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

Sanne A.E. Peters,[1,2] Yvonne T. van der Schouw,[2] Angela M. Wood,[3,4] Michael J. Sweeting,[3,4] Karel G.M. Moons,[2] Elisabete Weiderpass,[5,6,7,8] Larraitz Arriola,[*9] Vassiliki Benetou,[*10,11], Heiner Boeing,[*12] Fabrice Bonnet,[*13] Salma T. Butt,[*14] Françoise Clavel-Chapelon,[*15] Isabel Drake,[*16] Diana Gavrila,[*17,18] Timothy J Key,[*19] Eleni Klinaki,[*11] Vittorio Krogh,[*20] Tilman Kühn,[*21] Camille Lassale,[*22] Giovanna Masala,[*23] Giuseppe Matullo,[*24,25] Melissa Merritt,[*22] Elena Molina-Portillo,[*18,26] Conchi Moreno-Iribas,[*27,28] Therese H. Nøst,[*5] Anja Olsen,[*29] N. Charlotte Onland-Moret,[*2] Kim Overvad,[*30,31] Salvatore Panico,[*32] M Luisa Redondo,[*33] Anne Tjønneland,[*29] Antonia Trichopoulou,[*10,11] Rosario Tumino,[*34] Renée Turzanski-Fortner,[*21] Ioanna Tzoulaki,[*22] Patrik Wennberg,[*35] Anna Winkvist,[*36,37] Simon G. Thompson,[3,4] Emanuele Di Angelantonio,[3,4] Elio Riboli,[21] Nicholas J. Wareham,[38] John Danesh,[3,4,39] Adam S. Butterworth[3,4]

*Denotes authors are listed alphabetically

1. The George Institute for Global Health, University of Oxford, Oxford, UK
2. Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, the Netherlands
3. Cardiovascular Epidemiology Unit, Department of Public Health & Primary Care, University of Cambridge, UK
4. The National Institute for Health Research Blood and Transplant Unit (NIHR BTRU) in Donor Health and Genomics at the University of Cambridge, UK
5. Department of Community Medicine, Faculty of Health Sciences, University of Tromsø, The Arctic University of Norway, Tromsø, Norway
6. Department of Research, Cancer Registry of Norway, Institute of Population-Based Cancer Research, Oslo, Norway
7. Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden
8. Genetic Epidemiology Group, Folkhälsan Research Center, Helsinki, Finland
9. Public Health Division of Gipuzkoa, Instituto Bio-Donostia, Basque Government, CIBERESP, Spain
10. WHO Collaborating Center for Nutrition and Health, Unit of Nutritional Epidemiology and Nutrition in Public Health, Department of Hygiene, Epidemiology and Medical Statistics, University of Athens Medical School, Athens, Greece
11. Hellenic Health Foundation, Athens, Greece
12. Department of Epidemiology, German Institute of Human Nutrition (DIfE), Potsdam-Rehbrücke, Germany
13. Centre Hospitalier Universitaire Rennes, University of Rennes, Villejuif, France
14. Department of Surgery, Clinical Sciences, Lund University, Skåne University Hospital, Malmö, Sweden
15. INSERM, Centre for Research in Epidemiology and Population Health (CESP), U1018, Nutrition, Hormones, and Women's Health Team, Institut Gustave Roussy, Villejuif, France
16. Department of Clinical Science, Lund University, Malmö, Sweden
17. Department of Epidemiology, Murcia Regional Health Council, IMIB-Arrixaca, Murcia, Spain
18. CIBER Epidemiología y Salud Pública (CIBERESP), Spain
19. Cancer Epidemiology Unit, Nuffield Department of Population Health, University of Oxford
20. Epidemiology and Prevention Unit, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy
21. German Cancer Research Center (DKFZ), Division of Cancer Epidemiology, Heidelberg, Germany
22. Department of Epidemiology and Biostatistics, Imperial College London, London, UK
23. Molecular and Nutritional Epidemiology Unit, Cancer Research and Prevention Institute - ISPO, Florence, Italy
24. Human Genetics Foundation, Turin, Italy
25. Department of Medical Sciences, University of Turin, Italy
26. Escuela Andaluza de Salud Pública. Instituto de Investigación Biosanitaria ibs.GRANADA. Hospitales Universitarios de Granada/Universidad de Granada, Granada, Spain
27. Public Health Institute of Navarra, Pamplona, Spain
28. Red de Investigación en Servicios de Salud en Enfermedades Crónicas, Madrid, Spain

