RERI, AP, and the Synergy Index provided a robust framework for assessing departure from additivity. These methodological choices enhance the public health interpretability and translational potential of the findings.

It is important to acknowledge some limitations in this study. First, BMI was measured solely at baseline, and weight changes may occur over time, particularly due to factors related to aging or menopausal transition, which were not captured in this analysis. This could lead to exposure misclassification. Additionally, reproductive history was self-reported, which may influence the accuracy of the estimation of fertile years. If the misclassification is non-differential, it could have diluted the observed associations.

Although attempts were made to adjust for significant confounders, we cannot entirely dismiss the possibility of residual confounding arising from unmeasured genetic, lifestyle, or pharmacological factors. The approach of complete case analysis was employed to address missing data, a method that, while standard, may introduce bias if the data are not missing completely at random. Key covariates with considerable missingness were evaluated and excluded from the multivariable models when necessary to uphold analytical robustness.

The findings from this study suggest that while the results provide valuable insights, their application may be limited due to the relative ethnic homogeneity of the cohort. To enhance generalizability, it is crucial to replicate the research in more diverse populations. Ideally,

such replications should also incorporate biomarkers of inflammation and estrogen metabolism to further confirm and extend the results obtained. This approach will contribute to a more comprehensive understanding of the effects observed.

This study underscores the importance of integrating various risk dimensions into public health and clinical practice. Just as recent guidelines from the American Diabetes Association have highlighted the need to assess body fat distribution alongside BMI, similar strategies should be considered for breast cancer risk assessment. Understanding that interactive risk pathways influence disease development enables a more nuanced identification of high-risk individuals and facilitates the creation of interventions that address multiple exposures concurrently. This approach could lead to more effective prevention and management strategies tailored to women's life-course risk profiles, ultimately enhancing health outcomes.

Ethical standards were rigorously upheld throughout the study. Approval was granted by the Lund University Ethical Committee, and informed consent was obtained from all participants (Bjarnadottir et al., 2020). Special care was taken to ensure privacy, data security, and ethical use of self-reported reproductive and lifestyle data**.** This commitment to ethical integrity strengthens the credibility of the research and reflects the responsibilities inherent in public health investigations.

5.0 Conclusion

This study demonstrates that the combined exposure to a high body mass index (BMI) and a prolonged reproductive lifespan significantly increases the risk of postmenopausal breast cancer, with nearly 40% of this risk stemming from their additive interaction. These findings emphasize the necessity of evaluating risk factors in conjunction rather than in isolation to more accurately identify high-risk subpopulations. From a public health perspective, the results underscore the urgent need for targeted prevention strategies. Specifically, postmenopausal women with extended reproductive durations may benefit from early lifestyle interventions, including weight management programs and hormonal health counseling. In clinical settings, risk prediction models should be refined to incorporate the interaction effects between metabolic and reproductive factors, thereby enhancing the precision of risk stratification and intervention planning. Future research should aim to replicate these findings

in ethnically and geographically diverse populations and to clarify the biological mechanisms underlying the observed interactions. Incorporating biomarkers related to estrogen metabolism, chronic inflammation, and adiposity may provide deeper mechanistic insights and support the development of personalized prevention strategies and public health policies tailored for this high-risk group.

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Table 1.

Baseline Characteristics of Postmenopausal Women in the Malmö Diet and Cancer Study (MDCS), by BMI Category (N = 6,628)

