Review

Parity and risk of maternal cardiovascular disease: A dose-response meta-analysis of cohort studies

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Abstract

Background: Parity has been reported to play an important role in the development of cardiovascular disease; however, the results are still controversial. We aimed to conduct a meta-analysis of cohort studies to assess quantitatively the association between parity and cardiovascular disease risk.

Methods: PubMed and Web of Science databases were searched to I June 2018, supplemented by manual searches of the bibliographies of retrieved articles. And multivariate-adjusted relative risks were pooled by using random-effects models. Restricted cubic spline analysis with four knots was used to explore the relationship of parity and the risk of cardiovascular disease.

Results: Ten cohort studies involving 150,512 incident cases of cardiovascular disease among 3,089,929 participants were included in the meta-analysis. A significant association between parity and cardiovascular disease risk was observed while comparing parity with nulliparity, with a summarised relative risk of 1.14 (95% confidence interval (Cl) 1.09–1.18; $l^2 = 62.0\%$, P = 0.002). In the dose–response analysis, we observed a potential non-linear J-shaped dose–response relationship between the number of parity and cardiovascular disease risk, the summary risk estimates for an increase of one live birth was 1.04 (95% Cl 1.02–1.05), with significant heterogeneity ($l^2 = 89.6\%$). In addition, the similar J-shaped associations between parturition number and cardiovascular disease, ischaemic heart disease or stroke risk were also observed. **Conclusions:** Our findings suggest that ever parity is related to cardiovascular disease risk and there is an association between the number of pregnancies and the risk of cardiovascular disease. Since the number of included studies was limited, further studies are warranted to confirm our findings.

Keywords

Parity, cardiovascular disease, dose-response meta-analysis

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Introduction

Many studies have shown that reproductive factors may affect women's health in later life.¹⁻⁴ A recent meta-analysis⁵ revealed that an increasing number of parity was associated with a linearly reduced hip fracture risk, while another meta-analysis⁶ indicated that higher parity was significantly associated with an increased risk of type 2 diabetes. Cardiovascular disease (CVD) is the leading cause of death in American women⁷ and in Chinese middle-aged and older women.⁸ In recent years, different reproductive factors, such as pregnancy, parturition, age at the first birth and preterm birth have been shown to play an important role in the progression of diseases that occur predominantly or exclusively in women.^{9,10} Previous studies have indicated that fluctuations of serum sex hormone levels may play a role in the aetiology of CVD.^{11–13} During the process of pregnancy and delivery, the

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change in functional vascular properties, blood volume, heart rate, oxidative stress and other gestational factors may exert short and potentially long-term impacts on the cardiovascular system.^{14–16} In addition, changes in lifestyle, for example, increased energy intake and reduced physical activity duration and intensity, may also impact maternal health in future life.

Parity (the number of live births during a woman's lifetime), as an important reproductive factor, has also been reported to play an important role in the development of CVD.¹⁷ The earliest study¹⁸ showed no association between reproductive experiences and the risk of coronary heart disease (CHD), while some subsequent studies indicated significant evidence for the association. In the study conducted by Lawlor et al.,¹⁶ each additional parturition could increase the risk of CHD in women, and other studies found that women with six or more pregnancies have an additional CVD risk,¹⁹ and that the CHD incidence rate was higher among working women with three or more children.²⁰ Until now, many studies have focused on the role of parity in the development of CVD; however, it remains controversial given the inconsistency of previous findings. Therefore, we conducted a systematic review and doseresponse meta-analysis of current available cohort studies to quantify the association between parity and the risk of CVD.

Methods

Literature search and selection

In accordance with the meta-analysis of observational studies in epidemiology (MOOSE) guidelines,²¹ two authors (WR and ZL) performed a systematic search of PubMed and Web of Science to identify published articles on parity and CVD risk from inception to 7 June 2018, with the following search terms without restriction: 'reproduction' or 'reproductive history' or 'live birth' or 'pregnancy' or 'parity' or 'gravidity' and 'cardiovascular disease' or 'coronary heart disease' or 'stroke' or 'ischaemic heart disease'. No language restrictions were imposed. We also manually searched the references of all identified relevant original publications and relevant reviews. Studies were identified on the basis of predefined inclusion criteria: the study design was cohort, the exposure of interest was parity number, the outcome was CVD risk, not CVD mortality, and the studies reported relative risks (RRs) with 95% confidence intervals (CIs) for at least three quantitative categories of parity numbers or provide risk estimates per live birth in original. If multiple publications were available for a study, data from the most recent and complete publication were included.