29. Diet, Genes and Environment, Danish Cancer Society Research Center, Copenhagen, Denmark
30. Department of Public Health, Section for Epidemiology, Aarhus University, Aarhus, Denmark
31. Department of Cardiology, Aalborg University Hospital, Aalborg, Denmark
32. Dipartimento di Medicina Clinica e Chirurgia, Federico II University, Naples, Italy
33. Public Health Directorate, Asturias, Spain
34. Cancer Registry and Histopathology Unit, Civic- M.P.Arezzo Hospital, ASP Ragusa , Italy
35. Department of Public Health and Clinical Medicine, Family Medicine, Umeå University, Umeå, Sweden
36. Nutritional Research, Umeå University, Umeå, Sweden
37. Department of Internal Medicine and Clinical Nutrition, The Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden
38. Medical Research Council Epidemiology Unit, University of Cambridge, Cambridge, UK
39. Wellcome Trust Sanger Institute, Genome Campus, Hinxton, UK

Address for correspondence

Dr. Sanne A.E. Peters
The George Institute for Global Health, University of Oxford
34 Broad Street, Oxford OX1 3BD, United Kingdom
T: +44 1865 617 200 | F: +44 1865 617 202
E: sanne.peters@georgeinstitute.ox.ac.uk

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Abstract

Objective: There is uncertainty about the direction and magnitude of 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 separately for each country followed by random-effects meta-analysis, 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: 1.01-1.41) among parous women; HRs were higher among women with more children (e.g., adjusted HR: 1.95, 1.19-3.20, for women with ≥5 children). Compared with women who did not breastfeed, the adjusted HR was 0.71 (0.52-0.98) among women who breastfed. For childbearing women who never breastfed, the adjusted HR was 1.58 (1.09, 2.30) compared with nulliparous women, whereas for childbearing women who breastfed the adjusted HR was 1.19 (0.99, 1.43).

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 have a non-significantly higher risk of CHD.

Key messages

What is already known about this subject?

- Pregnancy poses a substantial challenge to the cardiovascular system of the mother and breastfeeding has been suggested to reverse some of the pro-atherogenic changes.
- The direction and magnitude of the associations between parity, breastfeeding, and their combined effects, and the risk of coronary heart disease (CHD) are uncertain.

What does this study add?

- Compared with nulliparous women, parous women were at 20% increased risk of CHD and the excess risk was higher with increasing number of children.
- Breastfeeding was associated with a 30% lower risk of CHD, compared with parous women who did not breastfeed.
- Compared with nulliparous women, childbearing was more strongly associated with a higher risk of CHD among women who had never breastfed. This is despite the higher number of children among women who had ever breastfed.

How might this impact on clinical practice?

- Breastfeeding might reverse the physiological changes in pregnancy more quickly and more completely.
- If causal, promotion of prolonged breastfeeding in parous women may confer long-term cardiovascular benefit.

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, 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 to 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] Models were adjusted for age at study entry and centre (Model I), and then additionally for level of attained education, smoking status, and number of livebirths (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. 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. 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. Parous women who had ever breastfed had more children than parous women who had never breastfed. Supplementary Table 1 shows the descriptive statistics for main characteristics by centre. Overall, 88% of women were parous, with rates ranging from 83% in the UK to 93% in Norway. Of these 87% had ever breastfed, ranging from 77% of women in France to over 92-96% of women in Sweden, Norway, and Denmark. During a median follow-up of 11.1 years (interquartile range 8.0-13.4), 5,138 women developed CHD, of whom 206 were also in the subcohort (27 women without follow-up data available were excluded). The number of participants contributing to each of the main analyses is shown in Supplementary Table 2.

Parity and risk of coronary heart disease

In total, 12,319 women had complete data on parity, including 3,336 incident CHD cases. The HR (95% CI) for CHD in parous versus nulliparous women was 1.27 (1.09, 1.47) in the age- and centre adjusted model and attenuated to 1.19 (1.01, 1.41) following adjustment for potential confounders and mediators (Table 2). The I^2 statistic for the multiple-adjusted analyses was 0% (0%-67%), indicating that there was minimal heterogeneity between countries. Compared to nulliparous women, the multiple-adjusted HRs for CHD were 1.17 (0.92, 1.49), 1.15 (1.02, 1.28), 1.15 (0.94, 1.40), 1.39 (1.14, 1.70), and 1.95 (1.19, 3.20) 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 3 and 4).

