Original Article

Is there a differential impact of parity on blood pressure by age?

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Objective: In pregnancy, women experience metabolic and hemodynamic changes of potential long-term impact. Conflicting evidence exists on the impact on blood pressure (BP). We investigated the association between parity and BP in the Swiss Study on Air Pollution And Lung and Heart Disease In Adults cohort.

Methods: Multilevel linear and logistic regression analyses were performed in 2837 women aged 30–73 years, with data on parity, number of births, BP, and doctor-diagnosed hypertension adjusting for potential confounders. Hypertension was defined as at least 140/90 mmHg, doctor diagnosed or taking relevant treatment. Stratified analyses were performed by age (<40, 40–59, and ≥60 years) and menopausal status.

Results: Parous women had a mean of 2.3 pregnancies (SD 0.95, range 1–7). A total of 26% were nulliparous. Mean BP was 119/76 mmHg in nulliparous and 121/76 mmHg in parous women. Parity had a significant adverse effect on BP in women at least 60 years [SBP 5.6 mmHg, 95% confidence interval (CI) 2.3 to 8.9; DBP 1.8 mmHg, 95% CI 0.1 to 3.6] and protective effect in women below 40 years (SBP −3.4 mmHg, 95% CI −5.8 to −1.0; DBP −0.2 mmHg, 95% CI −1.0 to 0.6). With increasing number of births, SBP (mmHg/birth; 95% CI) increased in older (1.2, 95% CI 0.2 to 2.2) and decreased in younger women (−1.6, 95% CI −2.6 to −0.5). Opposite effects by age were also found for diagnosed hypertension. No interaction by menopausal status was found.

Conclusion: Our analyses yield differential effects of parity on BP in older vs. younger women. Reductions in BP in younger parous women have been described before; the opposite impact in older women is new. The findings may constitute biological mechanisms in an aging population or reflect birth cohort effects.

Keywords: blood pressure, cardiovascular health, hypertension, parity, reproductive factors, women

Abbreviations: BP, blood pressure; CVD, cardiovascular disease; SAPALDIA, Swiss Study on Air Pollution and Lung and Heart Disease in Adults

BACKGROUND

Cardiovascular disease (CVD) and hypertension, a main CVD risk factor, remain highly prevalent and cause of major disease burden and mortality [1]. In pregnancy, the cardiovascular system undergoes considerable changes, such as increase in blood volume and heart rate (HR) and change in functional vascular properties, leading to short and potentially long-term impact on the cardiovascular system [2–5]. Animal studies yield evidence for augmented responses to acute stressors and increased peripheral resistance after pregnancy [6], others identified endothelium dysfunction in multiparous compared to nulliparous rats [7]. In humans, however, postpregnancy blood pressure (BP) has been shown to be lower [2] and endothelial function improved in the early postpartum [8,9]. A number of epidemiological studies looked into long-term associations between parity and cardiovascular health outcomes, such as hypertension [10–14] or CVD [15–18] and mortality [19–23]. Results are, however, inconsistent, which can partly be explained by the differences in study design and size, and differences in confounder adjustments. A seemingly important difference is the age of the study populations pointing to potential birth cohort effects or impact by menopausal status. The controversy on the role of parity in CVDs is not resolved. We therefore aimed to investigate the association between parity and BP, a main risk factor of CVD, in women participating in the 'Swiss Study on Air Pollution and Lung and Heart Disease in Adults' (SAPALDIA) 2 cohort, stratifying by age and menopausal status.

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METHODS

SAPALDIA is a population-based Swiss cohort of adults [24,25]. The cohort was recruited in 1991 (18–60 years of age), and followed up twice since (2001, 2010/2011). In 2001, cardiometabolic biomarkers, BP, and HR variability were assessed and a detailed women's health questionnaire was introduced in 2001, collecting data on reproductive history, including parity, age at menarche, menopausal status, and hormone use. Family history of CVD was collected in 2010 and 2011 by means of a paper questionnaire.