Data extraction and quality assessment

We extracted details on the first author, publication year, country, age, number of cases and participants, parity number categories, exposure and outcome assessment, confounding factors adjusted in the analysis and RRs and corresponding 95% CIs for all categories of parity number. Two reviewers (WL and WR) independently extracted all information and assessed the methodological quality of eligible studies using the Newcastle-Ottawa quality assessment scale, which is a validated scale for non-randomised studies in three areas: the selection of exposed and unexposed participants; the comparability of the groups; and the assessment of the outcome. This scale awards a maximum of 9 points to each study: 4 for the selection of participants and measurement of exposure, 2 for the comparability of cohorts on the basis of the design or analysis, and 3 for the assessment of outcomes and adequacy of follow-up. We assigned scores of 0-3, 4-6 and 7-9 for low, moderate and high quality of studies, respectively. When studies had several adjustment models, we extracted those that reflected the maximum extent of adjustment for potentially confounding variables. Any disagreements were solved by discussion with the senior reviewer (DW).

To perform a dose–response meta-analysis, we assigned the median or mean parity number in each category to the corresponding RR for each study. If the mean or median parity per category was not reported, the midpoint of the upper and lower boundaries in each category was assigned. When the most usual category was open-ended, we assumed that the parity number according to the open-ended category $\times 1.2$ times.

Statistical analysis

In this meta-analysis, the RR and 95% CIs were considered as the effect size for all studies, and the hazard ratios were deemed equivalent to RRs. Any results stratified by different outcomes were treated as two separate reports. First, we evaluated the summary RR and 95% CIs for parous women compared to nulliparous women. Furthermore, we used a fixed-effects doseresponse meta-analysis described by Greenland and Longnecker²² to calculate the trend from the correlated estimates for log RR across categories of parity number. The distributions of cases and participants, and RRs and 95% CIs, in each parity category were extracted according to this method. We set the lower bound to zero. We tested for potential non-linearity in the association between parity and CVD risk using a restricted cubic splines model with four knots at percentiles 5%, 35%, 65% and 95% of the distribution, and a *P* value for curve linearity or non-linearity was calculated by testing the null hypothesis that the coefficient of the second spline is equal to zero.²³ The dose–response curves were shown in figures using a linear model and spline model. We used the Cochran Q test and I^2 statistic to measure heterogeneity: values of 0–25% represented minimal heterogeneity, 26–75% moderate heterogeneity, and greater than 75% substantial heterogeneity.²⁴ The Mantel–Haenszel fixed-effect model was used to pool results across studies when heterogeneity was negligible, and the Mantel–Haenszel random-effect model was used when heterogeneity was not 0 live births, we used the method proposed by Hamling and colleagues to convert risk estimates.²⁶

We also conducted subgroup analyses stratified by the category of CVD, geographial location, controlling for body mass index (BMI), diabetes mellitus, hypertension, cigarette smoking, income, physical activity and cholesterol for parous versus nulliparous and dose-response analysis of the parity number. Publication bias was evaluated by inspection of the funnel plots for asymmetry with the Egger test and Begg test. Additional sensitivity analyses were performed by omitting one study at each time to test the robustness of the results and the influence of an individual study on heterogeneity. All statistical analyses were performed with Stata version 11 (Stata Corp, College Station, TX, USA), and all tests were two sided with a significance level of 0.05.

Results

Study selection

Figure 1 shows the results of the literature research and study selection, 2032 articles from PubMed and 2714 articles from Web of Science prior to 1 June 2018.



Figure 1. Flow chart for the selection of eligible studies.