Breastfeeding history and risk of coronary heart disease

Complete data on breastfeeding history was available for 8,044 parous women, including 2,404 incident CHD cases. Parous women who had ever breastfed had a multiple-adjusted HR for CHD of 0.71 (95% CI: 0.52, 0.98) compared with parous women who never breastfed (Table 2). There was substantial heterogeneity between countries; the I^2 statistic was 58% (2%-82%). 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 0.73 (0.60, 0.89), 0.68 (0.56, 0.83), 0.69 (0.55, 0.87), 0.63 (0.51, 0.76), and 0.62 (0.45, 0.86), 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 3 and 4).

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 never breastfed were at a significantly higher risk of CHD compared to nulliparous women (HR: 1.58 [1.09, 2.30]; Table 3). There was no significant evidence for a higher risk of CHD in parous women who had ever breastfed (HR: 1.19 [0.99, 1.43]), 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, atherosclerosis, and increased systemic inflammation,[1, 30, 31] 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, 32] Despite the large sample size of this study, we were unable to conclusively distinguish between a threshold effect between never breastfeeding and any duration of breastfeeding or an inverse dose-response curve between longer cumulative breastfeeding duration and CHD risk. Findings 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 cumulative breastfeeding duration of two years or more had a significantly lower risk of incident CHD compared to women who had never breastfed.[23] Moreover, while a history of breastfeeding was associated with a slightly lower risk of fatal CHD in a cohort of 267,400 women from Shanghai, the association did not strengthen with increased duration of breastfeeding.[10] In contrast, 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]

Third, our study constitutes one of the few available analyses of the combined associations of parity and breastfeeding on the incidence of CHD. Despite the higher number of children among women who had ever breastfed, we found that childbearing women who had never breastfed were at higher risk of CHD than childbearing women who had ever breastfed. This 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,[33] 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 offspring 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 preclude 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 such as high fruit and vegetable consumption and abstinence from smoking.[34-36] 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 potentially 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. Finally, data on the number of children in men was not available, so we were not able to dissect whether the association between parity and CHD was due to biological effects of childbearing or factors related to childrearing.

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 were suggested to be at higher risk of CHD (albeit not statistically significantly), suggesting the need for studies to determine whether breastfeeding compensates for the CHD risk associated with greater parity.

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Conflicts of interest

None

Author contributions: SP, YS, AW, KM, MS, EW, and AB were involved in the concept and design of the study. SP and MS conducted the statistical analyses. SP prepared the first draft of the manuscript. All authors were involved in the acquisition and/or interpretation of the data, made critical revision of the manuscript for important intellectual content, and provided final approval of the version to be published. SP, YS, and AB are responsible for the integrity of the work as a whole.

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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. Adjusted for age at study entry, centre, level of attained education, smoking status, high blood pressure, HDL cholesterol, total cholesterol, history of diabetes mellitus, and BMI.

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. Adjusted for age at study entry, centre, level of attained education, smoking status, number of livebirths, high blood pressure, HDL cholesterol, total cholesterol, history of diabetes mellitus, and BMI.

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. Adjusted for age at study entry, centre, level of attained education, smoking status, number of livebirths, high blood pressure, HDL cholesterol, total cholesterol, history of diabetes mellitus, and BMI.

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

	Total	Nulliparous	Parous - never breastfed	Parous - ever breastfed
*% of overall subcohort**	-	12.4	11.2	76.4
Age at study entry, years	52.7 (9.1)	52.7 (10.1)	52.0 (8.4)	52.7 (9.0)
Education level, %				
None	11.3	7.0	9.1	12.4
Primary	34.3	23.9	34.9	35.6
Secondary	15.4	18.2	19.4	14.5
Tertiary	39.0	50.9	36.6	37.5
Current smoker, %	21.7	25.4	20.4	21.1
History of diabetes, %	2.6	2.3	3.5	2.5
BMI, kg/m^2	26.1 (4.7)	24.9 (4.3)	26.4 (4.9)	26.2 (4.7)
Systolic blood pressure, mmHg	130.8 (20.0)	129.6 (20.4)	129.3 (19.9)	131.0 (19.9)
Diastolic blood pressure, mmHg	80.3 (10.6)	79.2 (10.4)	80.2 (11.2)	80.5 (10.5)
History of high blood pressure, %	34.3	30.1	33.2	35.0
Total cholesterol, mmol/L	6.0 (1.1)	6.0 (1.2)	6.0 (1.1)	6.0 (1.1)
HDL cholesterol, mmol/L	1.6 (0.4)	1.7 (0.4)	1.6 (0.4)	1.6 (0.4)
Postmenopausal, %	52.7	53.9	47.7	52.9
Age at menopause[ƚ]	48.5 (4.9)	48.1 (5.3)	48.2 (5.0)	48.7 (4.9)
Number of children, %				
1 child	-	-	25.6	13.1
2 children	-	-	49.7	47.5
≥3 children	-	-	24.8	39.4
Lifetime duration of breastfeeding, months	-	-	-	9.7 (10.4)
Duration of breastfeeding per child, months	-	-	-	4.2 (3.7)

