Parity, breastfeeding and risk of coronary heart disease: A pan-European case-cohort study

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Abstract

Aim: There is uncertainty about the direction and magnitude the associations between parity, breastfeeding and the risk of coronary heart disease (CHD). We examined the separate and combined associations of parity and breastfeeding practices with the incidence of CHD later in life among women in a large pan-European cohort study.

Methods: Data were used from EPIC-CVD, a case-cohort study nested within the EPIC prospective study of 520,000 participants from 10 countries. Information on reproductive history was available for 14,917 women, including 5,138 incident cases of CHD. Using Prentice-weighted Cox regression stratified by country, we calculated hazard ratios (HRs) and 95% confidence intervals (CIs) for CHD, after adjustment for age, study centre, and several socioeconomic and biological risk factors.

Results: Compared with nulliparous women, the adjusted HR was 1.19 (95% CI: 1.03-1.38) among parous women; HRs were higher among women with more children (e.g., adjusted HR: 1.04, 1.27-3.27, for women with ≥5 children). Compared with women who did not breastfeed, the adjusted HR was 0.70 (0.50-0.97) among women who breastfed. For childbearing women who never breastfed, the adjusted HR was 1.27 (0.72-2.24) compared with nulliparous women, whereas for childbearing women who breastfed the adjusted HR was 0.92 (0.62-1.37).

Conclusion: Having more children was associated with a higher risk of CHD later in life, whereas breastfeeding was associated with a lower CHD risk. Women who both had children and breastfed did not have a higher risk of CHD.

Introduction

Pregnancy is associated with profound changes in the maternal metabolic system, including weight gain, accumulation of abdominal fat, increased insulin resistance, and higher circulating lipid levels.[1, 2] While these metabolic changes of pregnancy support the growth of the foetus and prepare the mother's body for breastfeeding in the short-term, they may also have a prolonged effect on maternal risk of cardiovascular diseases (CVD). However, previous studies have reported conflicting associations on parity (i.e., the number of live children to whom a woman has given birth) and risk of CVD later in life.[3-10]

Conversely, since the metabolic changes in pregnancy appear to reverse more quickly and more completely with breastfeeding, it has been proposed that breastfeeding could reduce maternal risk of cardiometabolic diseases.[11] Studies have reported that, compared with women who have never breastfed, women who have breastfed have favourable cardiometabolic profiles,[12, 13] and exhibit a lower burden of subclinical cardiovascular disease.[14] There may be a lower risk of developing metabolic syndrome,[15] hypertension,[16, 17] and type 2 diabetes[18-21] among women who have breastfed for longer cumulative durations. However, it is uncertain whether there is an association between breastfeeding and incident CVD outcomes.[10, 22-24] Also, while lifetime duration of breastfeeding will be affected by the number of children, it is unknown whether extended duration of breastfeeding for one child is associated with the same extent of inverse association with CHD risk as multiple periods of shorter breastfeeding across several pregnancies. Moreover, whether breastfeeding could compensate for the potential effect of parity on CHD risk has not been examined.

The EPIC (European Prospective Investigation into Cancer and Nutrition)-CVD study provides an opportunity to address these outstanding issues and to evaluate the separate and combined associations of parity and breastfeeding on the risk of incident CHD in a large sample of women from diverse European countries.

Methods

EPIC-CVD is a large, prospective, case-cohort study nested within the European Prospective Investigation into Cancer and Nutrition (EPIC) study. [25, 26] Briefly, the EPIC study involves 366,521 women and 153,457 men, mostly aged 35–70 years, recruited by 23 centres in 10 European countries (Denmark, France, Germany, Greece, Italy, the Netherlands, Norway, Spain, Sweden, and the United Kingdom) between 1991 and 1999. Participants completed questionnaires on their diet, lifestyle, and medical history, and data were centralized at the International Agency for Research on Cancer (IARC) in Lyon, France. A representative random subcohort of 18,249 participants (62% women), stratified by centre, was selected for the EPIC-CVD project.[27] After exclusion of 609 participants with a prior history of myocardial infarction or stroke at baseline, 17,640 subcohort members remained. This study complied with the Declaration of Helsinki; ethical review boards of IARC and all local institutions where participants had been recruited gave approval for the study, and all participants gave written informed consent.

Definition and ascertainment of CHD events

First-time CHD events, whether non-fatal or fatal, as defined by codes 410-414 of the International Classification of Diseases Ninth Edition (ICD-9), and codes I20-I25 of the Tenth Edition (ICD-10) were the primary study endpoint. Individual centres used different methods to ascertain first-time non-fatal CHD events, including self-report and linkage with morbidity or hospital registries. Non-fatal CHD events were further validated by additional review of medical records and/or linkage with registries.[26] Fatal CHD events were generally ascertained through mortality registries. End of follow-up for CHD events varied between centres and ranged between 2003 and 2010.

Study population and measurement

Of the 16,504 women in EPIC-CVD who did not have a known history of CHD or stroke at baseline and 14,917 women provided data on reproductive history. Two EPIC centres (Bilthoven, the Netherlands, and Umea, Sweden) did not assess parity and breastfeeding history and thus did not contribute to the analyses. Reproductive history, socioeconomic and lifestyle factors, and medical history were assessed once using a self-administrated questionnaire at study baseline. Trained health professionals measured blood pressure, weight, height, and waist circumference during a visit to each study centre, except in the France and Oxford centres where anthropometry was self-reported. Blood pressure measurements were not available for the Norway, Asturias, and Navarra centres. High blood pressure was defined as self-reported hypertension at baseline, systolic blood pressure>140 or diastolic blood pressure >90, or self-reported use of hypertension medication. Body mass index was calculated as weight divided by the square of height in meters. HDL cholesterol and total cholesterol levels, measured in baseline serum samples using a Roche MODULAR ANALYTICS EVO analyser, were available in all centres except Norway.