The present study population consists of female SAPALDIA participants, who participated in the second SAPALDIA survey with complete information on parity and BP (Fig. 1, $n = 2837$). Female SAPALDIA 2 participants who did not fill in the women's questionnaire were 1.4 years younger ($P = 0.002$) and reported current smoking more often (28.3 vs. 21.9%, $P < 0.001$) than participants, but otherwise did not differ significantly regarding mean BP, educational status, BMI, or alcohol use (Supplemental Table 1, http://links.lww.com/HJH/A387).

SAPALDIA complies with the Declaration of Helsinki, ethical approval was granted by the respective Swiss cantonal ethical committees, and participants gave written informed consent.

Exposure definition

Parity status (nulliparous vs. parous) was defined on the basis of the question: 'Have you ever had a baby (including still-born babies, if any)?' Participants, who answered 'Yes', were asked how many children they had given birth to. On the basis of this data, a categorical variable 'number of births' was built (0 births, 1–2 births, 3–4 births, and >4 births).

Outcome definition

SBP and DBP were measured by the Riva–Rocci method (in millimeters of mercury) at the SAPALDIA study centers by trained fieldworkers following a standard protocol: After at least 10 min of rest in a seated position, two BP measurements were taken 3 min apart using an automatic OMRON 705 CP (OMRON, Tokyo, Japan) and averaged for the analyses [25]. Hypertension was defined on the basis of reported physician diagnosis, measured average SBP greater than 140 mmHg and DBP greater than 90 mmHg at the study center, or reported antihypertensive medication intake.

Definition of covariates

Variables considered as potential confounders or effect modifiers were health relevant factors [smoking, physical activity, BMI, alcohol consumption, and sociodemographic characteristics (age, education, and employment status)], self-reported lifetime exposure to hormone replacement therapy or oral contraceptives, menopausal status (based on the Stages of Reproductive Aging Workshop menopause definitions) [26] and self-reported physician-diagnosed chronic diseases (myocardial infarction, stroke, diabetes, and kidney disease), and self-reported antihypertensive treatment within the last 30 days prior to the study center visit (calcium channel blocker, angiotensin-converting enzyme blockers, angiotensin receptor blockers, diuretics, beta blockers, and alpha blockers).

Analysis

First, descriptive and univariate associations of SBP, DBP, and hypertension with parity and other potential determinants were assessed and tested using Chi^2 tests or ANalysis Of VAriance, as appropriate. Secondly, we performed multilevel linear regression analyses investigating the adjusted association of parity status (dichotomized variable) and 'number of births' (categorical variable: 0, 1–2, 3–4, and <4) with SBP and DBP. Model 1 was adjusted for age and educational status and study area as random factor. Potential confounders were tested and included into the regression model based on a stepwise forward approach (significance level $P < 0.2$). Model 2 adjusted further for BMI, BMI squared, alcohol consumption, smoking status, cholesterol, and doctor-diagnosed diabetes mellitus. Interaction terms between age and parity and menopausal status and parity were tested, and stratified analyses by age groups (age <40 years, 40–59 years, and ≥60 years) and