Characteristic	BMI Categories (kg/m2)				Total
	Underweight (<18.5)	Normal (18.5–24.9)	Overweight (25–29.9)	Obese (≥30)	
Age at baseline (years)	62.0 (6.3)	61.0 (6.0)	62.2 (5.9)	62.2 (5.6)	61.7 (5.9)
Age at menarche (years)	10.2 (2.1)	9.9 (2.0)	10.2 (1.9)	10.3 (1.9)	10.1 (2.0)
Age at menopause (years)	52.2 (2.2)	52.2 (2.1)	52.4 (2.3)	52.4 (2.3)	52.3 (2.2)
Number of pregnancies	3.1 (1.5)	3.2 (1.0)	3.4 (1.2)	3.5 (1.4)	3.1 (1.5)
Breastfeeding duration (years)	1.5 (1.1)	1.6 (1.3)	1.8 (1.6)	1.9 (2.3)	1.5 (1.1)
Physical activity score (MET-min/week)	7266.0 (52)	8291.9 (56)	8073.9 (57)	7039.9 (58)	8000.7 (57)
Mean BMI (kg/m²)	17.6 (0.7)	22.6 (1.5)	27.1 (1.3)	33.2 (3.1)	25.8 (4.2)
Fertile years (years)	35.7 (3.2)	35.8 (2.7)	36.0 (6.0)	36.0 (3.2)	35.7 (3.2)
Fertile years category	n (%)	n (%)	n (%)	n (%)	n (%)
30–34.9 years	23 (30.0)	933 (30.5)	723 (30.2)	276 (26.9)	1955 (29.9)
35–39.9 years	38 (50.0)	1828 (59.7)	1356 (57.2)	616 (60.1)	3838 (58.8)
≥40 years	15 (19.7)	299 (9.7)	290 (12.2)	132 (12.9)	736 (11.3)
Hormone replacement therapy†					
Yes	10 (35.7)	363 (35.5)	285 (31.5)	98 (25.3)	756 (32.3)
No	18 (64.2)	658 (64.4)	619 (68.4)	289 (74.7)	1584 (67.7)
Contraceptive use					
Yes	33 (41.7)	1331 (43.0)	841 (34.9)	301 (28.4)	2506 (37.8)
No	46 (58.2)	1755 (56.8)	1564 (65.0)	757 (71.5)	4122 (62.2)
Education level					
Low (elementary)	34 (42.3)	1196 (38.7)	1219 (50.6)	624 (58.9)	3073 (46.0)
Middle school	22 (27.5)	1013 (32.8)	693 (28.8)	271 (25.6)	1999 (30.2)
High school	5 (6.3)	185 (5.9)	136 (5.6)	39 (3.7)	365 (5.5)
University	14 (17.5)	402 (13.0)	211 (8.7)	72 (6.8)	699 (10.5)
Smoking status					
Never smoker	31 (38.7)	1481 (47.9)	1286 (53.4)	587 (55.4)	3385 (51.1)
Ex-smoker	12 (15.0)	805 (26.0)	647 (26.9)	293 (27.0)	1757 (22.4)
Current smoker	37 (46.2)	800 (25.9)	472 (19.6)	178 (16.8)	1487 (22.4)
Breast cancer diagnosis					
Yes	3 (3.7)	255 (8.2)	273 (11.4)	94 (8.9)	625 (9.4)
No	77 (96.2)	2832 (91.7)	2132 (88.6)	964 (91.1)	6005 (90.6)
Follow-up time (years)	29.0 (9.4)	29.5 (9.2)	29.6 (9.5)	29.2 (9.4)	29.5 (9.3)

Abbreviations: BMI, Body mass index. SD, Standard deviation. IQR, Interquartile Range.
Note: Values are presented as Mean (SD) unless otherwise specified.
Hormone replacement therapy data are available for 2,340 women.
Fertile years: The time from first menstruation to menopause, with deductions for breastfeeding, miscarriages, and pregnancy duration.
Physical activity refers to the number of minutes per week, per activity, and season.
Follow-up time (years) starts from the date of menopause till the breast cancer diagnosis, death, emigration, or end of the study.

Table 2.

Incidence Rates of Postmenopausal Breast Cancer by BMI and Fertile Years in the Malmö Diet and Cancer Study (MDCS), Sweden (N = 6,628)

Exposure	N (%)	Breast Cancer Cases n (%)	Person-Years	IR (95% CI)
BMI (kg/m²)				
<18.5	88 (1.3%)	3 (3.8%)	2.2	1.3 (0.4, 4.1)
18.5–24.9	3086 (46.5%)	255 (41.0%)	86.9	2.9 (2.5, 3.3)
25–29.9	2405 (36.2%)	273 (43.9%)	67.3	4.0 (3.5, 4.5)
≥30	1058 (15.9%)	94 (15.1%)	29.1	3.2 (2.6, 3.9)
Fertile years				
30–34.9 years	1955 (29.4%)	190 (30.5%)	64.0	3.3 (2.8, 3.8)
35–39.9 years	3838 (57.9%)	350 (56.3%)	101.8	3.2 (2.9, 3.6)
≥40 years	736 (11.1%)	81 (13.0%)	19.8	4.3 (3.4, 5.3)

Abbreviations: IR = Incidence Rate (per 1,000 person-years); CI = Confidence Interval.

