ORIGINAL RESEARCH

Breastfeeding and Cardiovascular Disease Hospitalization and Mortality in Parous Women: Evidence From a Large Australian Cohort Study

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***Background*—**Few studies have investigated the longitudinal association between breastfeeding and maternal cardiovascular disease (CVD) outcomes. This study examined the association between breastfeeding and CVD hospitalization and mortality in a large Australian cohort.

***Methods and Results*—**Baseline questionnaire data (2006–2009) from a sample of 100 864 parous women aged ≥45 years from New South Wales, Australia, were linked to hospitalization and death data until June 2014 and December 2013, respectively. Analysis was restricted to women without self-reported medically diagnosed CVD at baseline or without past CVD hospitalization 6 years before study entry. Never versus ever breastfeeding and average breastfeeding duration per child, derived from self-reported lifetime breastfeeding duration and number of children, and categorized as never breastfed, <6, >6 to 12, or >12 months/child, were assessed. Cox proportional hazards models were used to explore the association between breastfeeding and CVD outcomes. Covariates included sociodemographic characteristics, lifestyle risk factors, and medical and reproductive history. There were 3428 (3.4%) first CVD-related hospital admissions and 418 (0.4%) deaths during a mean follow-up time of 6.1 years for CVD hospitalization and 5.7 years for CVD mortality. Ever breastfeeding was associated with lower risk of CVD hospitalization (adjusted hazard ratio [95% CI]: 0.86 [0.78, 0.96]; *P*=0.005) and CVD mortality (adjusted hazard ratio [95% CI]: 0.66 [0.49, 0.89]; *P*=0.006) compared with never breastfeeding. Breastfeeding ≤12 months/child was significantly associated with lower risk of CVD hospitalization.

***Conclusions*—**Breastfeeding is associated with lower maternal risk of CVD hospitalization and mortality in middle-aged and older Australian women. Breastfeeding may offer long-term maternal cardiovascular health benefits. **(*J Am Heart Assoc*. 2019;8: e011056. DOI: 10.1161/JAHA.118.011056.)**

Key Words: breastfeeding • cardiovascular diseases • lactation • maternal health • prospective studies

Cardiovascular disease (CVD) is the leading cause of death for women worldwide.[1] Preventing CVD through modifying known lifestyle risk factors, such as being overweight and an unhealthy diet, is a key public health priority. Whereas changes in established lifestyle risk factors can lead to substantial reduction in risk of developing CVD, prevention approaches should also incorporate emerging knowledge about novel risk factors of CVD, including behaviors that are specific to women. There has been an urgent, global call to conduct more sex-specific research to better inform public health strategies.[2] Sex differences exist in the epidemiology, diagnosis, risk profile, and treatment of CVD. Compared with men, women generally develop CVD at a later age, present with different symptoms and risk factors, are underdiagnosed, and respond differently to various treatments.[2]

Breastfeeding has emerged in recent years as a lifestyle risk factor that may be associated with CVD; however, the evidence is limited by the small number of observational studies, particularly longitudinal studies.[3] Prevalence of early initiation of breastfeeding within 1 hour of birth is ≈30% in high-income countries,[4] and around 79% of newborns in high-income countries are ever breastfed.[5] Globally, prevalence of exclusive

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Accompanying Tables S1 through S5 are available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.118.011056

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Clinical Perspective

What Is New?

- Findings from this study add to the growing evidence base for the long-term benefits of breastfeeding for maternal cardiovascular health.
- Among parous women aged ≥45 years, ever breastfeeding and average breastfeeding duration per child up to 12 months were associated with substantially lower risk of developing and dying from cardiovascular disease.
- Findings were mostly consistent among women from different socioeconomic backgrounds and with different lifestyle risk.

What Are the Clinical Implications?

- This study provides evidence that breastfeeding is associated with long-term benefits for maternal cardiovascular health, in addition to its known benefits for infants and mothers.
- Breastfeeding may be promoted as an additional strategy by which parous women can reduce their risk of developing and dying from cardiovascular disease.

breastfeeding for infants aged <6 months is ≈43%.[5] During pregnancy, profound metabolic changes occur in a mother's body to support fetal growth and prepare for lactation.[6] It has been hypothesized that breastfeeding, which increases metabolic expenditure by an estimated 480 kcal/day, may enable a more rapid reversal of metabolic changes in pregnancy, including improved insulin sensitivity, lipid metabolism, and greater mobilization of accumulated fat stores, thereby "resetting" maternal metabolism after pregnancy and potentially reducing maternal risk of cardiometabolic disease.[7] Multiple studies have reported the short-term benefits of breastfeeding, including lipid homeostasis,[8,9] glucose homeostasis, and insulin sensitivity.[10,11] However, whether these benefits can contribute to long-term maternal health is unclear.

Emerging evidence suggests that breastfeeding may reduce the risk of developing type 2 diabetes mellitus,[12] hypertension,[13] and metabolic syndrome[14] later in life. Although a number of studies have examined the associations between breastfeeding and CVD outcomes, such as incidence of CVD[3,15–18] or death from CVD,[3,19–22] findings from these studies are inconclusive.

An important issue to consider in interpreting these observational studies is confounding.[3] Mothers who have breastfed tend to be older, from a higher socioeconomic background, have achieved higher levels of education, and participate in health-promoting behaviors in comparison with non-breastfeeding mothers.[23,24] Maternal characteristics, such as living in lower socioeconomic areas, have been strongly associated with not breastfeeding over subsequent births,[25] but residual confounding attributed to unmeasured factors may remain an issue. These socioeconomic factors and health-promoting behaviors may also potentially bias the association between breastfeeding and CVD outcomes, and although previous studies have adjusted for their confounding effects,[14–17,20,21] they did not investigate potential effect modification by socioeconomic status and overall lifestyle.

The aims of this article were to examine the association between breastfeeding and CVD hospitalization and mortality in a large cohort of middle-aged and older parous women. Findings from this study can help build the evidence base for breastfeeding as an additional strategy to prevent CVD.

Methods

The authors declare that all supporting data are available within the article (and its online supplementary files).

Study Population

The Sax Institute's 45 and Up Study is a large-scale, prospective cohort study of 123 815 men and 143 073 women aged ≥45 years residing in the state of New South Wales (NSW), Australia. From 2006 to 2009, potential participants were randomly sampled from the Department of Human Services enrollment database, the national health insurance provider, and were invited to take part in the study. Individuals joined the study by completing a postal questionnaire and providing informed consent for follow-up, which included linkage of questionnaire data to population health databases. The study methods have been described in detail elsewhere.[26]

We included all women who completed a baseline questionnaire. Women who reported that they had ever been diagnosed with or recently treated for CVD (self-reported heart disease, stroke, or blood clot: n=21 797) or with a hospital admission in the 6 years preceding study entry (with a CVD diagnosis code in any diagnostic field or a CVD-related procedure code in any procedure code field[27]; n=13 323) were excluded from analysis. We further excluded those who were nulliparous (never given birth; n=15 654) or with unknown parity (n=918) at baseline and parous women with unknown breastfeeding duration (n=2187). The final study sample included 100 864 women with reported breastfeeding duration. A participant flow chart for this study is provided in Figure.

The 45 and Up Study received ethics approval from the University of NSW Human Research Ethics Committee. Approval to use data from the 45 and Up Study for this article was obtained from the NSW Population and Health Services Ethics Committee.