Table I. Chi	aracteristics o	of included st	tudies of pari	ity in relation to C	VD risk.				
First author, year	Follow-up, years	Country	Age, years	Exposure categories	Case/subjects	Exposure assessment	Outcomes (assessment)	Adjusted factors	Quality score
Colditz, 1987	9	NSA	30–55	0, 1, 2, 3, 4, 5	299/11,9963	Questionnaires	CHD (self-reported and pertinent medical records)	Age	7
Cooper, 1999	52	NSA	6381	0, 1–3, 4+	45/867	Self-administered questionnaire	IHD (self-reported)	Age	ω
Steenland, 1996	ω	SU	4574	0, 1–2, 3–5, 6+	579/585,445	Questionnaires	CHD (medical records)	Age, BMI, total cholesterol, SBP, education, smoking, history of diabetes mellitus	ω
Parikh, 2010	9.5	Sweden	-> 50	0, I, 2, 3, 4, 5+	65,204/ 1,332,062	Multi-generation Register	CHD and stroke, (hospital discharge register or death register)	Age, birth year, highest income before age 50 years, education level and country of birth	ω
Peters, 2016	ω	European	52.7±9.1	0, I, 2, 3, 4, 5+	5138/14,917	Self-administered questionnaire	CHD (self-report, medical records and linkage with morbidity or hos- pital registries)	Age, education, smoking status, number of live births high blood pressure, high-density lipoprotein cholesterol, history of diabetes mellitus and BMI	ω
Zhang, 2009	7.3	China	40-70	l, 2, 3, 4, 5+	2343/74,942	In-person interviews	Stroke (in-person inter- views and linkage with vital statistics registries)	Age, education, occupation, family income, oral contra- ceptive use, menopausal status, hormone therapy use, cigarette smoking, alcohol consumption, BMI and history of hypertension or diabetes	ω
Peters, 2013	7.1	China	30-79	0, I, 2, 3, 4, +	24,432 CHD and 35,736 stroke/ 489,762	Laptop-based questionnaires	CHD and stroke (regional disease and death registers or medical records)	Age, level of attained education, household income, smoking status, alcohol use, SBP, his- tory of hypertension, physical activity, BMI and history of diabetes	ω
Durazo, 2018	9	USA	57.3 ± 5.2	0, I–2, 3-4, 5+	1211/23,905	Questionnaires	CHD and stroke (medical records)	Age, race/ethnicity, income, education, hypertension, hypercholesterolemia, dia- betes, BMI, smoking status, physical activity, age of menarche, job strain and depression/anxiety symptoms	6

(continued)

Table I. Con	tinued								
First author, year	Follow-up, years	Country	Age, years	Exposure categories	Case/subjects	Exposure assessment	Outcomes (assessment)	Adjusted factors	Quality score
Magnus, 2017	7	ž	40-69	0, 1, 2, 3, 4+	6471/180,626	Questionnaires and interview	IHD (hospital and death registers)	Age, ethnicity, qualifications, income, Townsend depriv- ation index and family history of cardiovascular disease, in addition to smoking, fre- quency of alcohol intake, fre- quency of physical activity, BMI, diabetes, DBP and SBP	ω
Peters, 2017	7	Х	4069	0, 1, 2, 3, 4+	9054/267,440	Self-reported	CHD and stroke (hospital and death registers)	Age, Townsend deprivation index, smoking status, SBP, history of diabetes and BMI	ω
CVD: cardiovasc	ular disease; B	MI: body mass	s index; CHD	: coronary heart dise	sase; IHD: ischaemic	c heart disease; DBP:	diastolic blood pressure; SBP: sys	stolic blood pressure.	

After the exclusion of duplicates and studies that did not fulfill the inclusion criteria, 13 remaining articles seemed to be relevant for this meta-analysis. After evaluating the full texts of these 13 publications, we excluded three articles as follows: one article was excluded as a result of lack of sufficient data,¹⁶ and another two articles were excluded because the outcomes were CVD risk factors.^{1,27} Finally, 10 articles were included in our meta-analysis.