Values are mean (standard deviation) for continuous variables. *131 of 9,985 women with incomplete information about breastfeeding history were excluded. ƚ postmenopausal 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	12,319	12,319	12,319
Parous vs. not	1.27 (1.09, 1.47)	1.24 (1.07, 1.44)	1.19 (1.01, 1.41)
I^2 for heterogeneity (95% CI)	7% (0%, 67%)	0% (0%, 65%)	0% (0%, 65%)
Number of children, n	9,701	9,701	9,701
None	1.00 (0.82, 1.22)	1.00 (0.82, 1.22)	1.00 (0.82, 1.23)
1 child	1.21 (1.00, 1.45)	1.16 (0.95, 1.42)	1.17 (0.92, 1.49)
2 children	1.21 (1.10, 1.33)	1.17 (1.10, 1.25)	1.15 (1.02, 1.28)
3 children	1.21 (1.05, 1.39)	1.20 (1.02, 1.40)	1.15 (0.94, 1.40)
4 children	1.46 (1.20, 1.77)	1.43 (1.18, 1.75)	1.39 (1.14, 1.70)
5 or more children	2.19 (1.41, 3.38)	2.02 (1.27, 3.20)	1.95 (1.19, 3.20)
Breastfeeding, n	8,044	8,044	8,044
Ever vs. never	0.71 (0.59, 0.85)	0.69 (0.57, 0.85)	0.71 (0.52, 0.98)
I^2 for heterogeneity	8% (0%, 73%)	16% (0%, 59%)	58% (2%, 82%)
Lifetime duration of breastfeeding , n	8,012	8,012	8,012
Never breastfed	1.00 (0.84, 1.19)	1.00 (0.83, 1.21)	1.00 (0.75, 1.34)
>0 to <3 months	0.69 (0.57, 0.83)	0.69 (0.57, 0.83)	0.73 (0.60, 0.89)
≥3 to <6 months	0.71 (0.55, 0.91)	0.73 (0.60, 0.88)	0.68 (0.56, 0.83)
≥6 to <12 months	0.73 (0.61, 0.87)	0.70 (0.58, 0.84)	0.69 (0.55, 0.87)
≥12 to <23 months	0.65 (0.57, 0.74)	0.63 (0.53, 0.74)	0.63 (0.51, 0.76)
≥23 months	0.66 (0.50, 0.87)	0.60 (0.46, 0.78)	0.62 (0.45, 0.86)
Duration of breastfeeding per child, n	8,012	8,012	8,012
Never breastfed	1.00 (0.85, 1.17)	1.00 (0.84, 1.20)	1.00 (0.73, 1.37)
>0 to <1 months	0.79 (0.66, 0.94)	0.73 (0.61, 0.88)	0.77 (0.63, 0.94)
≥1 to <3 months	0.72 (0.62, 0.85)	0.71 (0.61, 0.83)	0.69 (0.61, 0.78)
≥3 to <6 months	0.66 (0.56, 0.78)	0.65 (0.55, 0.75)	0.67 (0.57, 0.77)
≥6 months	0.63 (0.51, 0.78)	0.66 (0.53, 0.82)	0.67 (0.56, 0.80)

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 livebirths (for breastfeeding history 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

	N	Nulliparous	Parous – never breastfed	Parous – ever breastfed
Model I	9,511	1.00 [reference]	1.73 (1.30, 2.30)	1.24 (1.05, 1.46)
Model II	9,511	1.00 [reference]	1.72 (1.34, 2.20)	1.22 (1.02, 1.46)
Model III	9,511	1.00 [reference]	1.58 (1.09, 2.30)	1.19 (0.99, 1.43)