Table 3.

Crude and Adjusted Hazard Ratios for Breast Cancer by BMI and Fertile Years in MDCS Postmenopausal Women (N = 6,628)

Exposure	Crude HR (95% CI)	P-value	Adjusted HR (95% CI)	P-value
BMI (kg/m²)				
<18.5	0.46 (0.15, 1.44)	0.18	0.44 (0.14, 1.39)	0.16
18.5–24.9 (Ref)	1.00	—	1.00	—
25–29.9	1.38 (1.17, 1.64)	<0.001	1.43 (1.20, 1.71)	<0.001
≥30	1.10 (0.87, 1.39)	0.44	1.16 (0.91, 1.47)	0.22
Fertile years				
30–34.9 years (Ref)	1.00	—	1.00	—
35–39.9 years	1.04 (0.87, 1.23)	0.68	1.01 (0.84, 1.20)	0.90
≥40 years	1.34 (1.04, 1.73)	0.03	1.30 (0.93, 1.74)	0.13

Note: Cox proportional hazards models adjusted for baseline age, contraception use, hormone replacement therapy, education level, physical activity, and smoking status.
Abbreviations: HR = Hazard Ratio; CI = Confidence Interval; Ref = Reference category.

Table 4.

Multiplicative Interaction Between BMI and Fertile Years on Breast Cancer Risk in MDCS Postmenopausal Women (N = 6,628)

BMI (kg/m²)	Fertile Years	N	Breast Cancer Cases	Person-Years	Adjusted HR (95% CI)	P-value
18.5–24.9 (normal)	35–39.9	1743	151	48.5	1.14 (0.86, 1.52)	0.36
	≥40	315	23	8.1	0.99 (0.58, 1.70)	0.99
25–29.9 (overweight)	35–39.9	1301	132	35.9	0.90 (0.67, 1.19)	0.46
	≥40	307	47	7.8	1.48 (0.94, 2.34)	0.09
≥30 (obese)	35–39.9	598	53	16.0	1.19 (0.72, 1.96)	0.49
	≥40	140	14	3.4	1.80 (0.81, 4.00)	0.15

Note: Adjusted for age, contraception use, hormone replacement therapy, educational level, physical activity, and smoking status.
Abbreviations: HR = Hazard Ratio; CI = Confidence Interval.

Table 5.

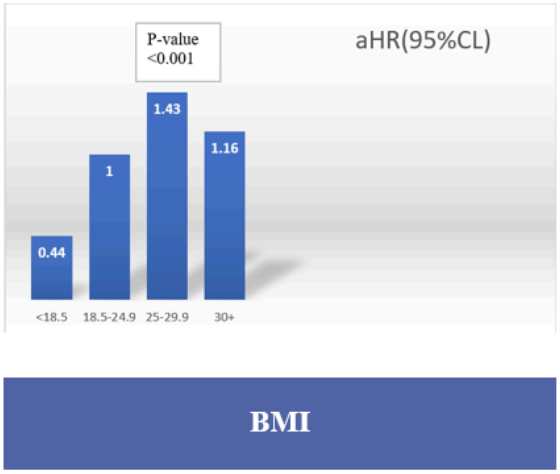
Additive Interaction Indicators Between BMI and Fertile Years on Breast Cancer Risk in MDCS Postmenopausal Women (N = 6,628)

BMI (kg/m²)	Fertile Years	Excess Relative Risk (ERR, 95% CI)	P-value
<25	≥40	0.01 (−0.34, 0.57)	0.95
≥25	<40	0.29 (0.09, 0.54)	0.003
≥25	≥40	1.17 (0.62, 1.91)	<0.001
RERI		0.86 (0.14, 1.58)	0.018
AP		**0.39 (0.13, 0.66)**	**0.003**
Synergy Index (SI)		3.76 (0.71, 19.90)	0.12

Note: BMI and fertile years were dichotomized: BMI (<25 vs. ≥25 kg/m²), fertile years (<40 vs. ≥40 years).
Models were adjusted for age, contraception use, hormone replacement therapy, educational level, physical activity, and smoking status.
Abbreviations: ERR = Excess Relative Risk; RERI = Relative Excess Risk due to Interaction; AP = Attributable Proportion; SI = Synergy Index; CI = Confidence Interval.