Statistical analyses

Baseline characteristics for the subcohort by parity were presented as means (standard deviation) or medians (interquartile range) for continuous variables and as percentages for categorical variables. Cox proportional hazards models, modified for the case-cohort design using the Prentice method[28], were used to estimate hazard ratios and 95% confidence intervals for first-time CHD by parity and breastfeeding history. Participants contributed only the first CHD outcome (whether non-fatal or fatal) experienced during follow-up, so fatal events that followed non-fatal events were not included. Given the multilevel structure of the data, models were first fitted separately within each country before pooling the country-specific estimates by multivariate random-effects meta-analysis using inverse variance weights. Age was used as the underlying time variable, with entry time defined as the participant's age at recruitment, and exit time as the age of first-time CHD, loss-to-follow-up or censoring at the end of the follow-up, whichever came first. The I^2 statistic was used to quantify the percentage of total variability between countries due to between-country heterogeneity. Parity, defined as the number of live births, was categorized as nulliparous (reference), 1 child, 2 children, 3 children, 4 children, or 5 or more children. Breastfeeding history was examined among parous women, comparing women who ever breastfed to women who had never breastfed, and categorized into groups of lifetime duration of breastfeeding (never [reference], >0-<3 months, 3-<6 months, 6-<12 months,

12-<23 months, and 23 months or more), and into groups of mean duration of breastfeeding per live-born child (never [reference], >0-<1 months, 1-<3 months, 3-<6 months, and 6 months or more). Group-specific 95% confidence intervals were estimated only from the variances that correspond to the amount of information underlying each group (including the reference group).[29] To assess the combined effect of parity and breastfeeding on CHD risk, we also examined the association between parity, history of breastfeeding and risk of first-time CHD in models including nulliparous women as the reference group.

Models were adjusted for age at study entry and centre (Model I), and then additionally for level of attained education, smoking status, and parity (for breastfeeding history only) (Model II), followed by further adjustment for other confounders and potential mediators (history of high blood pressure, HDL cholesterol, total cholesterol, history of diabetes mellitus, and BMI) (Model III). Model III was used as our primary, most conservative, analyses model. To account for the impact of missing covariate data on our results, we restricted our main analyses to individuals with complete data for all models. Secondary analyses allowed the set of individuals to vary between models and used all individuals with non-missing values for the covariates separately for each model. To investigate whether age or number of live births modified the association between parity or breastfeeding with CHD risk, we calculated the HRs for CHD in women <55 years versus ≥ 55 years of age, and in women with 1 or 2 children versus those with 3 children or more. Statistical interaction was evaluated by adding a cross-product term to the country-specific regression models and pooling these using random-effects meta-analysis. In a sensitivity analysis, we excluded women younger than 45 in whom reproductive history may not yet be complete. All statistical analyses were performed using STATA, version 12.0 (Stata, College Station, TX).

Results

The baseline characteristics of the 9,985 women in the subcohort with information on reproductive history are shown in Table 1. The mean (SD) age at entry was 52.7 (9.1) years, 88% of these women were parous, of these 87% had ever breastfed. Women who were parous had a lower level of attained education, had higher levels of BMI, and were less likely to smoke than those who were nulliparous. During a median follow-up of 11.1 years (interquartile range 8.0-13.4), 5,138 of 14,890 women developed CHD, of whom 206 were also in the subcohort. Supplementary Table 1 shows the descriptive statistics for main characteristics by centre.

Parity and risk of coronary heart disease

Of 12,481 women with complete data, 3,336 developed CHD during follow-up. The HR (95% CI) for CHD in parous versus nulliparous women was 1.25 (1.07, 1.46) in the age- and country stratified model and attenuated to 1.19 (1.03, 1.38) following adjustment for potential confounders and mediators (Table 2). The I^2 statistic for the multiple-adjusted analyses was 29% (0%-67%), indicating that there was moderate heterogeneity between countries. Compared to nulliparous women, the multiple-adjusted HRs for CHD were 1.16 (0.89, 1.51), 1.14 (1.02, 1.28), 1.16 (0.96, 1.41), 1.40 (1.18, 1.66), and 2.03 (1.27, 3.26) for women with 1, 2, 3, 4, or 5 or more children, respectively (Table 2 and Figure 1). Results were similar in analyses

including the largest set of women with complete data available, irrespective of incomplete data in subsequent models, or when restricting the analyses to women aged 45 years or older at study entry (Supplementary Tables 2 and 3).

Breastfeeding history and risk of coronary heart disease

Data on breastfeeding history were available on 12,779 parous women and 4348 CHD events; 8,074 women (2,404 CHD events) had complete data on all variables. Parous women who had ever breastfed had a multiple-adjusted HR for CHD of 0.70 (95% CI: 0.50, 0.97) compared with parous women who never breastfed (Table 2). There was substantial heterogeneity between countries; the I^2 statistic was 82% (65%-91%). Compared with parous women who had never breastfed, women with a lifetime duration of breastfeeding of >0-<3 months, 3-<6 months, 6-<12 months, 12-<23 months, or 23 months or more had a multiple-adjusted HR for CHD of 0.71 (0.59, 0.86), 0.67 (0.57, 0.79), 0.68 (0.55, 0.84), 0.61 (0.52, 0.71), and 0.59 (0.44, 0.79), respectively (Figure 2 and Table 2). Similar results were obtained in the analyses on the mean duration of breastfeeding per child and CHD risk (Figure 3 and Table 2). Analyses restricted to women 45 years or older or including women with missing data on some covariables did not change the findings materially (Supplementary Tables 2 and 3).