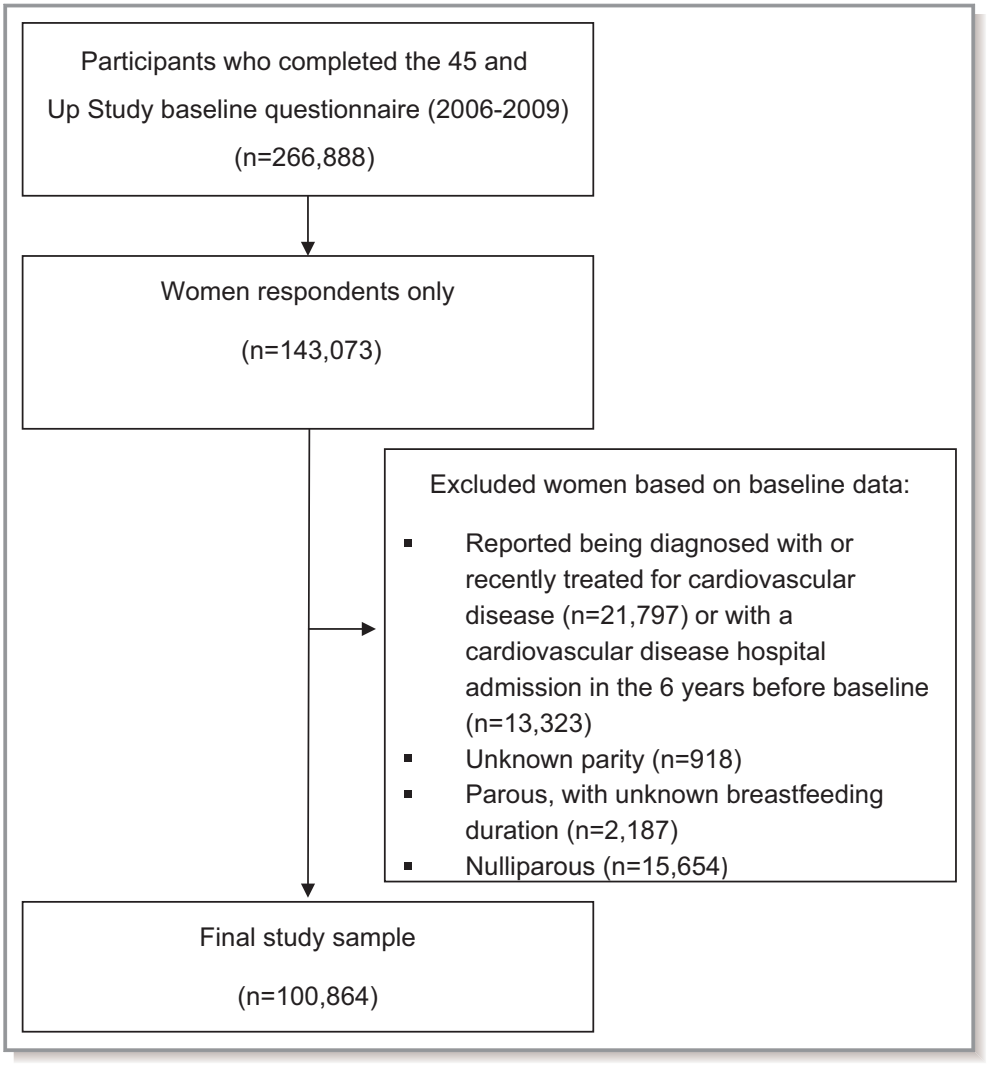

Figure. Participant flow chart.

Measurement

Exposure

The baseline questionnaire for women (available at http://www.saxinstitute.org.au/our-work/45-up-study/questionnaires/) included self-reported information on sociodemographic and lifestyle factors, height and body weight, and medical and reproductive history. Women were asked to report the number of children they had given birth to and also the cumulative amount of time spent breastfeeding across all pregnancies, based on the question: "For how many months, in total, have you breastfed?" The average breastfeeding duration per child was derived from answers to these questions and categorized as never breastfed, >0 to 6 (<6) months, >6 to 12 months, or >12 months. Breastfeeding was also explored as a binary variable in terms of whether a woman had ever versus never breastfed (also referred to as breastfeeding history).

Outcomes

Baseline questionnaire data were linked to hospital data from the NSW Admitted Patient Data Collection (APDC; until June 2014), mortality data from the NSW Registry of Births, Deaths, and Marriages (until June 2014), and data on causes of death from the Cause of Death Unit Record File (until December 2013) by the Centre for Health Record Linkage (CHeReL, NSW, Australia) using probabilistic record linkage methods and a commercially available software (ChoiceMaker; ChoiceMaker Technologies Inc., New York, NY). The probabilistic data linkage conducted by CHeReL has been reported to be highly accurate with false-positive and -negative rates below 0.4% (http://www.cherel.org.au/quality-assurance). A recent study has also shown that the accuracy of probabilistic linkage is unlikely to vary by socioeconomic status in older adults.[28]

The APDC is a complete census of all public and private hospital admissions in NSW that includes details of

admissions, such as dates of admission and discharge, and records all related diagnoses for each admission. These are coded using the World Health Organization *International Classification of Diseases, Tenth Revision–Australian Modification* (*ICD-10-AM*) system. The NSW Registrar of Births, Deaths, and Marriages captures all deaths in NSW with causes subsequently coded using the *ICD-10-AM* classification. In both data sources, the first CVD hospitalization or death since baseline was based on a primary diagnosis of CVD of either ischemic heart disease (*ICD-10-AM* codes: I20–I25) or cerebrovascular disease (*ICD-10-AM* codes: I61–I67, I69).[29,30]

Covariates

Multivariable analyses were adjusted for a range of sociodemographic and lifestyle factors, and medical and reproductive history based on self-reported responses in the baseline survey. Sociodemographic variables included age (45–54, 55–64, or ≥65 years), country of birth (Australia/other), highest educational qualification (≤10 years of schooling, high school/trade apprenticeship/certificate/diploma, or university degree/higher), marital status (married/living with a partner or single/widowed/divorced/separated) and area-level socioeconomic status (population-level quintiles based on the Socio-Economic Indexes For Area—Index of Relative Socio-Economic Disadvantage[31]). Lifestyle factors were based on responses at baseline and used as a marker of health-related behaviors. These included body mass index (kg/m^2; calculated as weight divided by height squared), smoking status (never, past, or current), alcohol intake (≤14 or >14 drinks/week[32]), physical activity (assessed using validated questions from the Active Australia Survey[33]; categorized as <150, 150–299, or ≥300 minutes per week), multivitamin use (for most of the last 4 weeks; yes/no), omega 3 or fish oil use (yes/no), use of aspirin (yes/no), and oral contraceptive use (ever/never). Reproductive history was based on number of children given birth to (1, 2, 3, or ≥4), mother's age for first child, and mother's age for last child. Medical history was assessed using family history of CVD (yes/no), family history of hypertension (yes/no), family history of diabetes mellitus (yes/no), self-reported hypertension/recent treatment for hypertension (yes/no), and self-reported diabetes mellitus/recent treatment for diabetes mellitus (yes/no).