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

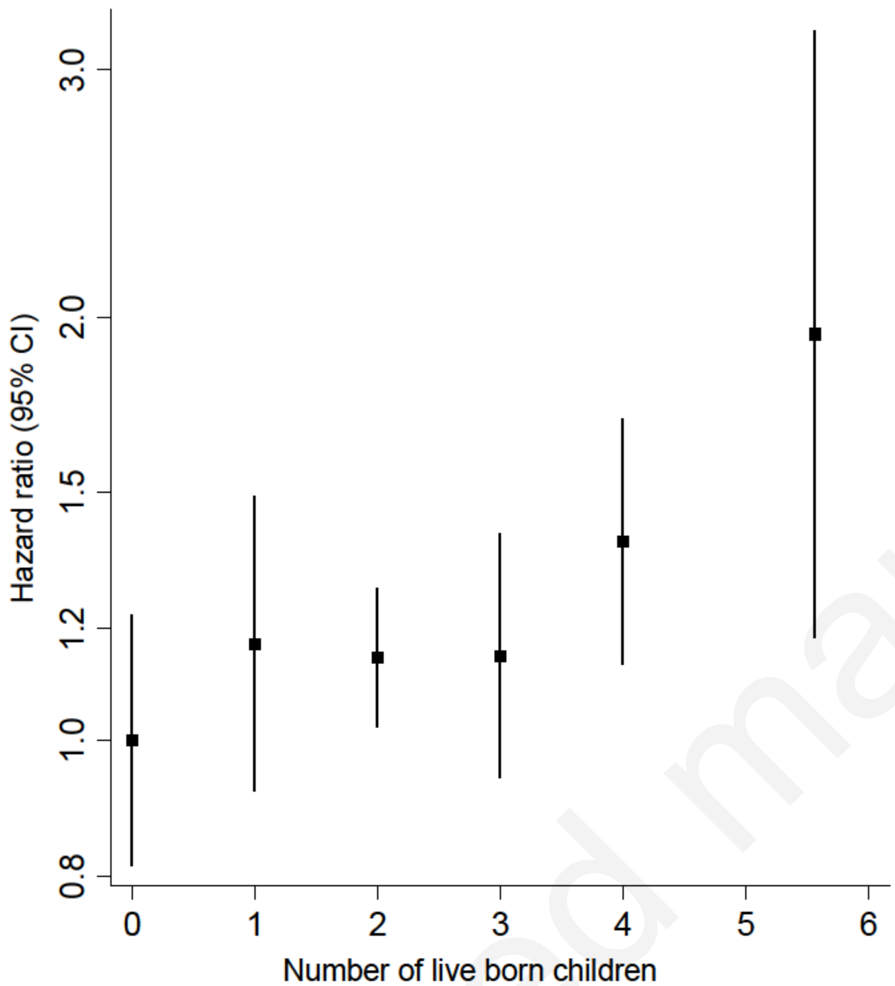
Table 4: Hazard ratios (95% confidence intervals) for incident coronary heart disease by parity and history of breastfeeding in subgroups

	Age			Parity	
	<55 years	≥55 years		1-2 children	≥3 children
Parous (yes vs. no)	1.14 (0.83, 1.55)	1.20 (0.99, 1.46)		-	-
Number of children					
None	1.00 (0.77, 1.31)	1.00 (0.78, 1.28)		-	-
1 child	1.37 (0.79, 2.38)	1.07 (0.63, 1.80)		-	-
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)		-	-
Ever breastfed (yes vs. no)	0.71 (0.52, 0.95)	0.77 (0.54, 1.08)		0.69 (0.51, 0.94)	0.76 (0.54, 1.08)
Lifetime duration of breastfeeding					
Never breastfed	1.00 (0.69, 1.45)	1.00 (0.72, 1.38)		1.00 (0.71, 1.41)	1.00 (0.71, 1.41)
>0 to <3 months	0.74 (0.49, 1.11)	0.67 (0.41, 1.10)		0.67 (0.45, 0.99)	0.87 (0.53, 1.41)
≥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					
Never breastfed	1.00 (0.77, 1.31)	1.00 (0.70, 1.42)		1.00 (0.72, 1.39)	1.00 (0.72, 1.39)
>0 to <1 months	0.79 (0.54, 1.14)	0.71 (0.44, 1.15)		0.65 (0.42, 1.01)	0.96 (0.66, 1.40)
≥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)

Analyses of parity are conducted in all women. Analyses of breastfeeding are conducted in parous women only.