Combination of parity and breastfeeding and risk of coronary heart disease

Analyses of the combination of parity and breastfeeding indicated that parous women who had ever breastfed were at a similar risk of CHD compared to nulliparous women (HR: 0.92 [0.62, 1.37]; Table 3). There was no significant evidence for a higher risk of CHD in parous women who had never breastfed (HR: 1.27 [0.72, 2.24]), although power to detect weak effects was limited.

Subgroup analyses

Analyses in subgroups of women younger than 55 years versus those 55 years or above at study entry provided no evidence for a different effect of parity by age, and neither did the association between number of children and risk of CHD differ between the age groups (Table 4). A history of breastfeeding was associated with similar reductions in risk of CHD in younger as in older women, and in women with 1 or 2 children as in those with 3 or more children. The associations between lifetime duration of breastfeeding and duration of breastfeeding per child and CHD risk also did not differ between age groups or by parity (Table 4).

Discussion

In this case-cohort analysis, nested within the 10-country EPIC prospective cohort study, we examined the separate and combined associations of parity and breastfeeding on the risk of incident CHD. Our main findings are threefold.

First, we report that parous women are at higher risk of CHD as compared to nulliparous women; with the highest risk seen among women who had the most offspring. These findings, therefore, add to the accumulating evidence that repeated

pregnancies could result in an accumulation of cardiometabolic changes, including elevated pro-atherogenic lipid levels, accumulation of abdominal fat, endothelial dysfunction, and increased systemic inflammation,[1, 30] that may have permanent effects on the cardiovascular system, leading to a higher risk of CHD later in life.[3-7]

Second, in agreement with previous observations that breastfeeding is associated with lower risk of the metabolic syndrome,[15] hypertension,[16, 17] and diabetes,[18-21] our study supports the existence of inverse associations between breastfeeding and CHD risk. Previous studies have reported that prolonged periods of breastfeeding could have beneficial effects on maternal cardiovascular risk factors, including on lipids, blood pressure, insulin and glucose homeostasis, and body mass index.[12, 31] Our results extend previous work by supporting the possibility of stronger inverse associations between breastfeeding and CHD risk among women who had longer cumulative lifelong duration of breastfeeding. However, the dose-response curve between breastfeeding and CHD risk requires further investigation, since it may be context-dependent. For example, a previous study of more than 20,000 Norwegian women reported that breastfeeding was associated with a lower risk of CVD mortality, potentially in a U-shaped fashion, but only among parous women younger than 65 years at study baseline.[22] Results from the Nurses' Health Study suggested that the association between lifetime duration of breastfeeding and risk of incident CHD was characterized by a threshold effect; only women with lifetime duration of two years or more had a significantly lower risk of incident CHD compared to women who had never breastfed.[23] Conversely, while a history of breastfeeding was associated with a slightly lower risk of fatal CHD in a cohort of 267,400 women from Shanghai, increasing duration of breastfeeding did not strengthen the association.[10]

Third, our study constitutes one of the few available analyses of the combined associations of parity and breastfeeding on the incidence of CHD. We found that women who both had children and breastfed did not have a higher risk of CHD, which is consistent with the notion that the physiological changes in pregnancy could reverse more quickly and more completely with breastfeeding, which in turn may confer cardiovascular protection later in life.[11]

Our observations are consistent with the conclusions of previous studies that attempted to disentangle biological processes related to pregnancy from lifestyle factors related to childrearing by comparing results from men and women within the same cohort. For example, a study among men from prospective cohorts in the US found no relationship between the number of children and the paternal risk of CHD,[32] whereas there was a positive association between having 6 or more pregnancies and CHD risk among women from the same cohort.[5] A cross-sectional analysis of men and women from the British Women's Heart and Health Study and the British Regional Heart Study reported that having more offspring was associated with higher body mass index for both male and female parents, and with more adverse lipid profiles and diabetes in women only.[6] However, as there was a positive association between parity and CHD among women (but not men) in these cohorts, the authors concluded that the biological effects of pregnancy in women persist into later life.

The strengths and potential limitations of our study merit consideration. Our analysis maximized power and efficiency by conducting a case-cohort analysis of incident CHD in the large prospective EPIC cohort, thereby focusing measurement of lipids and other biochemical risk factors on the most relevant subset of the cohort. The validity of our findings was enhanced by our ability to adjust for a range of relevant covariates, and by the robustness of our results to a variety of sensitivity and subgroup analyses. The generalisability of our findings was enhanced by the inclusion of women from 10 diverse European countries. However, we cannot discount the possibility that the associations observed in this study were, at least partly, due to unmeasured or residual confounding. For example, confounding is a major concern in studies of breastfeeding and health outcomes, because mothers who breastfeed are more likely to engage in other health-promoting behaviours.[33-35] Nevertheless, we found that adjustment in our study for several relevant factors did not materially affect the relationships we observed. Our study had insufficient data to account for CHD risk factors before or during pregnancy that determine breastfeeding initiation and duration as well as future CHD risk, leaving our results potential liable to "reverse causality". For example, women with pre-existing CHD risk factors such as obesity, type 1 diabetes, preeclampsia, or polycystic ovary syndrome, might be less likely to initiate breastfeeding and or could breastfeed for shorter durations than women without these CHD risk factors. Because our study involved self-reported information on parity and breastfeeding, information that was sometimes recalled and recorded decades after childbirth and weaning (with the added limitation that duration of breastfeeding was recorded in EPIC only for a woman's first three children and final child), the true strength of any associations we observed could have been underestimated. Data on the number of children in men was not available, so we were no able to dissect whether the association between parity and CHD was due to biological effects of childbearing or factors related to childrearing. Finally, we noted between-country heterogeneity in some of our results, a finding which requires further investigation.