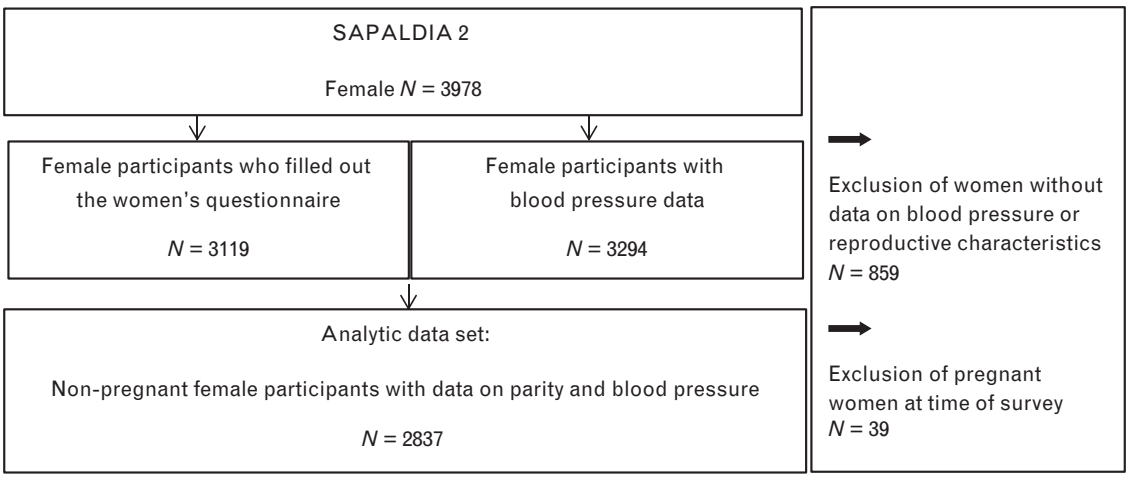

FIGURE 1 Flow chart on analytic sample.

menopausal status (premenopausal, perimenopausal and postmenopausal status) were performed. Trend analyses by age group were performed for number of births (multilevel linear regression). Multilevel logistic regression analyses were run with parity as exposure and hypertension as outcome variable, adjusted for relevant confounders and stratified by the same age groups.

All analyses were conducted using the software program STATA version 12 for Windows (STATA Corp, College Station, Texas, USA). Statistical significance was assumed at a level of P less than 0.05.

RESULTS

Among 2837 women, aged 27–73 years (mean 52 years, SD 11.3), participating in SAPALDIA 2 in 2001, 26% were nulliparous. Parous women had a mean number of 2.3 pregnancies (SD 0.95; range 1–7); 59 women had at least five children. Mean BP was 119/76 mmHg in nulliparous and 121/77 mmHg in parous women (SBP: $P < 0.001$; DBP: $P = 0.081$). In total, 29% were hypertensive patients, 31% among parous women vs. 24% among nonparous women ($P < 0.001$). Nulliparous women were significantly more often highly educated (29%/16.4%, $P = <0.001$), smokers (26%/20%, $P = 0.002$), and reported a higher alcohol consumption (19%/16%, $P = 0.02$). Further characteristics of the study population stratified by parity status are displayed in Supplemental Table 2 [http://links.lww.com/HJH/A387]. Differences by age groups (age <40 years, 40–59 years, and ≥60 years) were found for all covariates included into the model (Supplemental Table 3, http://links.lww.com/HJH/A387).

The adjusted estimated differences in SBP and DBP by parity status are presented in Table 1. For the full sample, we found no significant association with parity status and SBP or DBP neither in model 1 nor model 2. However, there was a significant interaction between age and parity (interaction term age × parity, $P < 0.001$). The stratification by age group yielded a differential impact of parity on BP. In parous women aged at least 60 years, we observed significantly higher BPs than in the same age nulliparous participants [model 2: SBP 5.6 mmHg, 95% confidence interval (CI) 2.3 to 8.9, $P = <0.01$; DBP 1.8 mmHg, 95% CI 0.1 to 3.6]. Parous women in either age group less than 40 years or 40–59 years had lower BP values compared with the nulliparous women of the same age group (model 2 <40 years: −3.4 mmHg, 95% CI −5.8 to −1.0; 40–59 years: −2.1 mmHg, 95% CI −4.0 to −0.3; Table 1). The effect estimates for DBP were of the same direction, but less large and of borderline significance. The differential effect by age was also seen in the logistic regression on hypertension and parity (Table 2).

Although the interaction between menopausal status and parity as such was far from significant (menopausal status × parity; $P = 0.700$), there was evidence of differential effects for single categories of the interaction term: compared with the reference category, 'premenopausal/nonparous' women, 'perimenopausal/parous' ($P = 0.032$) and 'postmenopausal/nonparous' ($P < 0.001$) were significantly different. After stratification by menopausal status, a negative association was observed in premenopausal women (SBP −2.9 mmHg, 95% CI −5.0 to −0.8; DBP −1.40, 95% CI −2.8 to −0.05; Table 3). The analyses in postmenopausal women did not yield significant results, although the effect estimates for parity and SBP were of the same positive direction (1.23 mmHg, 95% CI −1.35 to 3.8; Table 4) as found in older women.