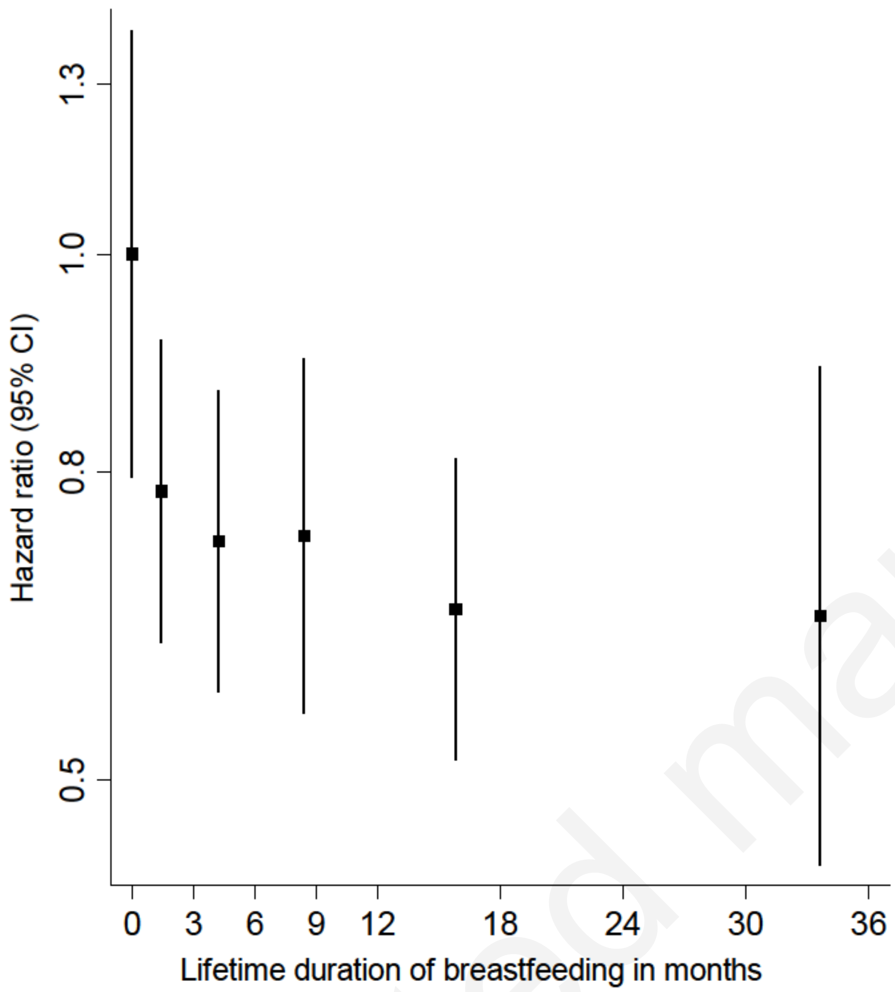
Models are adjusted for age at study entry, centre, level of attained education, smoking status, , and number of livebirths (for breastfeeding history only), high blood pressure, HDL cholesterol, total cholesterol, history of diabetes mellitus, and BMI.