Statistical Analysis

Baseline participant characteristics by breastfeeding history and duration are presented as means (SD) for continuous variables and as percentages for categorical variables. Differences in baseline characteristics were assessed using chi-square tests for categorical variables, Student *t* tests for continuous variables with binary breastfeeding categories, and F statistics from ANOVA for continuous variables with multiple lactation categories. Crude and adjusted hazard ratios (HRs) with 95% CIs were estimated for associations between either breastfeeding history or average breastfeeding duration per child and CVD outcomes by using Cox proportional hazards models. Separate models were used for CVD hospitalizations and CVD deaths with a time scale in years. In the analyses of incident CVD hospitalization, CVD death before hospitalization was not treated as a competing outcome; instead, participants were censored at death irrespective of cause of death. Eligible women contributed person-years from date of recruitment until admission date, date of death, or end of follow-up (June 18, 2014), whichever was the earliest; end of follow-up was December 31, 2013 for analyses of CVD mortality. Proportionality assumptions were verified based on the methods of Lin et al.[34] The "never breastfed" category was used as the reference category. Left-truncated data were used to adjust for different CVD risk exposure times for each woman before baseline entry into the study.[35] This approach helped to account for differences in the time that some women may have been diagnosed with CVD in the months or years preceding enrollment in the study. For each of the CVD outcomes, 4 sequential models were used: unadjusted models (model 1), models adjusted for parity and sociodemographic characteristics (number of children, age, country of birth, educational level, marital status, and area-level socioeconomic status; model 2), models further adjusted for lifestyle factors (body mass index, smoking status, alcohol intake, and physical activity; model 3), and models further adjusted for medical and reproductive covariates (multivitamin use, omega 3 or fish oil use, use of aspirin, oral contraceptive use, mother's age for first child, mother's age for last child, family history of CVD, family history of hypertension, family history of diabetes mellitus, self-reported hypertension/recent treatment for hypertension, and self-reported diabetes mellitus/recent treatment for diabetes mellitus; model 4). To account for potential interaction by socioeconomic status and lifestyle risk, multiplicative interaction terms were tested in the model, and analyses were stratified by educational attainment and a healthy lifestyle index, used as a marker for CVD lifestyle risk factors. The healthy lifestyle index has been adapted from a lifestyle risk index previously developed using the 45 and Up Study cohort[36] and the Healthy Heart Score developed by the Harvard School of Public Health.[37] It is based on the following 6 lifestyle risk factors scored individually as healthy (score=1) or not healthy (score=0): body mass index (<25 kg/m^2=1, ≥25 kg/m^2=0), physical activity level (<150 min/week=1; ≥150 min/week=0), smoking status (past/current smoker=0; never smoker=1), alcohol intake (≤14 drinks/week=1; >14 drinks/week=0), sleep (>7 to <9 h/day=1; <7 h/day or >9 h/day=0), and fruit and vegetable intake (<2 serves of fruit/day or <3 serves of fruit/day=0; ≥2 serves of fruit/day,

and ≥3 serves of vegetables/day=1). For the stratified analyses, the healthy lifestyle index was dichotomized as either healthy (sum of scores=5–6) or not healthy (sum of scores=0–4). Interactions were considered significant if $P<0.05$. Statistical significance was defined as $P<0.05$ and analyses were conducted using SAS software (version 9.3; SAS Institute Inc., Cary, NC).

Results

Participant Characteristics

Table 1 shows baseline sociodemographic characteristics and parity of the 100 864 parous women included in our study. Mean age of the sample was 60.2 (SD, 10.2) years. More than three-quarters (76.7%) of women were born in Australia, more than one-third (40%) had ≤10 years of education, three-quarters (75.4%) were married, and nearly two-thirds (61.3%) belonged to the 3 lowest socioeconomic population-level quintiles. Of all parous women, 87.6% had a history of breastfeeding. On average, women had 2.7 (SD, 1.2) children and breastfed for 5.4 (SD, 5.4) months per child. Compared with women who never breastfed, women who ever breastfed were more likely to be younger at baseline, have more children, a higher level of education, be married/living with a partner, and live in an area with higher socioeconomic quintile. Women that had ever breastfed were also less likely to be obese, smoke, and were more likely to engage in higher levels of physical activity and consume omega 3 or fish oil. The 45 to 54 years age group was more likely to have a higher breastfeeding duration per child than the older age groups. Those who breastfed >12 months, on average, per child were more likely to have a university degree. The lifestyle, medical, and reproductive characteristics of women at baseline are presented in Table S1.

Breastfeeding and CVD Hospitalization/Mortality

Table S2 presents HR and 95% CI for the incidence of CVD hospitalization and mortality by breastfeeding history. During a mean follow-up of 6.1 years for CVD hospitalization, and 5.7 years for CVD mortality, there were 3428 (3.4%) first CVD-related admissions and 418 (0.4%) deaths. Compared with parous women who never breastfed, women who ever breastfed had lower risk of CVD hospitalization (model 4, HR [95% CI]: 0.86 [0.78, 0.96] $P=0.005$) and mortality from CVD (model 4, HR [95% CI]: 0.66 [0.49–0.88] $P=0.006$), in both unadjusted and adjusted models ($P<0.01$).

Table 2 shows HR and 95% CI for the incidence of CVD hospitalization and mortality by average breastfeeding duration per child. In both unadjusted and adjusted models, women who breastfed, on average, for >0 to 6 or >6 to 12 months per child had lower risk of CVD hospitalization (model 4, <6 months, HR [95% CI]: 0.86 (0.78, 0.96); >6–12 months: 0.85 [0.75–0.97]) and mortality (model 4, <6 months: 0.69 (0.51, 0.94); >6–12 months: 0.59 [0.41–0.84]), compared with women who never breastfed.

Stratified Analyses

Overall, none of the tests for interaction were statistically significant (all $P>0.05$). In the stratified analysis by education, the association between breastfeeding and CVD outcomes were similar across education strata (Table S3), whereas, in the stratified analysis by healthy lifestyle index (Table S4), the association between breastfeeding and CVD hospitalization was nonsignificant in those with lower lifestyle scores ("not healthy") while protective in those with higher lifestyle scores ("healthy"). However, the association with CVD mortality was similarly protective in those with low and high lifestyle scores.

Discussion

In this large cohort of parous women aged ≥45 years, ever breastfeeding and average breastfeeding duration up to 12 months per child were associated with lower risk of incident CVD hospitalization and CVD mortality. Following adjustment for sociodemographic, lifestyle-related, and reproductive variables, ever breastfeeding was associated with a 14% lower risk of CVD hospitalization and a 34% lower risk of mortality from CVD compared with never breastfeeding. Average breastfeeding duration per child up to 12 months was significantly associated with a ≈15% lower risk of incident CVD and a ≈40% lower risk of CVD mortality compared with never breastfeeding. Findings were mostly consistent among women from different socioeconomic backgrounds and with different lifestyle risk.

This longitudinal study provides further evidence that among childbearing women, breastfeeding may offer long-term cardiovascular health benefits. The protective nature of the association between breastfeeding history and CVD outcomes is generally consistent with findings from the few previous studies that have examined similar associations among parous women from large cohorts (Table S5).[15,16,20] Differences between studies in magnitude of the associations could be attributed to variation in follow-up periods, types of CVD and outcomes examined, covariate adjustment, and cohort characteristics. Compared with previous studies, this study was novel in that it examined associations in an Australian setting, included more sociodemographic and lifestyle covariates, and stratified analyses by socioeconomic status and a healthy lifestyle index.

Whereas previous studies have typically expressed breastfeeding duration in terms of lifetime breastfeeding duration, we

Table 1. Baseline Sociodemographic Characteristics and Parity of Parous Women (n=100 864) in the 45 and Up Study by Breastfeeding History and Average Breastfeeding Duration Per Child*