Study characteristics and quality assessment

The main characteristics of the eligible articles (10 cohort studies) are summarised in Table 1. All studies were published between 1987 and 2018 and one study was conducted in Sweden,²⁸ four in the United States,^{18,29–31} two in China,^{32,33} two in the United Kingdom^{34,35} and one in European countries (10 countries).³⁶ The study samples ranged from 867 to 1,332,062 and the number of CVD cases varied from 45 to 65,204. The average follow-up duration ranged from 6 to 52 years. The quality score ranged from 7 to 9 with a median score of 8 for all cohorts, which suggested a high quality of the studies included in the meta-analysis. One report³³ considered one live birth as the lowest category of parity number and others included nulliparity in the category of parity.

The CVD risk among parous women compared to nulliparous women

Thirteen reports from nine studies^{18,28–32,34–36} (involving 3,014,987 participants and 148,169 CVD cases) were included to explore the CVD risk in parous women compared to nulliparous women, and the summary RR of CVD for the ever parity compared with nulliparity was 1.14 (95% CI 1.09–1.18), with moderate heterogeneity ($I^2 = 62.0\%$; P = 0.002; Figure 2). We observed no publication bias through Egger's test or Begg's test (P > 0.05 for both tests) (Supplementary Figure 1(a)). In a sensitivity analysis, the exclusion of one study at a time from the pooled estimate had little impact on the overall effect size (Supplementary Figure 2(a)).

Dose-response analysis between parity number and the CVD risk

Eleven reports from eight studies^{18,28–30,32–35} (involving 3,051,107 participants and 144,163 CVD cases) were included in the dose–response analysis, and the summary risk estimates for an increase of one live birth was 1.04 (95% CI 1.02–1.05), with significant heterogeneity ($I^2 = 89.6\%$). We observed a significant non-linear relationship between parity number and CVD



Figure 2. Forest plot of the summary relative risk of cardiovascular disease risk among parous women compared to nulliparous women.

risk using a restricted cubic splines model (P < 0.001; Figure 3). There was evidence of a J-shaped association in the non-linear dose–response meta-analysis of parity number and CVD risk (Figure 4). Similar associations between parity number and CHD or IHD or stroke risk were also observed (Supplementary Figure 3). The sensitivity analysis evaluated the effect of each study on the overall estimate by sequentially excluding one study in one turn showing that no study could probably affect the summary of risk estimate in this study (Supplementary Figure 4). Begg and Egger regression tests for the studies per one live birth and CVD risk provided no evidence of substantial publication bias (P > 0.05 for both tests, Supplementary Figure 1(b)).

Subgroup analyses

To explore the potential source of statistical heterogeneity among the studies and assess the stability of the results, we conducted subgroup analyses by category of CVD, geographical location, whether there was adjustment for BMI, diabetes mellitus, hypertension, cigarette smoking, income, physical activity and cholesterol. The associations of parity number with risk of CVD were similar in subgroup analyses, which are shown in Tables 2 and 3.

Discussion

Our results identified a significant association between parity number and the risk of CVD, and the risk of CVD increased by 16% among parous women compared with nulliparous women. In particular, a nonlinear J-shaped association between parity number and CVD risk was also observed in the cubic spline model, and a 4% increased risk of CVD was associated with one live birth among women. In previous studies, a meta-analysis conducted by Lv et al.⁴ studied associations between parity and CVD, but the authors mainly focused on relationships with CVD mortality rather than risk. Our meta-analysis was different from their study because we studied the association with the risk of cardiovascular events. We found that parity could be



Figure 3. Forest plot of the summary relative risk of cardiovascular disease risk per live birth.



Figure 4. Dose-response relationship plot between parity number and the risk of cardiovascular disease.

associated with the risk of CVD in a dose-dependent manner.

A quantified I^2 test and Q test were also applied to assess the heterogeneity among the included studies. Moderate heterogeneity was found among the included studies ($I^2 = 62.0\%$, P = 0.002). The differences in characteristics of populations, and adjustment for confounding factors (see Tables 2 and 3) may contribute to the source of heterogeneity. Therefore, we conducted subgroup analysis by disease type and study location. Considering the potential effect of BMI, physical activity, hypertension, diabetes, smoking, income and cholesterol, we performed subgroup analyses according to whether these factors were controlled in the original studies. We detected significant heterogeneity in the subgroups when the outcome was CHD, and the study location was Europe, indicating that different study locations and more specific disease outcomes were effective ways to avoid heterogeneity. In addition, we further conducted sensitivity analysis to evaluate the effect of each study on the overall estimation, and the results showed that no study could probably affect the summary of risk estimates in this study.