Figure 1



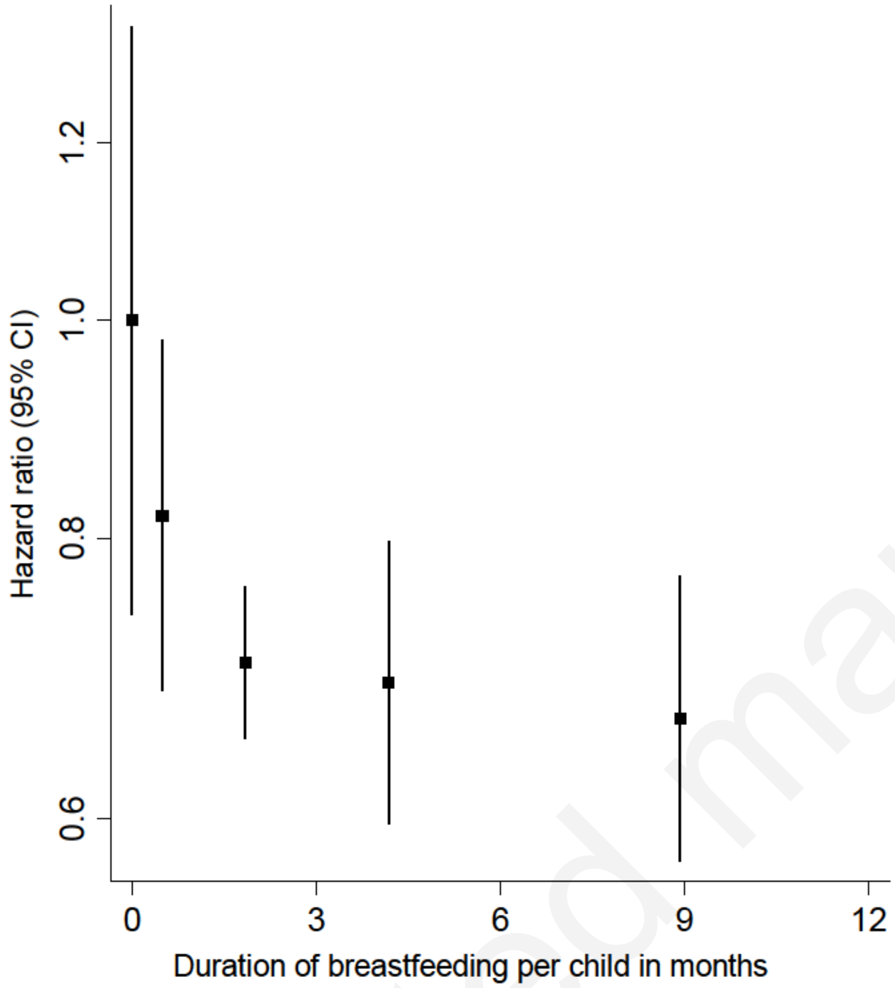
Hazard ratio (95% CI)
3.0
2.0
1.5
1.2
1.0
0.8
0
1
2
3
4
5
6
Number of live born children

Figure 2



1.3
1.0
0.8
0.5
Hazard ratio (95% CI)
0
3
6
9
12
18
24
30
36
Lifetime duration of breastfeeding in months

Figure 3


Hazard ratio (95% CI)
0.6
0.8
1.0
1.2
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: Numbers of participants contributing to the primary analyses

	N total (events)	N subcohort (events)
Overall	14,890 (5,138)	9,985 (206)
Parous vs. not	12,319 (3,336)	9,170 (187)
Number of children	9,701 (2,685)	7,016 (170)
Breastfeeding, ever vs. never	8,044 (2,404)	5,789 (149)
Breastfeeding duration	8,012 (2,392)	5,766 (146)

Supplementary Table 3: 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	14,138	12,319
Parous (yes vs. no)	1.20 (1.03, 1.41)	1.19 (1.01, 1.41)	1.19 (1.01, 1.41)
I^2 for heterogeneity (95% CI)	25% (0%, 63%)	26% (0%, 64%)	0% (0%, 65%)
Number of children			
None	1.00 (0.85, 1.18)	1.00 (0.82, 1.22)	1.00 (0.82, 1.23)
1 child	1.23 (1.06, 1.42)	1.14 (0.99, 1.31)	1.17 (0.92, 1.49)
2 children	1.11 (1.00, 1.23)	1.11 (1.09, 1.13)	1.15 (1.02, 1.28)
3 children	1.14 (0.98, 1.32)	1.11 (0.98, 1.25)	1.15 (0.94, 1.40)
4 children	1.47 (1.24, 1.75)	1.45 (1.24, 1.70)	1.39 (1.14, 1.70)
5 or more children	1.92 (1.34, 2.76)	2.05 (1.30, 3.24)	1.95 (1.19, 3.20)
History of breastfeeding			
N	10,049	9,435	8,044
Ever breastfed (yes vs. no)	0.66 (0.57, 0.78)	0.64 (0.52, 0.78)	0.71 (0.52, 0.98)
I^2 for heterogeneity	0% (0%, 68%)	20% (0%, 62%)	58% (2%, 82%)
Lifetime duration of breastfeeding			
Never breastfed	1.00 (0.86, 1.16)	1.00 (0.83, 1.21)	1.00 (0.75, 1.34)
>0 to <3 months	0.71 (0.59, 0.84)	0.64 (0.53, 0.77)	0.73 (0.60, 0.89)
≥3 to <6 months	0.67 (0.56, 0.81)	0.62 (0.52, 0.74)	0.68 (0.56, 0.83)
≥6 to <12 months	0.66 (0.59, 0.75)	0.62 (0.55, 0.69)	0.69 (0.55, 0.87)
≥12 to <23 months	0.62 (0.58, 0.67)	0.54 (0.49, 0.59)	0.63 (0.51, 0.76)
≥23 months	0.56 (0.46, 0.70)	0.51 (0.41, 0.65)	0.62 (0.45, 0.86)
Duration of breastfeeding per child			
Never breastfed	1.00 (0.93, 1.08)	1.00 (0.84, 1.19)	1.00 (0.73, 1.37)
>0 to <1 months	0.79 (0.68, 0.93)	0.68 (0.58, 0.81)	0.77 (0.63, 0.94)
≥1 to <3 months	0.69 (0.64, 0.75)	0.64 (0.57, 0.72)	0.69 (0.61, 0.78)
≥3 to <6 months	0.59 (0.49, 0.71)	0.59 (0.52, 0.67)	0.67 (0.57, 0.77)
≥6 months	0.56 (0.47, 0.67)	0.58 (0.50, 0.67)	0.67 (0.56, 0.80)