Graphs

Results



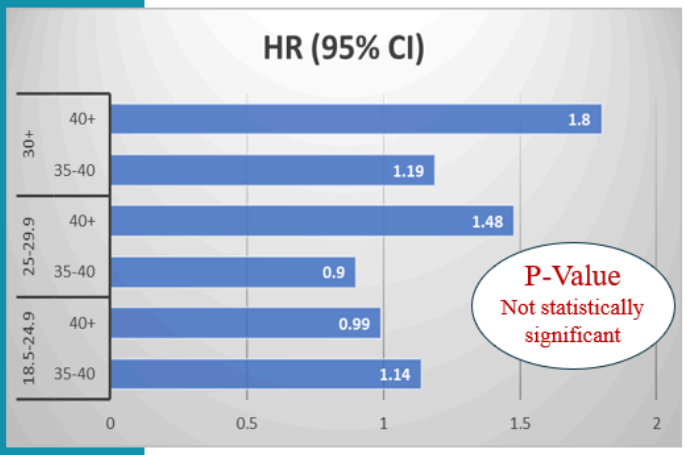
BMI

Fertile Years

aHR, Adjusted Hazard Ratio. Models were adjusted for age, contraception use, hormonal replacement therapy, educational level, physical activities, and smoking status.

Interaction

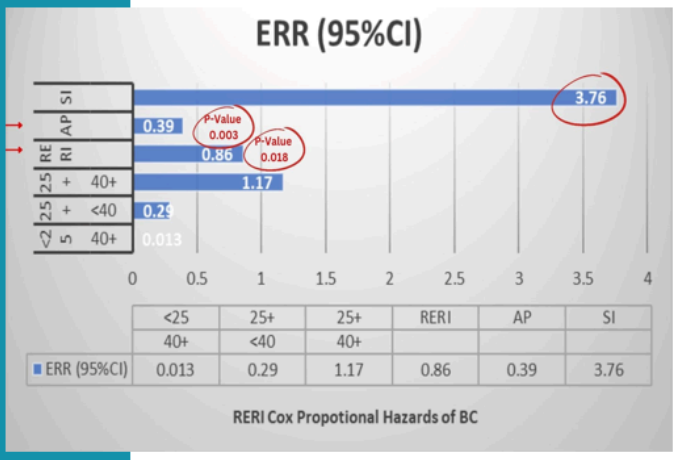
Multiplicative Interaction Results



Models were adjusted for age, contraception use, hormonal replacement therapy, educational level, physical activities, and smoking status.

RERI
Relative Excess Risk due to Interaction

AP: Attributable proportion due to interaction; SI: The synergy index. Models were adjusted for age, contraception use, hormonal replacement therapy, educational level, physical activities, and smoking status.



*In this model we categorized BMI to 2 categories: >25, and <25. Also, we categorized the Fertile years into 2 categories: <40, and 40+

Popular science summary

In 2020, more than two million cases of breast cancer were documented worldwide. In Sweden, breast cancer is the most common form of cancer among women. According to the most recent report from the National Board of Health and Welfare (*Socialstyrelsen*) in 2021, over 8,600 Swedish women were newly diagnosed with breast cancer, a 3.9% increase from previous years. Sadly, 16% of those women died with BC as the main cause.

Researchers have made a significant discovery in the ongoing fight against breast cancer. This discovery reveals how weight and reproductive history may interact to influence breast cancer risk in postmenopausal women. This study focused on a previously unexplored area: how body mass index (BMI), a measure based on weight and height, and fertile years**,** the total time a woman has menstruated, might interact to affect breast cancer risk.

Interestingly, the study found that high BMI or longer fertile years did not significantly increase the risk of breast cancer. However, when these two factors were considered together, they revealed a meaningful interaction: their combined effect on breast cancer risk was stronger than when examined separately. This type of combined effect is called an additive interaction.

Understanding that BMI and reproductive history can interact in this way helps us better identify women who may be at higher risk. This insight is valuable for improving prevention strategies and developing more personalized health interventions for postmenopausal women.

This research adds an important piece to the puzzle of breast cancer and highlights the importance of looking at risk factors in combination, not just in isolation. It is a step forward in reducing breast cancer rates and improving outcomes for women around the world.