The analyses with 'number of births' as exposure variable yielded a J-shaped association in the full dataset (Table 4). The pattern was similar for DBP, although less pronounced and mostly not statistically significant (Supplemental Table 4, http://links.lww.com/HJH/A387). When stratified by age groups, there was an increase in SBP in all categories of at least one birth and largest in women with more than four children compared with nulliparous women (model 2: SBP 9.5 mmHg, 95% CI 2.6 to 16.4). Consistent with the dichotomous parity status variable, the categorical parity variable was associated with lower SBP in the younger generations. The largest negative effect was found in parous women below age 40 years with 3–4 children (model 2: SBP −7.9 mmHg, 95% CI −11.8 to −3.9; Fig. 2; Supplemental Table 5, http://links.lww.com/HJH/A387).

DISCUSSION

In the SAPALDIA cohort, we found a differential impact of parity on BP by age. On one hand, there was a significantly increased SBP and DBP in older parous women,

TABLE 1. Adjusted difference in mean blood pressure by parity status stratified by age groups and hypertension

	Model 1						Model 2					
	Nulliparous (reference), *n*	Parous, *n*	Difference (mmHg)	95% CI		*P*	Nulliparous (reference), *n*	Parous, *n*	Difference (mmHg)	95% CI		*P*
SBP	735	2099	−0.6	−2.0	0.9	0.44	686	1981	−0.8	−2.3	0.6	0.24
By age group												
<40 years	199	254	−3.0	−5.3	−0.6	0.01	187	238	−3.4	−5.8	−1.0	0.01
40–59 years	370	1202	−1.7	−3.6	0.3	0.09	344	1137	−2.1	−4.0	−0.3	0.03
≥60 years	166	643	5.6	2.3	8.8	<0.01	155	606	5.6	2.3	8.9	<0.01
DBP	735	2099	−0.1	−1.0	0.7	0.81	686	1981	−0.2	−1.0	0.6	0.63
By age group												
<40 years	199	254	−1.4	−3.0	0.3	0.11	187	238	−1.5	−3.1	0.2	0.08
40–59 years	370	1202	−0.9	−2.1	0.3	0.14	344	1137	−1.1	−2.2	0.0	0.06
≥60 years	166	643	1.9	0.1	3.6	0.04	155	606	1.8	0.1	3.6	0.04

Model 1: adjusted for age, education and study area (random variable). Model 2: model 1 and additionally adjusted for smoking status, BMI, BMI squared, alcohol consumption, cholesterol, diabetes. CI, confidence interval.

TABLE 2. Association between parity and odds of hypertension stratified by age

By age group	Model 1						Model 2					
	Nulliparous (reference), *n*	Parous, *n*	Odds ratio	95% CI		*P*	Nulliparous (reference), *n*	Parous, *n*	Odds ratio	95% CI		*P*
<60 years	569	1457	0.80	0.61	1.05	0.103	531	1357	0.72	0.53	0.98	0.032
≥60 years	186	704	1.43	1.03	1.99	0.034	173	661	1.30	0.90	1.88	0.164

Model 1: adjusted for age, education and study area (random variable). Model 2: adjusted in addition for smoking status, BMI, alcohol consumption, cholesterol, and diabetes. CI, confidence interval.

irrespective of the number of children they gave birth to. On the other hand, in younger women, born after 1940, the analyses yielded a protective parity effect on BP. Similarly, we saw a differential impact of number of births on BP by age strata. The results in the older study population, born before 1940, are consistent with the findings by other epidemiological studies on increased risk of CVD in older parous populations [17,18,20,23,27], but inconsistent with the few studies on hypertension, which found no association [12,28] or a small reduction of BP [14]. A protective association has been mainly observed in studies in younger parous women. Khalid [29] report a negative association between parity and hypertension in a study sample in women predominantly less than 40 years of age (~66%), and an increased risk of hypertension for nulliparity in the same population. Ness *et al.* [14] found a more significant reduction of BP in younger, premenopausal women compared with older women. In normal pregnancies, BP is slightly lowered in the first two trimesters and rises again in the third [30]. Studies on the persistence of cardiovascular changes in postpartum are few, but often report a persistent lowering of BP of up to 20 years after pregnancy [2] and improvement of the endothelial function [8,9], if not complicated by the gestational complications. Although most authors consider vascular changes in pregnancy to be the origin of the observed association, Lupton *et al.* [31] suggest breastfeeding to be the main explanatory factor of the parity effect on BP, having observed protective parity effects in breastfeeding mothers only. In his study, breastfeeding was much more common in the younger women (40–54 years) and the protective effect was in fact limited to women less than 64 years [31].