Variables	Breastfeeding History			Average Breastfeeding Duration Per Child†			
	Never Breastfed	Ever Breastfed	*P* Value‡	>0 to 6 Months	>6 to 12 Months	>12 Months	*P* Value§
No. of subjects, %	12 517 (12.4)	88 347 (87.6)		56 049 (63.4)	24 549 (27.8)	7749 (8.8)	
Age group, %							
45 to 54 y	26.5	37.7	<0.0001	29.5	47.3	66.9	<0.0001
55 to 64 y	42.7	34.0		36.5	29.7	28.9	
≥65 y	30.8	28.3		34.0	23.0	4.2	
Mean (SD) age for first child, y	24.3 (5.15)	25.1 (4.89)	<0.0001	24.3 (4.66)	26.0 (4.74)	28.1 (5.29)	<0.0001
Mean (SD) age for last child, y	28.9 (5.24)	30.6 (4.96)	<0.0001	29.8 (4.93)	31.6 (4.64)	33.4 (4.7)	<0.0001
Parity							
Mean (SD) parity (no. of births)	2.4 (1.13)	2.7 (1.18)	<0.0001	2.8 (1.2)	2.8 (1.15)	2.6 (1.13)	<0.0001
1 child, %	19.0	8.7	<0.0001	16.7	9.5	3.9	<0.0001
2 children, %	43.7	39.8		47.7	46.4	41.5	
3 children, %	23.8	31.2		24.3	29.8	35.0	
≥4 children, %	13.5	20.3		11.3	14.3	19.6	
Country of birth, %							
Australia	72.0	77.3	<0.0001	74.0	76.1	79.7	<0.0001
Other	28.0	22.7		26.0	23.9	20.3	
Highest education, %‖							
University and higher	11.1	23.8	<0.0001	16.3	21.3	27.0	<0.0001
High school/trade apprenticeship/ certificate/diploma	33.3	38.4		37.1	37.9	39.4	
≤10 y	55.6	37.8		46.6	40.8	33.6	
Marital status, %¶							
Married/living with a partner	72.7	75.8	<0.0001	74.6	75.0	76.7	<0.0001
Single/divorced/separated/widowed	27.3	24.2		25.4	25.0	23.3	
Socioeconomic status (SEIFA-IRSD), %#							
Quintile 1 (most disadvantaged)	23.2	19.7	<0.0001	21.1	19.8	18.2	<0.0001
Quintile 2	20.3	19.5		20.1	18.8	19.0	
Quintile 3	22.5	21.4		21.8	21.2	20.7	
Quintile 4	19.0	19.6		19.7	19.6	20.0	
Quintile 5 (least disadvantaged)	15.0	19.8		17.3	20.5	22.0	

SEIFA-IRSD indicates Socio-Economic Indexes For Area—Index of Relative Socio-Economic Disadvantage.
*Data are presented as means (SD) or percentages.
†Average breastfeeding duration per child was calculated as self-reported lifetime breastfeeding duration divided by the reported number of children.
‡Based on chi-square test for categorical variables and Student *t* test for continuous variables.
§Based on chi-square test for categorical variables and F statistics from ANOVA for continuous variables.
‖1325 missing.
¶268 missing.
#66 missing.

chose to present breastfeeding duration as the average duration per child to help standardize findings, better account for parity, and facilitate interpretation of findings. We modeled average breastfeeding duration as a categorical variable because of the nonlinearity of the distribution and chose clinically relevant cut points based on breastfeeding guidelines. This study showed that an average breastfeeding duration per child up to 12 months was associated with lower risk of incident CVD hospitalization and mortality compared with never breastfeeding. To our knowledge, there have been only 2 previous studies that have examined the

Table 2. Hazard Ratios and 95% CIs for the Incidence of CVD Hospitalization and Mortality in Parous Women by Average Breastfeeding Duration Per Child*

Average Breastfeeding Duration Per Child*	No. of People, n	Person-Years From Baseline	No. of Incident Cases/Deaths	Model 1† (95% CI)	Model 2‡ (95% CI)	Model 3§ (95% CI)	Model 4‖ (95% CI)
CVD hospitalization							
Never breastfed	12 517	76 164	527	Reference	Reference	Reference	Reference
>0 to 6 months	56 049	342 296	2076	0.82 (0.74, 0.91)	0.84 (0.76, 0.93)	0.86 (0.77, 0.95)	0.86 (0.78, 0.96)
>6 to 12 months	24 549	150 489	708	0.77 (0.68, 0.87)	0.79 (0.70, 0.89)	0.84 (0.74, 0.96)	0.85 (0.75, 0.97)
>12 months	7749	47 911	117	0.80 (0.65, 0.99)	0.84 (0.68, 1.04)	0.89 (0.71, 1.12)	0.89 (0.71, 1.12)
CVD mortality							
Never breastfed	12 517	71 730	66	Reference	Reference	Reference	Reference
>0 to 6 months	56 049	321 326	247	0.69 (0.53, 0.92)	0.74 (0.56, 0.98)	0.69 (0.51, 0.94)	0.69 (0.51, 0.94)
>6 to 12 months	25 549	140 605	96	0.53 (0.38, 0.73)	0.56 (0.40, 0.79)	0.59 (0.41, 0.85)	0.59 (0.41, 0.84)
≥12 months	7749	44 453	9	0.76 (0.36, 1.61)	0.80 (0.38, 1.69)	0.70 (0.30, 1.65)	0.67 (0.28, 1.57)

CVD indicates cardiovascular disease.
*Average breastfeeding duration per child was calculated as self-reported lifetime breastfeeding duration divided by the reported number of children.
†Model 1 was unadjusted.
‡Model 2 was adjusted for parity (number of children) and sociodemographic characteristics (age, country of birth, educational level, marital status, area-level socioeconomic status).
§Model 3 was further adjusted for lifestyle factors: body mass index, smoking status, alcohol intake, physical activity.
‖Model 4 was additionally adjusted for medical and reproductive covariates: multivitamin use, omega 3 or fish oil use, use of aspirin, oral contraceptive use, mother's age for first child, mother's age for last child, family history of CVD, family history of hypertension, family history of diabetes mellitus, self-reported hypertension/recent treatment for hypertension, and self-reported diabetes mellitus/recent treatment for diabetes mellitus.

association between average breastfeeding duration per child and CVD outcomes (Table S5)[15,16] and both have reported inverse associations. In the case-cohort study nested within EPIC (European Prospective Investigation into Cancer and Nutrition), an average breastfeeding duration ≥6 months, the highest breastfeeding duration considered, was associated with a 33% lower risk of incident ischemic heart disease.[15] In the China Kadoorie Biobank study, each additional 6 months of breastfeeding per child was associated with a 4% and 3% lower risk of incident ischemic heart disease and stroke, respectively.[16] However, different breastfeeding measures and study settings may limit the comparability of findings across studies.

In the present study, there was no clear evidence for a dose-response relationship between average lactation duration per child and CVD outcomes. In agreement with findings from our study, there was no solid evidence for a threshold or dose-response effect in the few studies that have examined average breastfeeding duration per child.[15,16] Whereas inconsistent associations have been shown between lifetime breastfeeding duration and CVD mortality, findings from some studies suggest a potential threshold effect[18] or a U-shaped association.[21] However, further longitudinal research is needed.

Strengths and Limitations

Strengths of this study include a large cohort size and prospective follow-up, which enabled us to examine the association between breastfeeding and long-term cardiovascular outcomes. Compared with previous studies, this study adjusted for a comprehensive range of covariates including relevant sociodemographic, lifestyle and reproductive factors, and sensitivity analyses stratified by socioeconomic status and a healthy lifestyle index were conducted.

Several limitations should be mentioned. As for all observational studies, residual confounding may be an issue. Mothers that have breastfed may generally lead healthier lifestyles and come from higher socioeconomic backgrounds[23,24] that could have contributed to the observed associations. However, adjusting for socioeconomic factors and lifestyle-related covariates did not alter the findings of this study, and associations appeared mostly consistent across different education and lifestyle categories. Some of the findings should nonetheless be interpreted with caution because of small cell-sample sizes in some of the stratified analyses, and particularly in relation to CVD mortality. Our results may also be subject to reverse causation. From the data collected, we could not assess whether women had pre-existing metabolic conditions, such as obesity and type 1 diabetes mellitus, or conditions during pregnancy, such as pre-eclampsia and gestational diabetes mellitus, which could have unfavorably influenced breastfeeding practice.[38–40] Breastfeeding duration was assessed retrospectively many years later and may be prone to recall bias, which can lead to under- or over-reporting of breastfeeding duration.[41] However,

maternal recall of lactation has been shown to be a valid and reliable measure,[41] even many years following weaning.[42] Finally, it was also not possible to assess the exclusivity of breastfeeding (ie, whether other complementary foods were being offered to breastfed children), which is a measure of breastfeeding intensity.