In conclusion, this analysis of women from 10 European countries found that having more children was associated with a higher risk of CHD later in life, whereas breastfeeding was associated with a lower CHD risk. Women who both had children and breastfed did not have a higher risk of CHD, suggesting the need for studies to determine whether breastfeeding can compensate for the CHD risk associated with greater parity.

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Conflicts of interest

None

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Figure legend

Figure 1: Adjusted hazard ratios (with group-specific 95% confidence intervals) for incident coronary heart disease associated with number of live born children.
The highest category of live born children (5 or more) is plotted at 5.5.

Figure 2: Adjusted hazard ratios (with group-specific 95% confidence intervals) for incident coronary heart disease associated with lifetime duration of breastfeeding in parous women.
Categories are never, 0-<3 months, 3-<6 months, 6-<12 months, 12-<23 months, and 23 months or more. On the x-axis, results are placed on the mean lifetime duration of breastfeeding within category.

Figure 3: Adjusted hazard ratios (with group-specific 95% confidence intervals) for incident coronary heart disease associated with mean duration of breastfeeding per live born child.
Categories are never, 0-<1 months, 1-<3 months, 3-<6 months, and 6 months or more. On the x-axis, results are placed on the mean duration of breastfeeding per child within category.

Table 1: Baseline characteristics of women in the EPIC-CVD subcohort by parity

	Overall subcohort	Nulliparous	Parous
N (% of overall subcohort)	9,985	1,220 (12.2)	8,765 (87.8)
Age at study entry, years	52.7 (9.1)	52.7 (10.1)	52.7 (9.0)
Education level, %			
None	11.3	7.0	11.9
Primary	34.3	23.9	35.8
Secondary	15.4	18.2	15.0
Tertiary	39.0	50.9	37.4
Current smoker, %	21.7	25.4	21.1
History of diabetes, %	2.6	2.3	2.7
BMI, kg/m^2	26.1 (4.7)	24.9 (4.3)	26.2 (4.7)
Systolic blood pressure, mmHg	130.8 (20.0)	129.6 (20.4)	131.0 (19.9)
Diastolic blood pressure, mmHg	80.3 (10.6)	79.2 (10.4)	80.5 (10.6)
History of high blood pressure, %	34.3	30.1	34.9
Total cholesterol, mmol/L	6.0 (1.1)	6.0 (1.2)	6.0 (1.1)
HDL cholesterol, mmol/L	1.6 (0.4)	1.7 (0.4)	1.6 (0.4)
Postmenopausal, %	52.7	53.9	52.5
Age at menopause[ł]	48.5 (4.9)	48.1 (5.3)	48.6 (4.9)
Number of children*, %			
1 child	-	-	14.8
2 children	-	-	47.5
≥3 children	-	-	37.7
History of breastfeeding*, %	-	-	87.2
Lifetime duration of breastfeeding*, months	-	-	6.4 (3.0, 13.0)
Duration of breastfeeding per child*, months	-	-	3.0 (1.5, 6.0)

Values are mean (standard deviation) or median (25th and 75th percentile) for continuous variables. ł postmenopausal women only, *parous women only.

Table 2: Hazard ratios (95% confidence intervals) for incident coronary heart disease associated with parity in all women and history of breastfeeding in parous women only

	Model I	Model II	Model III
Parity			
N	12,481	12,481	12,481
Parous (yes vs. no)	1.25 (1.07, 1.46)	1.23 (1.05, 1.43)	1.19 (1.03, 1.38)
I^2 for heterogeneity (95% CI)	40% (0%, 72%)	40% (0%, 72%)	29% (0%, 67%)
Number of children			
None	1.00 (0.84, 1.19)	1.00 (0.83, 1.20)	1.00 (0.85, 1.18)
1 child	1.18 (0.97, 1.43)	1.13 (0.93, 1.38)	1.16 (0.89, 1.51)
2 children	1.20 (1.10, 1.32)	1.16 (1.12, 1.20)	1.14 (1.02, 1.28)
3 children	1.23 (1.07, 1.41)	1.21 (1.04, 1.41)	1.16 (0.96, 1.41)
4 children	1.51 (1.27, 1.79)	1.49 (1.23, 1.79)	1.40 (1.18, 1.66)
5 or more children	2.28 (1.51, 3.45)	2.05 (1.31, 3.22)	2.03 (1.27, 3.26)
History of breastfeeding			
N	8,074	8,074	8,074
Ever breastfed (yes vs. no)	0.68 (0.59, 0.80)	0.61 (0.50, 0.74)	0.70 (0.50, 0.97)
I^2 for heterogeneity	54% (0%, 80%)	62% (12%, 83%)	82% (65%, 91%)
Lifetime duration of breastfeeding			
Never breastfed	1.00 (0.83, 1.21)	1.00 (0.83, 1.23)	1.00 (0.73, 1.37)
>0 to <3 months	0.67 (0.59, 0.77)	0.66 (0.57, 0.77)	0.71 (0.59, 0.86)
≥3 to <6 months	0.70 (0.58, 0.85)	0.69 (0.59, 0.81)	0.67 (0.57, 0.79)
≥6 to <12 months	0.72 (0.61, 0.84)	0.67 (0.57, 0.79)	0.68 (0.55, 0.84)
≥12 to <23 months	0.63 (0.57, 0.70)	0.60 (0.52, 0.70)	0.61 (0.52, 0.71)
≥23 months	0.63 (0.48, 0.83)	0.56 (0.43, 0.73)	0.59 (0.44, 0.79)
Duration of breastfeeding per child			
Never breastfed	1.00 (0.88, 1.14)	1.00 (0.85, 1.18)	1.00 (0.74, 1.35)
>0 to <1 months	0.82 (0.71, 0.95)	0.75 (0.64, 0.89)	0.82 (0.68, 0.98)
≥1 to <3 months	0.73 (0.65, 0.81)	0.71 (0.64, 0.79)	0.70 (0.65, 0.76)
≥3 to <6 months	0.69 (0.57, 0.84)	0.66 (0.57, 0.78)	0.69 (0.60, 0.80)
≥6 months	0.64 (0.53, 0.78)	0.66 (0.54, 0.81)	0.66 (0.57, 0.77)

Hazard ratios are from Prentice-weighted Cox proportional hazards models stratified by country and with age as timescale. Analyses of parity are conducted in all women. Analyses of breastfeeding are conducted in parous women only.