Our findings were consistent with previous studies that have indicated that parity could be associated with a higher risk of CVD. For instance, Shen et al.³⁷ found a higher CHD risk in every category compared with one live birth, and another study¹⁶ conducted in

	No. of studies	Summary RR (95% CI)	l ² value	P _h*
Overall	13	1.14 (1.09–1.18)	62.0%	0.002
Subgroup analyses				
Category of CVD				
CHD	7	1.14 (1.12–1.16)	51.1%	0.056
IHD	2	1.23 (1.08–1.39)	0.0%	0.709
Stroke	4	1.08 (1.05–1.10)	0.0%	0.405
Geographical location	on			
North America	5	1.27 (1.16–1.40)	30.5%	0.218
Europe	6	1.11 (1.09–1.12)	67.9%	0.008
Asia	2	1.08 (0.99–1.17)	22.5%	0.256
Adjustment for pot BMI	ential confo	ounders		
Yes	9	1.15 (1.10–1.21)	61.2%	0.008
No	4	1.11 (1.09–1.12)	64.1%	0.039
DM				
Yes	9	1.15 (1.10–1.21)	61.2%	0.008
No	4	1.11 (1.09–1.12)	64.1%	0.039
Hypertension				
Yes	3	1.28 (1.16–1.42)	64.3%	0.061
No	10	1.11 (1.09–1.12)	51.1%	0.031
Smoking				
Yes	9	1.15 (1.10–1.21)	61.2%	0.008
No	4	1.11 (1.09–1.12)	64.1%	0.039
Income				
Yes	7	1.11 (1.09–1.13)	75.1%	<0.001
No	6	1.14 (1.06–1.22)	28.5%	0.221
Physical activity		. ,		
Yes	5	1.17 (1.10–1.24)	70.8%	0.008
No	8	1.11 (1.09–1.12)	54.0%	0.033
Cholesterol		. ,		
Yes	4	1.25 (1.15–1.36)	50.8%	0.107
No	9	1.11 (1.09–1.12)	53.5%	0.028

Table 2. Summary risk estimates of the association between parity number and CVD risk (parous women compared to nulliparous women).

Table 3. Summary risk estimates of the association between parity number and CVD risk (per live birth).

	No. of studies	Summary RR (95% CI)	l ² value	P _h*
Overall	11	1.04 (1.02–1.05)	89.6%	<0.001
Subgroup analyses				
Category of CVD				
CHD	5	1.06 (1.06–1.07)	88.7%	<0.001
IHD	2	1.02 (0.97–1.08)	0.0%	0.497
Stroke	4	1.03 (1.02–1.03)	69.7%	0.020
Geographical location	on			
North America	3	1.02 (0.99–1.05)	0.0%	0.554
Europe	5	1.05 (1.05–1.06)	93.4%	<0.001
Asia	3	1.03 (1.02–1.03)	70.3%	0.034
Adjustment for pote BMI	ential confo	ounders		
Yes	7	1.03 (1.02-1.03)	94.2%	0.023
No	4	1.06 (1.05-1.06)	59 .1%	<0.001
DM				
Yes	7	1.03 (1.02-1.03)	94.2%	0.023
No	4	1.06 (1.05-1.06)	59 .1%	<0.001
Hypertension				
Yes	3	1.03 (1.02-1.03)	89.3%	0.034
No	8	1.06 (1.05-1.06)	70.3%	<0.001
Smoking				
Yes	7	1.03 (1.02-1.03)	59.1%	0.023
No	4	1.06 (1.05-1.06)	94.2%	<0.001
Income				
Yes	6	1.04 (1.04–1.05)	94.1%	<0.001
No	5	1.03 (1.01–1.05)	55.9%	0.059
Physical activity				
Yes	3	1.02 (1.02-1.03)	0.0%	0.538
No	8	1.05 (1.05–1.06)	89.3%	<0.001
Cholesterol		. ,		
Yes	I	1.03 (1.00-1.07)	0.0%	NA
no	10	1.04 (1.04–1.05)	90.6%	<0.001
		` /		

*P value for heterogeneity within each subgroup.