Implications and Conclusions

With CVD being the leading cause of death in women, it is important to explore a range of strategies by which CVD can be prevented, involving established as well as emerging lifestyle behaviors. This study provides evidence that ever breastfeeding and average breastfeeding duration up to 12 months per child were associated with substantially lower risk of CVD hospitalization and mortality. Although further longitudinal studies are needed to achieve greater consensus, findings from this study add to the growing evidence base for the long-term benefits of breastfeeding for maternal cardiovascular health, promoting added benefits of breastfeeding beyond known benefits for infants and short-term benefits for mothers, and support breastfeeding as an important strategy by which parous women can reduce their risk of developing and dying from CVD.

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Disclosures

None.

References

1. World Health Organization. Women's Health. Fact sheet No. 334. Geneva, Switzerland: WHO; 2013.
2. Maas AH, van der Schouw YT, Regitz-Zagrosek V, Swahn E, Appelman YE, Pasterkamp G, Ten Cate H, Nilsson PM, Huisman MV, Stam HC, Eizema K, Stramba-Badiale M. Red alert form women's heart: the urgent need for more research and knowledge on cardiovascular disease in women: proceedings of the workshop held in Brussels on gender differences in cardiovascular disease, 29 September 2010. *Eur Heart J*. 2011;32:1362–1368.
3. Nguyen B, Jin K, Ding D. Breastfeeding and maternal cardiovascular risk factors and outcomes: a systematic review. *PLoS One*. 2017;12:e0187923.
4. Victora CG, Bahl R, Barros AJ, França GV, Horton S, Krasevec J, Murch S, Sankar MJ, Walker N, Rollins NC. Breastfeeding in the 21st century: epidemiology, mechanisms, and lifelong effect. *Lancet*. 2016;387:475–490.
5. UNICEF. Infant and young child feeding. Current status and progress. Part one: focus on breastfeeding. July 2018. Available at: http://data.unicef.org/topic/nutrition/infant-and-young-child-feeding/#. Accessed January 21, 2019.
6. Lain KY, Catalano PM. Metabolic changes in pregnancy. *Clin Obstet Gynecol*. 2007;50:938–948.
7. Stuebe AM, Rich-Edwards JW. The reset hypothesis: lactation and maternal metabolism. *Am J Perinatol*. 2009;26:81–88.
8. Knopp RH, Walden CE, Wahl PW, Bergelin R, Chapman M, Irvine S, Albers JJ. Effect of postpartum lactation on lipoprotein lipids and apoproteins. *J Clin Endocrinol Metab*. 1985;60:542–547.
9. Qureshi IA, Xi XR, Limbu YR, Bin HY, Chen MI. Hyperlipidemia during normal pregnancy, parturition and lactaction. *Ann Acad Med Singapore*. 1999;28:217–221.
10. Gunderson EP, Hedderson MM, Chiang V, Crites Y, Walton D, Azevedo RA, Fox G, Elmasian C, Young S, Salvador N, Lum M, Quesenberry CP, Lo JC, Sternfeld B, Ferrara A, Selby JV. Lactation intensity and postpartum maternal glucose tolerance and insulin resistance in women with recent GDM. *Diabetes Care*. 2012;35:50–56.
11. Tigas S, Sunehag A, Haymond MW. Metabolic adaptation to feeding and fasting during lactation in humans. *J Clin Endocrinol Metab*. 2002;87:302–307.
12. Aune D, Norat T, Romundstad P, Vatten LJ. Breastfeeding and the maternal risk of type 2 diabetes: a systematic review and dose-response meta-analysis of cohort studies. *Nutr Metab Cardiovasc Dis*. 2014;24:107–115.
13. Stuebe AM, Schwarz EB, Grewen K, Rich-Edwards JW, Michels KB, Forster ME, Curhan G, Forman J. Duration of lactation and incidence of maternal hypertension: a longitudinal cohort study. *Am J Epidemiol*. 2011;174:1147–1158.
14. Gunderson EP, Jacobs DR Jr, Chiang V, Lewis CE, Feng J, Quesenberry CP Jr, Sidney S. Duration of lactation and incidence of the metabolic syndrome in women of reproductive age according to gestational diabetes mellitus status: a 20-year prospective study in CARDIA (Coronary Artery Risk Development in Young Adults). *Diabetes*. 2010;59:495–504.
15. Peters SAE, van der Schouw YT, Wood AM, Sweeting MJ, Moons KG, Weiderpass E, Arriola L, Benetou V, Boeing H, Bonnet F, Butt ST, Clavel-Chapelon F, Drake I, Gavrila D, Key TJ, Klinaki E, Krogh V, Kühn T, Lassale C, Masala G, Matullo G, Merritt M, Molina-Portillo E, Moreno-Iribas C, Nøst TH, Olsen A, Onland-Moret NC, Overvad K, Panico S, Redondo ML, Tjønneland A, Trichopoulou A, Tumino R, Turzanski-Fortner R, Tzoulaki I, Wennberg P, Winkvist A, Thompson SG, Di Angelantonio E, Riboli E, Wareham NJ, Danesh J, Butterworth AS. Parity, breastfeeding and risk of coronary heart disease: a pan-European case-cohort study. *Eur J Prev Cardiol*. 2016;23:1755–1765.
16. Peters SAE, Yang L, Guo Y, Chen Y, Bian Z, Du J, Yang J, Li S, Li L, Woodward M, Chen Z. Breastfeeding and the risk of maternal cardiovascular disease: a prospective study of 300,000 Chinese women. *J Am Heart Assoc*. 2017;6:e006081. DOI: 10.1161/JAHA.117.006081.
17. Schwarz EB, Ray RM, Stuebe AM, Allison MA, Ness RB, Freiberg MS, Cauley JA. Duration of lactation and risk factors for maternal cardiovascular disease. *Obstet Gynecol*. 2009;113:974–982.
18. Stuebe AM, Michels KB, Willett WC, Manson JE, Rexrode K, Rich-Edwards JW. Duration of lactation and incidence of myocardial infarction in middle to late adulthood. *Am J Obstet Gynecol*. 2009;200:138.e1–138.e8.
19. Gallagher LG, Davis LB, Ray RM, Psaty BM, Gao DL, Checkoway H, Thomas DB. Reproductive history and mortality from cardiovascular disease among women textile workers in Shanghai, China. *Int J Epidemiol*. 2011;40:1510–1518.
20. Merritt MA, Riboli E, Murphy N, Kadi M, Tjønneland A, Olsen A, Overvad K, Dossus L, Dartois L, Clavel-Chapelon F, Fortner RT, KAtzke VA, Boeing H, Trichopoulou A, Lagjou P, Trichopoulos D, Palli D, Sieri S, Turnino R, Sacerdote C, Panico S, Bueno-de-Mesquita HB, Peeters PH, Lund E, Nakamura A, Weiderpass E, Quirós JR, Agudo A, Molina-Montes E, Larrañaga N, Dorronsoro M, Cirera L, Barricarte A, Olsson A, Butt S, Idahl A, Lundin E, Wareham NJ, Key TJ, Brennan P, Ferrari P, Wark PA, Norat T, Cross AJ, Gunter MJ. Reproductive factors and risk of mortality in the European Prospective Investigation into Cancer and Nutrition; a cohort study. *BMC Med*. 2015;13:252.