The older age group born before 1940 (≥60 years) is at higher risk of higher BP because of aging per se. Confounding by age is a concern, similar to confounding by other cardiovascular risk factors associated with parity. However, the SAPALDIA data allowed adjusting for these factors, and adjusted stratified analyses by age groups further reduces the risk of confounding. With the extensive adjustments made, we are confident that the effects observed are not because of metabolic or lifestyle changes in parous women. One might speculate that menopausal status plays a role in the observed difference. Giubertoni *et al.* [11] recently reported no association between parity and incident hypertension in postmenopause; however, parity did play a role for hypertension in the menopausal transition. In our data, menopausal status was no significant confounder, nor did stratifying by menopausal status yield a different pattern for premenopause, perimenopause, or postmenopause. The analyses is potentially limited by missing menopausal data in 22%; however, we see no reason of a differential reporting with respect to BP values, and the analyses in this group of women was nonsignificant. Some authors have suggested that the adverse impact of parity on CVDs could be because of confounding by gestational complications. There are only few studies that assessed the effect of parity on CVD risk independent from pregnancy complications. Hannaford *et al.* [32] reported an increased CVD risk for nulliparous women compared with parous women with uncomplicated pregnancies. Catov *et al.* [16], however, reported that parous women with or without pregnancy complications had a higher CVD prevalence than nulliparous women. We currently have no data on gestational hypertension or diabetes available, and cannot exclude confounding. However, confounding by gestational complications would be present in both age groups. Also, the prevalence of hypertensive complications, such as preeclampsia, has rather increased than decreased in the last decades [33], partly because of increased presence of risk factors and improved diagnostic criteria. Social pathways have been suggested for the increase in risk factors and CVD associated with parity. In a study by Lawlor *et al.* [3], this relation was investigated both for men and women. Although after adjustment for potential CVD risk factors the significant positive association between CVD risk and parity in men was no longer present, it was only attenuated in women. The authors discuss that this result could support a direct

TABLE 3. Adjusted difference in blood pressure by parity status stratified by menopausal status

	Model 2 – SBP						Model 2 – DBP			
	Nulliparous, (reference), *n*	Parous, *n*	Difference (mmHg)	95% CI		*P*	Difference (mmHg)	95% CI		*P*
Premenopausal	313	592	−2.9	−5.0	−0.8	0.006	−1.40	−2.8	−0.05	0.043
Perimenopausal	64	209	−0.05	−4.4	4.3	0.981	0.09	−2.5	2.7	0.944
Postmenopausal	243	797	1.23	−1.35	3.8	0.350	0.35	−1.1	1.8	0.635
Missing menopausal status	116	503	−0.5	−4.0	3.0	0.781	−0.19	−2.2	1.8	0.848

Model 2: adjusted for age, education, smoking status, BMI, BMI squared, alcohol consumption, cholesterol, diabetes and study area (random variable). CI, confidence interval.

TABLE 4. Adjusted differences in SBP across parity categories

Number of births	Model 1						Model 2					
	Nulliparous (reference), *n*	Parous, *n*	Difference in SBP (mmHg)	95% CI		*P*	Nulliparous (reference), *n*	Parous, *n*	Difference in SBP (mmHg)	95% CI		*P*
0 Birth	735		Reference				686		Reference			
1–2 Births		1423	−0.4	−1.7	1.1	0.63		1345	−0.4	−1.9	1.1	0.60
3–4 Births		617	−1.5	−3.4	0.3	0.10		580	−2.3	−4.1	−0.5	0.01
>4 Births		59	4.9	0.5	9.3	0.03		56	2.4	−1.9	6.8	0.28

Model 1: adjusted for age, education and study area (random variable). Model 2: model 1 and additionally adjusted for smoking status, BMI, BMI squared, alcohol consumption, cholesterol, and diabetes. CI, confidence interval.

effect of pregnancy on CVD, but may also reflect sex roles in society.