Model I: Adjusted for age at study entry and centre; Model II: model I + level of attained education, smoking status, and number of live born children (for breastfeeding only); Model III: model II + high blood pressure, HDL cholesterol, total cholesterol, history of diabetes mellitus, and BMI.

Table 3: Hazard ratios (95% confidence intervals) for incident coronary heart disease associated with the combined effects of parity and a history of breastfeeding

	Nulliparous	Parous – never breastfed	Parous – ever breastfed
Model I	1.00 [reference]	1.63 (1.26, 2.11)	1.13 (0.95, 1.35)
Model II	1.00 [reference]	1.50 (1.07, 2.11)	0.91 (0.63, 1.31)
Model III	1.00 [reference]	1.27 (0.72, 2.24)	0.92 (0.62, 1.37)

Hazard ratios are from Prentice-weighted Cox proportional hazards models stratified by country and with age as timescale. Model I: Adjusted for age at study entry and centre; Model II: model I + level of attained education, smoking status, and number of live born children; Model III: model II + high blood pressure, HDL cholesterol, total cholesterol, history of diabetes mellitus, and BMI.

Table 4: Hazard ratios (95% confidence intervals) for incident coronary heart disease by parity and history of breastfeeding in subgroups

	Age			Parity		
	<55 years	55 years or older	P for interaction	1-2 children	3 or more children	P for interaction
Parous (yes vs. no)	1.17 (0.91, 1.52)	1.19 (0.89, 1.60)	0.94	-	-	-
Number of children						
1 child	1.37 (0.79, 2.38)	1.07 (0.63, 1.80)	0.76	-	-	-
2 children	1.12 (0.64, 1.96)	1.67 (0.79, 3.53)		-	-	
3 children	1.15 (0.75, 1.77)	1.36 (0.94, 1.96)		-	-	
4 children	1.13 (0.81, 1.57)	1.53 (0.45, 5.19)		-	-	
5 or more children	1.30 (0.91, 1.87)	1.84 (1.20, 2.82)		-	-	
History of breastfeeding (yes vs. no)	0.68 (0.50, 0.93)	0.72 (0.50, 1.04)	0.70	0.66 (0.45, 0.95)	0.67 (0.41, 1.08)	0.91
Lifetime duration of breastfeeding						
>0 to <3 months	0.74 (0.49, 1.11)	0.67 (0.41, 1.10)	0.31	0.67 (0.45, 0.99)	0.87 (0.53, 1.41)	0.30
≥3 to <6 months	0.51 (0.35, 0.74)	0.68 (0.40, 1.15)		0.63 (0.42, 0.94)	0.79 (0.51, 1.22)	
≥6 to <12 months	0.75 (0.46, 1.22)	0.61 (0.38, 1.01)		0.64 (0.36, 1.14)	0.72 (0.45, 1.17)	
≥12 to <23 months	0.54 (0.34, 0.86)	0.60 (0.34, 1.05)		0.61 (0.37, 1.01)	0.65 (0.37, 1.14)	
≥23 months	0.55 (0.29, 1.04)	0.55 (0.37, 0.81)		1.09 (0.48, 2.48)	0.62 (0.43, 0.89)	
Duration of breastfeeding per child						
>0 to <1 months	0.79 (0.54, 1.14)	0.71 (0.44, 1.15)	0.68	0.65 (0.42, 1.01)	0.96 (0.66, 1.40)	0.46
≥1 to <3 months	0.59 (0.42, 0.82)	0.66 (0.43, 1.03)		0.67 (0.46, 0.97)	0.70 (0.44, 1.10)	
≥3 to <6 months	0.62 (0.40, 0.98)	0.63 (0.40, 0.99)		0.63 (0.40, 0.99)	0.70 (0.41, 1.17)	
≥6 months	0.64 (0.44, 0.93)	0.59 (0.36, 0.97)		0.67 (0.43, 1.03)	0.63 (0.39, 1.01)	

Hazard ratios are from Prentice-weighted Cox proportional hazards models stratified by country and with age as timescale. Analyses of parity are conducted in all women; nulliparous women are the reference category. Analyses of breastfeeding are conducted in parous women only; parous women with no history of breastfeeding are the reference category.

Models are adjusted for age at study entry, centre, level of attained education, smoking status, number of live born children (for breastfeeding analyses only), high blood pressure, HDL cholesterol, total cholesterol, history of diabetes mellitus, and BMI.