21. Natland Fagerhaug T, Forsmo S, Jacobsen GW, Midthjell K, Andersen LF, Ivar Lund Nilsen T. A prospective population-based cohort study of lactation and cardiovascular disease mortality: the HUNT study. *BMC Public Health*. 2013;13:1070.
22. Vergnaud AC, Romaguera D, Peeters PH, van Gils CH, Chan DSM, Romieu I, Freisling H, Ferrari P, Clavel-Chapelon F, Fagherazzi G, Dartois L, Li K, Tikk K, Bergmann MM, Boeing H, Tjønneland A, Olsen A, Overvad K, Dahm CC, Redondo ML, Agudo A, Sánchez MJ, Amiano P, Chirlaque MD, Ardanaz E, Khaw KT, Wareham NJ, Crowe F, Trichopoulou A, Orfanos P, Trichopoulos D, Masala G, Sieri S, Tumino R, Vineis P, Panico S, Bueno-de-Mesquita HB, Ros MM, May A, Wirfält E, Sonestedt E, Johansson I, Hallmans G, Lund E, Weiderpass E, Parr CL, Riboli E, Norat T. Adherence to the World Cancer Research Fund/American Institute for Cancer Research guidelines and risk of death in Europe: results from the European Prospective Investigation into Nutrition and Cancer cohort study. *Am J Clin Nutr*. 2013;97:1107–1120.
23. Dennis CL. Breastfeeding initiation and duration: a 1990–2000 literature review. *J Obstet Gynecol Neonatal Nurs*. 2002;31:12–32.
24. Pesa JA, Shelton MM. Health-enhancing behaviors correlated with breastfeeding among a national sample of mothers. *Public Health Nurs*. 1999;16:120–124.
25. Bentley JP, Bond D, de Vroome M, Yip E, Nassar N. Factors associated with recurrent infant feeding practices in subsequent births: a population-based longitudinal study. *J Hum Lact*. 2016;32:721–729.
26. Banks E, Redman S, Jorm L, Armstrong B, Bauman A, Beard J, Beral V, Byles J, Corbett S, Cumming R, Harris M, Sitas F, Smith W, Taylor L, Wutzke S, Lujic S. Cohort profile: the 45 and Up Study. *Int J Epidemiol*. 2008;37:941–947.
27. Joshy G, Korda RJ, Attia J, Liu B, Bauman AE, Banks E. Body mass index and incident hospitalisation for cardiovascular disease in 158,546 participants from the 45 and Up Study. *Int J Obes (Lond)*. 2014;38:848–856.
28. Randall S, Brown A, Boyd J, Schnell R, Borgs C, Ferrante A. Sociodemographic differences in linkage error: an examination of four large-scale datasets. *BMC Health Serv Res*. 2018;18:678.
29. Joshy G, Korda RJ, Abhayaratna WP, Soga K, Banks E. Categorising major cardiovascular disease hospitalisations from routinely collected data. *Public Health Res Pract*. 2015;25:e2531532.
30. National Centre for Classification in Health. *International Statistical Classification of Diseases and Related Health Problems, 10th Revision, Australian Modification (ICD-10-AM)*, 5th ed. Sydney, Australia: National Centre for Classification in Health; 2006.
31. Australian Bureau of Statistics. *Information Paper: An Introduction to Socio-Economic Indexes for Areas (SEIFA) 2006*. Canberra, ACT: Australian Bureau of Statistics; 2008. (Information Paper Cat No: 2039.0.).
32. National Health and Medical Research Council. *Australian Guidelines to Reduce Health Risks From Drinking Alcohol*. Canberra, ACT: National Health and Medical Research Council; 2009.
33. Australian Institute of Health and Welfare. *The Active Australia Survey: A Guide and Manual for Implementation, Analysis and Reporting*. Canberra, ACT: Australian Institute of Health and Welfare; 2003.
34. Lin D, Wei LJ, Ying Z. Checking the Cox model with cumulative sums of martingale-based residuals. *Biometrika*. 1993;80:557–572.
35. Foreman AJ, Lai GP, Miller DP. Surviving left truncation using PROC PHREG. *Presented at the Western Users of SAS Software Meeting*. University City, CA: November 5; 2008.
36. Ding D, Rogers K, van der Ploeg H, Stamatakis E, Bauman AE. Traditional and emerging lifestyle risk behaviors and all-cause mortality in middle-aged and older adults: evidence from a large population-based Australian cohort. *PLoS Med*. 2015;12:e1001917.
37. Harvard School of Public Health. Healthy Heart Score uses lifestyle behaviors to estimate cardiovascular disease risk. November 19, 2014. Available at: http://www.hsph.harvard.edu/nutritionsource/2014/11/19/healthy-heart-score-uses-lifestyle-behaviors-to-estimate-cardiovascular-disease-risk/. Accessed January 21, 2019.
38. McDonald SD, Pullenayegum E, Chapman B, Vera C, Giglia L, Fusch C, Foster G. Prevalence and predictors of exclusive breastfeeding at hospital discharge. *Obstet Gynecol*. 2012;119:1171–1179.
39. Oza-Frank R, Chertok I, Bartley A. Differences in breast-feeding initiation and continuation by maternal diabetes status. *Public Health Nutr*. 2015;18:727–735.
40. Wojcicki JM. Maternal prepregnancy body mass index and initiation and duration of breastfeeding: a review of the literature. *J Womens Health (Latchmt)*. 2011;20:341–347.
41. Li R, Scanlon KS, Serdula MK. The validity and reliability of maternal recall of breastfeeding practice. *Nutr Rev*. 2005;63:103–110.
42. Promislow JH, Gladen BC, Sandler DP. Maternal recall of breastfeeding duration by elderly women. *Am J Epidemiol*. 2005;161:289–296.

SUPPLEMENTAL MATERIAL

Table S1. Baseline lifestyle, medical and reproductive characteristics of parous women (n=100,864) in the 45 and Up Study by breastfeeding history and average breastfeeding duration per child.[*]

Variables	Breastfeeding history			Average breastfeeding duration per child[†]			
	Never breastfed	Ever breastfed	P-value[‡]	>0-6 months	>6-12 months	>12 months	P-value[§]
Number of subjects (%)	12,517 (12.4)	88,347 (87.6)		56,049 (63.4)	24,549 (27.8)	7,749 (8.8)	
BMI category[‖] (%)							
Underweight/healthy weight (≤18.5 to <25.0 kg/m^2)	38.8	45.2	<0.0001	42.6	48.8	52.7	<0.0001
Overweight (25.0 to <30.0 kg/m^2)	33.0	33.4		23.2	18.5	17.5	
Obese (≥30.0 kg/m^2)	28.2	21.4		24.2	21.2	19.6	
Mean (SD) physical activity time (minutes/week)	599 (711)	602 (650)	0.68	601 (662)	601 (629)	606 (627)	0.90

Physical activity category[¶] (%)							
<150 minutes/week	26.8	21.2	<0.0001	22.8	19.0	16.5	<0.0001
150 to 299 minutes/week	14.8	16.0		15.6	16.4	18.1	
≥300 minutes/week	58.4	62.8		61.6	64.6	65.4	
Smoking status[**] (%)							
Never smoker	60.5	65.5	<0.0001	63.9	69.0	65.6	<0.0001
Past regular smoker	28.8	28.0		28.7	26.1	29.1	
Current smoker	10.6	6.5		7.4	4.9	5.3	
Current alcohol intake (drinks/week)[††] (%)							
≤14 drinks/week	90.5	89.7	<0.0001	89.3	90.3	91.1	<0.0001
>14 drinks/week	9.5	10.3		10.7	9.7	8.9	
Healthy lifestyle index[‡‡]							
Healthy	72.7	63.5	<0.0001	66.6	59.1	56.5	<0.0001

Not healthy	27.3	36.5		33.4	40.9	43.5	
Current use of multivitamins (%)	25.5	30.1	<0.0001	29.2	30.6	34.6	<0.0001
Current use of omega 3 or fish oil (%)[§§]	34.2	37.0	<0.0001	38.0	35.5	34.8	<0.0001
Current use of aspirin[‖‖] (%)	14.7	13.3	<0.0001	14.8	11.5	7.6	<0.0001
History of oral contraceptive use[¶¶] (%)	80.1	83.6	<0.0001	83.0	83.4	89.3	<0.0001
Family history of cardiovascular disease[***] (%)	58.1	57.9	0.78	59.0	55.9	56.3	<0.0001
Family history of hypertension[†††] (%)	54.7	56.1	0.004	55.4	56.4	60.0	<0.0001
Family history of diabetes[‡‡‡] (%)	27.0	24.0	<0.0001	24.5	23.1	24.2	<0.0001
Self-reported hypertension/ recent treatment for hypertension (%)	24.9	20.5	<0.0001	23.2	17.6	10.6	<0.0001

Self-reported diabetes/ recent treatment for diabetes (%)	9.8	5.6	<0.0001	6.4	4.6	3.5	<0.0001

BMI= body mass index; SD=standard deviation.