Although we cannot explain the opposite effects of parity by age groups with our data, we consider the following hypotheses. The opposite impact of parity observed in women born prior to 1940 and thereafter implies that a considerable change of what parity induces or stands for must have occurred across these birth cohorts. In fact, changes in a fair number of reproductive as well as social and clinical determinants have occurred. Birth rates have decreased and maternal age has increased in the last decades [34]. Pregnancies are monitored more closely in the recent decades, and timepoint of diagnoses and clinical handling of gestational complications most certainly have changed. In fact, pregnancies may constitute a chance of an early health screening. Nulliparous women with CVD risk factors might not be identified and treated as early as pregnant women. And last, lifestyle associated with having children impacts on the parental health and considerable lifestyle changes have occurred in most western countries [3].

A clear strength of the presented results lies in the large and detailed cohort data that allowed for a well adjusted model and analyses across age groups. Although our results may be generalized to European populations, they need to be confirmed in other populations. In particular, our hypothesis on the potential impact of early screening in pregnancy may not be applicable globally. In fact, very little research has been done on parity and BP in developing countries.

In conclusion, this study presents new findings on an opposite effect of parity on BP and hypertension. Although parity and multiple pregnancies constitute a risk factor for older generations, they seem to have a protective effect in the younger generation. Reproductive as well as factors related to societal change and health management may partly explain the beneficial impact found in the younger women of the SAPALDIA cohort.

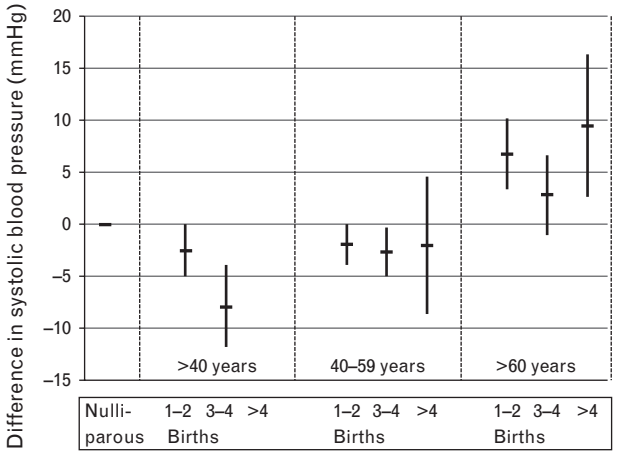

FIGURE 2 Difference in SBP in parous compared to nulliparous women by number of births and age groups. Mean SBP effect estimate ▬ 95% CI ┃ based on model 2: adjusted for age, education, smoking status, BMI, BMI squared, alcohol consumption, cholesterol, diabetes, and study area (random variable). Reference category: nulliparous. No result for women below 40 years in the more than four births category because of small number ($n = 1$).

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Conflicts of interest

All authors state no conflicts of interest.

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Reviewers' Summary Evaluations

Referee 1

Strengths: The results of this study are based on a large-scale and detailed cohort data, with a list of considerable confounders. The study reported a novel finding about differential effects of parity on BP in older vs. younger women. This finding may explain the controversial results regarding the effect of parity on BP in the literature.

Weaknesses: BP and women's health data were only collected once in 2001, thus the results were solely based on retrospective analysis, and no prospective analysis is available.

Referee 2

This is an interesting epidemiologic study investigating the association of parity and number of births on BP and hypertension among 2837 women in a Swiss registry (SAPALDIA 2). The authors found parity and numbers of births were associated with significantly increased BP among older ($\geq$60 years) women and decreased BP in women <40 years compared to nulliparous women. The data appears to have been carefully collected and the analyses appear appropriate. The finding of differential effects of parity by age is novel and may relate to biological mechanisms associated with an aging population.