Figure 1

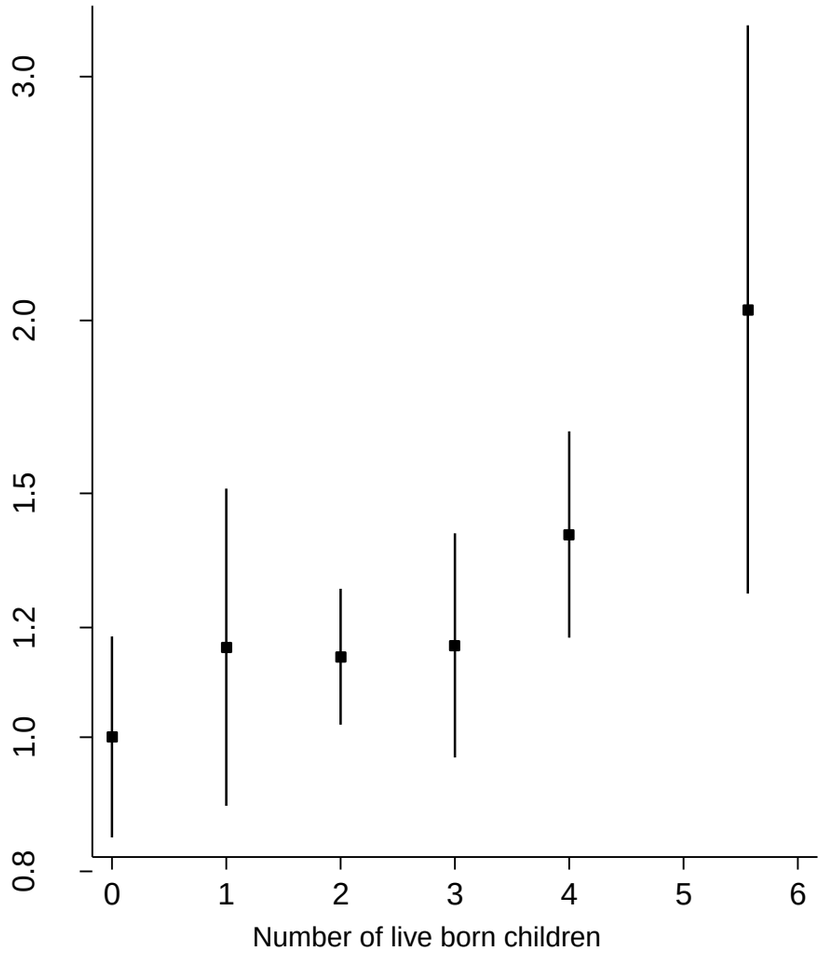


Figure 2

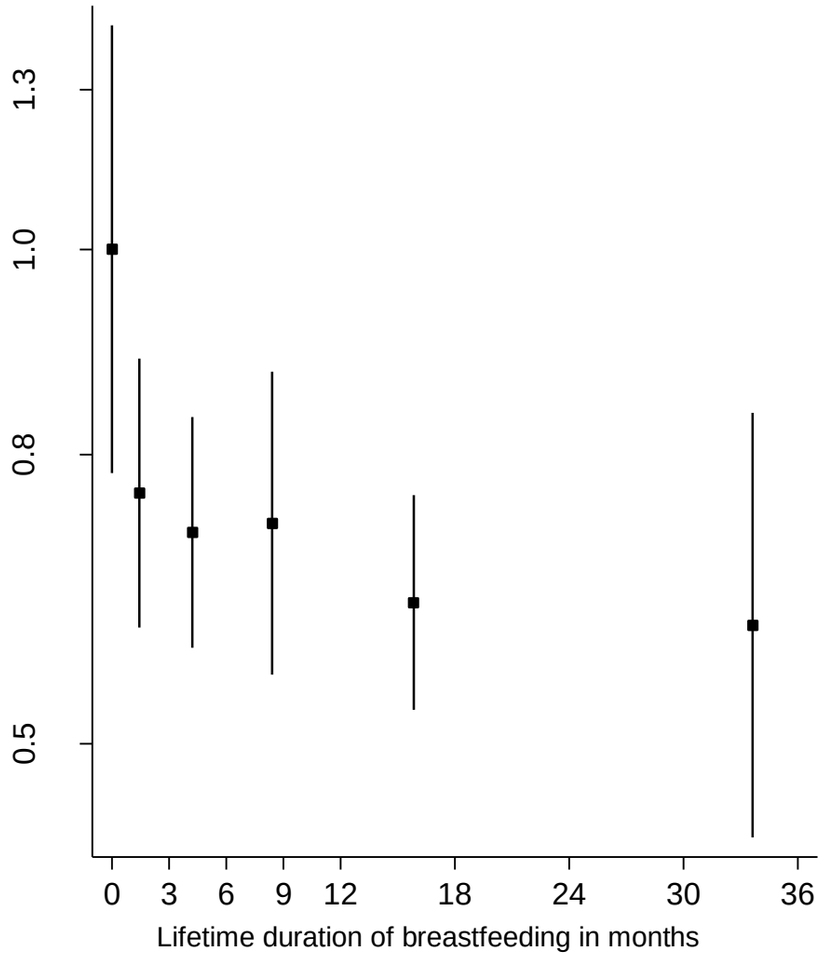
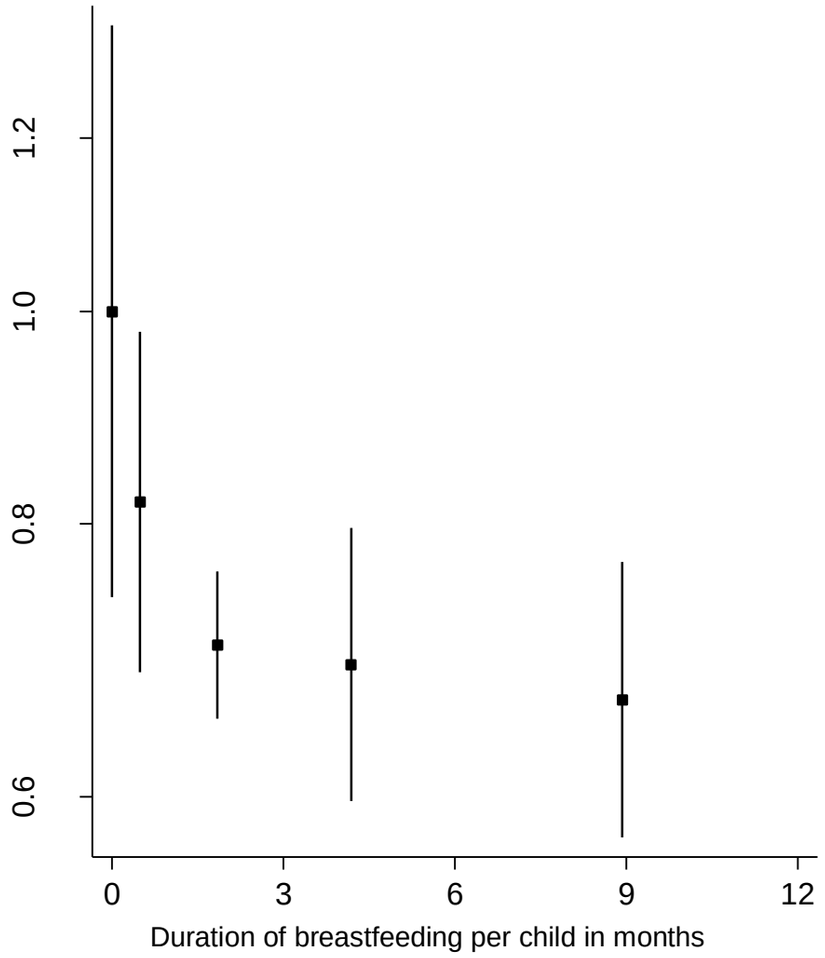