* Data are presented as means (SD) or percentages.

† Average breastfeeding duration per child was calculated as self-reported lifetime breastfeeding duration divided by the reported number of children.

‡ Based on chi-square test for categorical variables and student t-test for continuous variables.

§ Based on chi-square test for categorical variables and F statistics from ANOVA for continuous variables.

‖ 8,273 missing.

¶ 1,370 missing.

** 5 missing.

†† 2,091 missing.

‡‡ 15,623 missing. Based on six lifestyle risk factors scored individually as either healthy (score=1) or not healthy (score=0), as follows: body mass index (<25 kg/m^2=score 1, ≥25 kg/m^2=score 0), physical activity level (<150 min/week=score 0; ≥150 min/week=score 1), smoking status (past/current smoker=score 0; never smoker=score 1), alcohol intake (≤14 drinks/week=score 0; >14 drinks/week=score 1), sleep (>7-<9 hours/day=score 0; <7 hours/day or >9 hours/day=score 1), fruit and vegetable intake (<2 serves of fruit/day and <3 serves of fruit/day=score 0; ≥2 serves of fruit/day and ≥3 serves of vegetables/day=score 1). Based on the

sum of these scores, the healthy lifestyle index was dichotomised as either healthy (sum of scores=5-6) or not healthy (sum of scores=0-4).

§§ 1 missing.

‖‖ 6 missing.

¶¶ 1,571 missing.

*** 9 missing.

††† 9 missing.

‡‡‡ 9 missing.

Table S2. Hazard ratios and 95% confidence intervals for the incidence of CVD hospitalisation and mortality in parous women, by breastfeeding history.

Breastfeeding history	**No. of persons, n**	**Person-years from baseline**	**No. of incident cases/deaths**	**Model 1*** **(95% CI)**	**Model 2†** **(95% CI)**	**Model 3‡** **(95% CI)**	**Model 4§** **(95% CI)**
CVD hospitalisation							
Parous, Never breastfed	12,517	76,164	527	Reference	Reference	Reference	Reference
Parous, Ever breastfed	88,347	540 696	2,901	0.81 (0.73,0.89)	0.83 (0.75,0.91)	0.85 (0.77,0.95)	0.86 (0.78,0.96)
P-value‖				<0.001	<0.001	0.003	0.005
CVD mortality							

Parous, Never breastfed	12,517	71 730	66	Reference	Reference	Reference	Reference
Parous, Ever breastfed	88,347	506,383	352	0.65 (0.49,0.85)	0.69 (0.52,0.91)	0.66 (0.50,0.89)	0.66 (0.49,0.89)
P-value[‖]				0.002	0.008	0.006	0.006

CI= confidence interval, CVD=cardiovascular disease.

[*] Model 1 was unadjusted.

[†] Model 2 was adjusted for parity (number of children) and socio-demographic characteristics (age, country of birth, educational level, marital status, area-level socio-economic status).

[‡] Model 3 was further adjusted for lifestyle factors: body mass index, smoking status, alcohol intake, physical activity.

[§] Model 4 was additionally adjusted for medical and reproductive covariates: multi-vitamin use, omega 3 or fish oil use, use of aspirin, oral contraceptive use, mother's age for first child, mother's age for last child, family history of CVD, family history of hypertension, family history of diabetes, self-reported hypertension/recent treatment for hypertension, and self-reported diabetes/recent treatment for diabetes.

[‖] From Type 3 Wald chi-square test.

Table S3. Adjusted hazard ratios and 95% confidence intervals for associations between average breastfeeding duration per child and the incidence of CVD hospitalisation and mortality in parous women, stratified by highest educational level.

Highest educational level	Average breastfeeding duration per child	No. of persons, n	Person-years from baseline (from birth of first child)	No. of incident cases/deaths	Multivariate-adjusted* (95% CI)
CVD hospitalisation					
University and higher	**Never breastfed**	1,362	8,364	38	Reference
	>0-6 months	9,915	61,035	239	0.90 (0.62, 1.30)
	>6-12 months	7,462	46,238	111	0.81 (0.55, 1.20)
	>12 months	3,383	21,027	39	0.92 (0.57, 1.48)
High school/trade apprenticeship/ certificate/diploma	**Never breastfed**	4,089	24,986	152	Reference
	>0-6 months	20,696	126,795	680	0.89 (0.74, 1.08)

	>6-12 months	9,730	59,834	238	0.83 (0.66, 1.03)
	>12 months	3,101	19,141	49	0.94 (0.66, 1.33)
≤10 years	**Never breastfed**	6,830	41,444	320	Reference
	>0-6 months	24,669	149,919	1,113	0.85 (0.74, 0.97)
	>6-12 months	7,098	42,878	348	0.90 (0.76, 1.07)
	>12 months	1,204	7,374	25	0.75 (0.48, 1.18)
CVD mortality					
University and higher	**Never breastfed**	1,362	7,808	<5	Reference
	>0-6 months	9,915	56,884	20	0.66 (0.19, 2.26)
	>6-12 months	7,462	42,910	<5	0.28 (0.06, 1.27)
	>12 months	3,383	19,477	0	-

High school/trade apprenticeship/ certificate/diploma	**Never breastfed**	4,089	23,470	20	Reference
	>0-6 months	20,696	118,767	63	0.51 (0.30, 0.87)
	>6-12 months	9,730	55,765	32	0.65 (0.36, 1.17)
	>12 months	3,101	17,769	<5	0.26 (0.03, 1.94)
≤10 years	**Never breastfed**	6,830	39,118	41	Reference
	>0-6 months	24,669	141,360	154	0.77 (0.53, 1.13)
	>6-12 months	7,098	40,484	51	0.52 (0.33, 0.84)
	>12 months	1,204	6,860	6	1.06 (0.37, 3.02)

CI= confidence interval, CVD=cardiovascular disease.

* Adjusted for age, country of birth, educational level, marital status, area-level socio-economic status, body mass index, smoking status, alcohol intake, physical activity, multi-vitamin use, omega 3 or fish oil use, use of aspirin, oral contraceptive use, number of children, mother's age for first child, mother's age for last child, family history of CVD, family history of hypertension, family history of diabetes, self-reported hypertension/recent treatment for hypertension, and self-reported diabetes/recent treatment for diabetes.

Table S4. Adjusted hazard ratios and 95% confidence intervals for associations between average breastfeeding duration per child and the incidence of CVD hospitalisation and mortality in parous women, stratified by the healthy lifestyle index.

Healthy lifestyle index*	Average breastfeeding duration per child†	No. of persons, n	Person-years from baseline (from birth of first child)	No. of incident cases/deaths	Multivariate-adjusted‡ (95% CI)
CVD hospitalisation					
Healthy	**Never breastfed**	2,812	17,354	77	Reference
	>0-6 months	15,724	96,582	490	1.11 (0.87, 1.42)
	>6-12 months	8,652	53,261	197	1.01 (0.77, 1.32)
	>12 months	2,948	18,230	37	1.15 (0.77, 1.72)
Not healthy	**Never breastfed**	7,487	45,413	345	Reference
	>0-6 months	31,297	191,309	1,157	0.79 (0.70, 0.90)

	>6-12 months	12,485	76,576	371	0.80 (0.68, 0.93)
	>12 months	3,836	23,718	61	0.82 (0.62, 1.09)
CVD mortality					
Healthy	**Never breastfed**	2,812	16,201	10	Reference
	>0-6 months	15,724	90,369	43	0.68 (0.34, 1.36)
	>6-12 months	8,652	49,616	15	0.40 (0.18, 0.90)
	>12 months	2,948	16,894	<5	0.93 (0.20, 4.31)
Not healthy	**Never breastfed**	7,487	42,853	39	Reference
	>0-6 months	31,297	179,631	130	0.68 (0.47, 0.99)
	>6-12 months	12,485	71,602	48	0.59 (0.38, 0.92)
	>12 months	3,836	22,019	<5	0.57 (0.18, 1.88)

CI= confidence interval, CVD=cardiovascular disease.