CI: confidence interval; RR: relative risk; CVD: cardiovascular disease; BMI: body mass index; CHD: coronary heart disease; IHD: ischaemic heart disease; DM: diabetes mellitus.

4286 women and 4252 men aged 60–79 years found a J-shaped association between the number of children and CHD, which was also found in the study by Parikh et al.²⁸ Conversely, no evidence supported the direct association between parity and CVD risk in previous studies,^{18,30} which makes the present meta-analysis study more meaningful. The biological mechanisms that underlie these associations are complex. Pregnancy could lead to the accumulation of abdominal fat, endothelial dysfunction, atherosclerosis and increased pro-atherogenic lipid levels and systemic inflammation;^{1,15,27,38,39} these cardiometabolic changes may

*P value for heterogeneity within each subgroup.

CI: confidence interval; RR: relative risk; CVD: cardiovascular disease; BMI: body mass index; CHD: coronary heart disease; IHD: ischaemic heart disease; DM: diabetes mellitus.

permanently impact the cardiovascular system, leading to a higher risk of CVD in parous women later in life.^{16,28,40}

Several potential mechanisms might contribute to the J-shaped association between parity and CVD risk. Generally, women who did not have any children may suffer from infertility,⁶ and polycystic ovary syndrome, ovulation disorders and tubal factor^{41,42} could partly explain the platform stage of the J-shaped relationship between parity and CVD risk. Increasing parity after two children could result in repeated exposure to hormone alterations, which may lead to the accumulation of physiological changes, such as pancreatic β-cell proliferation and progressive insulin resistance.^{43,44} In addition, repeated and continuous lifestyle changes may induce excess gestational weight gain and postpartum obesity, which could have an impact on a woman's health in the future.⁴⁵ Furthermore, the recurrence of pregnancy complications in subsequent pregnancies may exert a cumulative burden on CVD. These cumulative effects may contribute to the above-noted J-shaped association between parity and CVD risk. Even so, it is still unclear whether normal pregnancies with increasing parity could exert a cumulative burden on CVD proceeding, or whether other potential factors of multiparous women exert more CVD risk. Therefore, further studies with more potential confounders should be taken into consideration to understand thoroughly the association between parity and the maternal risk of CVD. Our study suggests that obtaining a better understanding of the mechanisms that lead to CVD among nulliparous women as well as multiparous women may lead to the uncovering of novel CVD pathways.

This meta-analysis has several strengths. First, we included only prospective cohort studies with a mean quality score of 8, and most studies were conducted with large sample sizes, which significantly minimised selection bias and considerably increased statistical power to detect potential association between parity and CVD risk. Second, we conducted a dose–response analysis to evaluate the association between parity and the risk of CVD, allowing us to quantify the association between parity and the risk of CVD, allowing us to quantify the association between parity and the risk of different types of CVD using the dose–response method. Finally, subgroup analyses were also conducted to explore whether some factors could explain the results.

Some limitations in the present meta-analysis should also be acknowledged. First, significant heterogeneity was present in the analyses, and sources of heterogeneity were not completely clear. Second, although the included studies controlled for many confounders, some of them still did not adjust for important confounding factors, such as lifestyle and age at the first birth. Third, only two studies conducted by Durazo³¹ and Magnus³⁴ adjusted for race; thus the results of our study may not generalise to other populations with diverse racial groups.

Conclusions

In summary, our meta-analysis of cohort studies reveals that an association exists between ever parity and CVD risk, and an increasing number of parity is associated with a non-linearly increased CVD risk. Further prospective large-scale studies are warranted to confirm our findings, and to establish causality and to elucidate the underlying mechanism.

Author contribution

DW and ZL contributed to the conception or design of the work. DW and WR performed searches, extracted data and conducted meta_analyses. ZL contributed to the acquisition, analysis, or interpretation of data for the work. WR and ZL drafted the manuscript. DW and ZL critically revised the manuscript. All authors gave final approval and agree to be accountable for all aspects of the work ensuring integrity and accuracy.

Declaration of conflicting interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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