1.3
1.0
0.8
0.5
0
3
6
9
12
18
24
30
36
Lifetime duration of breastfeeding in months

Figure 3


1.2
1.0
0.8
0.6
0
3
6
9
12
Duration of breastfeeding per child in months

Supplementary Table 1: Baseline characteristics for main variables by EPIC centre

					Subcohort characteristics			
Country	EPIC centre	Total, N	Subcohort, N	CHD, N	Age at study entry, years	Current smoker, %	Parous, %	Ever breastfed*, %
Denmark	Aarhus	475	312	170	56.2 (4.4)	29.9	87.2	94.1
	Copenhagen	1,048	654	408	56.6 (4.3)	37.7	87.9	92.4
France	France	593	557	38	56.4 (6.5)	9.0	90.5	77.2
Germany	Heidelberg	554	489	68	49.3 (8.4)	20.3	81.8	81.8
	Potsdam	785	709	78	48.7 (9.2)	16.8	90.7	83.7
Greece	Greece	882	766	121	52.6 (12.2)	20.4	90.6	88.3
Italy	Florence	493	420	77	51.6 (7.6)	26.0	85.2	88.2
	Varese	462	293	173	51.3 (8.2)	21.2	90.4	81.9
	Ragusa	216	178	39	45.9 (7.9)	23.0	85.4	89.5
	Turin	271	237	36	51.1 (7.7)	20.3	83.5	72.7
	Naples	313	223	93	50.1 (7.7)	35.4	91.0	91.6
Norway	Norway	105	60	45	48.7 (4.6)	29.3	93.3	96.4
Spain	Asturias	568	480	96	47.6 (8.1)	19.0	90.6	84.7
	Granada	526	436	100	49.4 (8.4)	14.5	93.1	90.4
	Murcia	585	536	56	47.9 (8.5)	18.1	89.4	89.5
	Navarra	450	410	41	48.6 (7.9)	23.2	85.6	93.1
	San Sebastian	466	414	59	48.2 (7.9)	18.1	89.6	86.0
Sweden	Malmo	1,765	1,128	679	57.1 (8.0)	28.9	86.9	95.4
The Netherlands	Utrecht	1,761	914	891	57.7 (6.0)	22.0	85.7	82.6
United Kingdom	Cambridge	1,457	523	970	59.0 (9.4)	14.4	87.8	83.3
	Oxford	1,142	246	900	49.1 (11.6)	6.5	73.6	90.2
Overall		14,917	9,985	5,138	52.7 (9.1)	21.7	87.8	87.2

* Amongst parous women

Supplementary Table 2: Hazard ratios (95% confidence intervals) for incident coronary heart disease associated with parity and history of breastfeeding in women with complete data on all covariates