* Based on six lifestyle risk factors scored individually as either healthy (score=1) or not healthy (score=0): body mass index (<25 kg/m^2=score 1, ≥25 kg/m^2=score 0), physical activity level (<150 min/week=score 0; ≥150 min/week=score 1), smoking status (past/current smoker=score 0; never smoker=score 1), alcohol intake (≤14 drinks/week=score 0; >14 drinks/week=score 1), sleep (>7-<9 hours/day=score 0; <7 hours/day or >9 hours/day=score 1), fruit and vegetable intake (<2 serves of fruit/day and <3 serves of fruit/day=score 0; ≥2 serves of fruit/day and ≥3 serves of vegetables/day=score 1). Based on the sum of these scores, the healthy lifestyle index was dichotomised as either healthy (sum of scores=5-6) or not healthy (sum of scores=0-4).

† Average breastfeeding duration per child was calculated as self-reported lifetime breastfeeding duration divided by the reported number of children.

‡ Adjusted for age, country of birth, educational level, marital status, area-level socio-economic status, multi-vitamin use, omega 3 or fish oil use, use of aspirin, oral contraceptive use, number of children, mother's age for first child, mother's age for last child, family history of CVD, family history of hypertension, family history of diabetes, self-reported hypertension/recent treatment for hypertension, and self-reported diabetes/recent treatment for diabetes.

Table S5. Summary of recent prospective/case-cohort studies that have examined the association between breastfeeding history/duration and CVD outcomes.

First author (year)	Country and cohort designation	Participants	Mean follow-up (years)	Outcome assessment	Breastfeeding comparison categories	Adjusted HR (95% CI) by breastfeeding history/ duration	Covariates
Merritt et al. (2015) [1]	10 European countries, EPIC study	322,972 parous women without a history of MI/heart attack, angina, stroke or cancer; 25-70 years	12.9	Mortality from:			Education level, BMI, physical activity, smoking status/intensity and duration, menopausal status
				Circulatory disease	Never	Reference	
					Ever	0.80 (0.70, 0.91)	
				Cerebrovascular disease	Never	Reference	
					Ever	0.94 (0.74, 1.21)	
				IHD	Never	Reference	
					Ever	0.69 (0.54, 0.87)	

Peters et al. (2016) [2]	10 European countries, case-cohort study nested within EPIC study	Parous women without a history of IHD or stroke; mean age=52.7 (SD: 9.1) years; n=8,044 for analyses comparing never vs. ever breastfeeding and n=8,012 for analyses involving breastfeeding duration	11	Incidence of first-time non-fatal/fatal IHD event	Never	Reference	Study centre, age, education level, BMI, smoking status, number of live births, high blood pressure, HDL cholesterol, total cholesterol, history of diabetes mellitus
					Ever	0.71 (0.52, 0.98)	
					Average breastfeeding duration/child		
					Never	1.00 (0.73, 1.37)	
					>0-<1 month	0.77 (0.63, 0.94)	
					≥1-<3 months	0.69 (0.61, 0.78)	
					≥3-<6 months	0.67 (0.57, 0.77)	
					≥6 months	0.67 (0.56, 0.80)	

Peters et al. (2017) [3]	10 diverse regions in China, China Kadoorie Biobank	289,573 without a history of IHD or stroke; 30-79 years	8.1 (median)	Incidence of:			Education level, household income, BMI, physical activity, smoking status, alcohol intake, systolic blood pressure, history of hypertension, history of diabetes mellitus
				All CVD	Never	1.00 (0.95, 1.05)	
					Ever	0.96 (0.95, 0.97)	
					Each additional 6 months/child*	0.98 (0.97, 0.99)	
				Major CVD	Never	1.00 (0.92, 1.09)	
					Ever	0.88 (0.87, 0.90)	
					Each additional 6 months/child*	0.97 (0.96, 0.99)	
				Fatal CVD	Never	1.00 (0.77, 1.29)	

		Ever	0.90 (0.87, 0.94)
		Each additional 6 months/child*	0.98 (0.95, 1.01)
	Stroke	Never	1.00 (0.93, 1.08)
		Ever	0.92 (0.90, 0.93)
		Each additional 6 months/child*	0.97 (0.96, 0.98)
	Haemorrhagic stroke	Never	1.00 (0.77, 1.31)
		Ever	0.84 (0.81, 0.88)

		Each additional 6 months/child*	0.99 (0.96, 1.03)
	Ischemic stroke	Never	1.00 (0.91, 1.09)
		Ever	0.88 (0.86, 0.90)
		Each additional 6 months/child*	0.97 (0.95, 0.98)
	IHD	Never	1.00 (0.92, 1.09)
		Ever	0.91 (0.89, 0.93)
		Each additional 6 months/child*	0.96 (0.95, 0.98)

BMI=body mass index, CVD=cardiovascular disease, EPIC=European Investigation into Cancer and Nutrition prospective cohort study, HDL=high-density lipoprotein, HR=hazard ratio, IHD=ischaemic heart disease, MI=myocardial infarction, SD=standard deviation.

* Among parous women that had ever breastfed.

Supplemental References:

1. Merritt MA, Riboli E, Murphy N, Kadi M, Tjønneland A, Olsen A, Overvad K, Dossus L, Dartois L, Clavel-Chapelon F, Fortner RT, KAtzke VA, Boeing H, Trichopoulou A, Lagjou P, Trichopoulos D, Palli D, Sieri S, Turnino R, Sacerdote C, Panico S, Bueno-de-Mesquita HB, Peeters PH, Lund E, Nakamura A, Weiderpass E, Quirós JR, Agudo A, Molina-Montes E, Larrañaga N, Dorronsoro M, Cirera L, Barricarte A, Olsson A, Butt S, Idahl A, Lundin E, Wareham NJ, Key TJ, Brennan P, Ferrari P, Wark PA, Norat T, Cross AJ, Gunter MJ. Reproductive factors and risk of mortality in the European Prospective Investigation into Cancer and Nutrition; a cohort study. *BMC Med.* 2015;13:252.

2. Peters SAE, van der Schouw YT, Wood AM, Sweeting MJ, Moons KG, Weiderpass E, Arriola L, Benetou V, Boeing H, Bonnet F, Butt ST, Clavel-Chapelon F, Drake I, Gavrila D, Key TJ, Klinaki E, Krogh V, Kühn T, Lassale C, Masala G, Matullo G, Merritt M, Molina-Portillo E, Moreno-Iribas C, Nøst TH, Olsen A, Onland-Moret NC, Overvad K, Panico S, Redondo ML, Tjønneland A, Trichopoulou A, Tumino R, Turzanski-Fortner R, Tzoulaki I, Wennberg P, Winkvist A, Thompson SG, Di Angelantonio E, Riboli E, Wareham NJ, Danesh J, Butterworth AS. Parity, breastfeeding and risk of coronary heart disease: A pan-European case-cohort study. *Eur J Prev Cardiol.* 2016;23:1755-1765.

3. Peters SAE, Yang L, Guo Y, Chen Y, Bian Z, Du J, Yang J, Li S, Li L, Woodward M, Chen Z. Breastfeeding and the risk of maternal cardiovascular disease: A prospective study of 300,000 Chinese women. *J Am Heart Assoc*. 2017;6:e006081. doi: 10.1161/JAHA.117.006081.