27 individuals with no follow-up were excluded from the analyses. 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 4: 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	10,420	10,420	10,420
Parous (yes vs. no)	1.25 (1.06, 1.48)	1.23 (1.04, 1.45)	1.19 (1.00, 1.41)
I^2 for heterogeneity (95% CI)	17% (0%, 59%)	12% (0%, 54%)	0% (0%, 65%)
Number of children			
None	1.00 (0.81, 1.23)	1.00 (0.81, 1.23)	1.00 (0.81, 1.24)
1 child	1.23 (1.03, 1.46)	1.18 (0.98, 1.43)	1.20 (0.94, 1.53)
2 children	1.19 (1.10, 1.28)	1.16 (1.08, 1.24)	1.13 (1.11, 1.16)
3 children	1.20 (1.04, 1.39)	1.19 (1.00, 1.40)	1.14 (0.90, 1.44)
4 children	1.44 (1.19, 1.75)	1.43 (1.17, 1.73)	1.37 (1.09, 1.73)
5 or more children	2.19 (1.41, 3.41)	2.03 (1.27, 3.24)	1.95 (1.20, 3.18)
History of breastfeeding			
N	7,090	7,090	7,090
Ever breastfed (yes vs. no)	0.72 (0.59, 0.89)	0.70 (0.56, 0.88)	0.73 (0.52, 1.02)
I^2 for heterogeneity	24% (0%, 66%)	24% (0%, 67%)	60% (9%, 83%)
Lifetime duration of breastfeeding			
Never breastfed	1.00 (0.81, 1.23)	1.00 (0.81, 1.23)	1.00 (0.74, 1.36)
>0 to <3 months	0.69 (0.57, 0.84)	0.69 (0.56, 0.84)	0.73 (0.59, 0.91)
≥3 to <6 months	0.72 (0.55, 0.94)	0.74 (0.60, 0.91)	0.69 (0.56, 0.86)
≥6 to <12 months	0.75 (0.62, 0.91)	0.71 (0.58, 0.88)	0.70 (0.55, 0.90)
≥12 to <23 months	0.67 (0.58, 0.78)	0.65 (0.54, 0.78)	0.65 (0.52, 0.81)
≥23 months	0.67 (0.51, 0.89)	0.61 (0.47, 0.81)	0.63 (0.46, 0.88)
Duration of breastfeeding per child			
Never breastfed	1.00 (0.85, 1.18)	1.00 (0.82, 1.21)	1.00 (0.71, 1.40)
>0 to <1 months	0.79 (0.67, 0.94)	0.73 (0.61, 0.88)	0.79 (0.64, 0.96)
≥1 to <3 months	0.73 (0.63, 0.85)	0.72 (0.62, 0.84)	0.70 (0.62, 0.80)
≥3 to <6 months	0.68 (0.55, 0.84)	0.66 (0.55, 0.79)	0.68 (0.58, 0.81)
≥6 months	0.65 (0.51, 0.83)	0.68 (0.54, 0.86)	0.69 (0.57, 0.83)

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.