	Model I	Model II	Model III
Parity			
N	14,890	14,319	12,481
Parous (yes vs. no)	1.19 (1.00, 1.40)	1.18 (0.99, 1.40)	1.19 (1.03, 1.38)
I^2 for heterogeneity (95% CI)	60% (21%, 80%)	59% (18%, 80%)	29% (0%, 67%)
Number of children			
None			
1 child	1.23 (1.06, 1.42)	1.14 (0.99, 1.31)	1.16 (0.89, 1.51)
2 children	1.11 (1.00, 1.23)	1.11 (1.09, 1.13)	1.14 (1.02, 1.28)
3 children	1.14 (0.98, 1.32)	1.11 (0.98, 1.25)	1.16 (0.96, 1.41)
4 children	1.47 (1.24, 1.75)	1.45 (1.24, 1.70)	1.40 (1.18, 1.66)
5 or more children	1.92 (1.34, 2.76)	2.05 (1.30, 3.24)	2.03 (1.27, 3.26)
History of breastfeeding			
N	12,779	9,466	8,074
Ever breastfed (yes vs. no)	0.68 (0.59, 0.80)	0.61 (0.50, 0.74)	0.70 (0.50, 0.97)
I^2 for heterogeneity	55% (8%, 78%)	61% (16%, 82%)	82% (65%, 91%)
Lifetime duration of breastfeeding			
Never breastfed	1.00 (0.86, 1.16)	1.00 (0.83, 1.21)	1.00 (0.73, 1.37)
>0 to <3 months	0.71 (0.59, 0.84)	0.64 (0.53, 0.77)	0.71 (0.59, 0.86)
≥3 to <6 months	0.67 (0.56, 0.81)	0.62 (0.52, 0.74)	0.67 (0.57, 0.79)
≥6 to <12 months	0.66 (0.59, 0.75)	0.62 (0.55, 0.69)	0.68 (0.55, 0.84)
≥12 to <23 months	0.62 (0.58, 0.67)	0.54 (0.49, 0.59)	0.61 (0.52, 0.71)
≥23 months	0.56 (0.46, 0.70)	0.51 (0.41, 0.65)	0.59 (0.44, 0.79)
Mean duration of breastfeeding per child			
Never breastfed	1.00 (0.93, 1.08)	1.00 (0.84, 1.19)	1.00 (0.74, 1.35)
>0 to <1 months	0.79 (0.68, 0.93)	0.68 (0.58, 0.81)	0.82 (0.68, 0.98)
≥1 to <3 months	0.69 (0.64, 0.75)	0.64 (0.57, 0.72)	0.70 (0.65, 0.76)
≥3 to <6 months	0.59 (0.49, 0.71)	0.59 (0.52, 0.67)	0.69 (0.60, 0.80)
≥6 months	0.56 (0.47, 0.67)	0.58 (0.50, 0.67)	0.66 (0.57, 0.77)

27 individuals with no follow-up were excluded from the analyses. Hazard ratios are from Prentice-weighted Cox proportional hazards models stratified by country and with age at study entry as timescale. Analyses of parity are conducted in all women. Analyses of breastfeeding are conducted in parous women only.

Model I: Adjusted for age at study entry and centre; Model II: model I + level of attained education, smoking status, and number of live born children (for breastfeeding analyses only); Model III: model II + high blood pressure, HDL cholesterol, total cholesterol, history of diabetes mellitus, and BMI.

Supplementary Table 3: Hazard ratios (95% confidence intervals) for incident coronary heart disease associated with parity and history of breastfeeding in women aged 45 years or older at study entry

	Model I	Model II	Model III
Parity			
N	12,608	12,049	10,351
Parous (yes vs. no)	1.19 (1.00, 1.42)	1.19 (1.01, 1.41)	1.19 (1.01, 1.39)
I^2 for heterogeneity (95% CI)	62% (24%, 81%)	55% (8%, 78%)	38% (0%, 72%)
Number of children			
None	1.00 (0.82, 1.22)	1.00 (0.85, 1.18)	1.00 (0.85, 1.18)
1 child	1.26 (1.11, 1.44)	1.18 (1.01, 1.37)	1.19 (0.93, 1.53)
2 children	1.11 (1.04, 1.18)	1.13 (1.11, 1.15)	1.13 (1.02, 1.26)
3 children	1.15 (0.98, 1.36)	1.14 (1.01, 1.28)	1.15 (0.95, 1.40)
4 children	1.50 (1.21, 1.86)	1.51 (1.28, 1.79)	1.40 (1.17, 1.67)
5 or more children	1.91 (1.34, 2.71)	2.02 (1.29, 3.15)	2.03 (1.27, 3.27)
History of breastfeeding			
N	10,832	8,307	6,998
Ever breastfed (yes vs. no)	0.69 (0.59, 0.81)	0.61 (0.50, 0.76)	0.71 (0.51, 1.00)
I^2 for heterogeneity	58% (15%, 79%)	66% (27%, 84%)	83% (66%, 91%)
Lifetime duration of breastfeeding			
Never breastfed	1.00 (0.89, 1.13)	1.00 (0.81, 1.24)	1.00 (0.72, 1.38)
>0 to <3 months	0.70 (0.60, 0.82)	0.64 (0.51, 0.80)	0.71 (0.57, 0.87)
≥3 to <6 months	0.68 (0.60, 0.79)	0.61 (0.50, 0.75)	0.69 (0.58, 0.82)
≥6 to <12 months	0.70 (0.58, 0.84)	0.63 (0.56, 0.70)	0.70 (0.57, 0.86)
≥12 to <23 months	0.65 (0.57, 0.74)	0.55 (0.50, 0.61)	0.64 (0.54, 0.75)
≥23 months	0.59 (0.46, 0.76)	0.50 (0.38, 0.65)	0.61 (0.45, 0.82)
Mean duration of breastfeeding per child			
Never breastfed	1.00 (0.90, 1.11)	1.00 (0.83, 1.21)	1.00 (0.73, 1.37)
>0 to <1 months	0.79 (0.67, 0.94)	0.67 (0.56, 0.81)	0.82 (0.67, 1.01)
≥1 to <3 months	0.71 (0.67, 0.75)	0.66 (0.59, 0.73)	0.73 (0.68, 0.79)
≥3 to <6 months	0.61 (0.50, 0.74)	0.61 (0.53, 0.69)	0.71 (0.62, 0.83)
≥6 months	0.59 (0.49, 0.72)	0.59 (0.51, 0.69)	0.70 (0.60, 0.81)

Hazard ratios are from Prentice-weighted Cox proportional hazards models stratified by country and with age at study entry as timescale. Analyses of parity are conducted in all women. Analyses of breastfeeding are conducted in parous women only.

Model I: Adjusted for age at study entry and centre; Model II: model I + level of attained education, smoking status, and number of live born children (for breastfeeding only); Model III: model II + high blood pressure, HDL cholesterol, total cholesterol, history of diabetes mellitus, and BMI.