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Higher parity is associated with an increased risk of type-II diabetes in Chinese women: the Singapore Chinese Health Study

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Abstract

Objective—The association between parity and type-II diabetes has been studied primarily in Western populations, and the findings have been inconsistent. Here, we examine whether parity was positively associated with incident type-II diabetes in Singaporean Chinese women.

Design—Prospective cohort study.

Setting—Singapore.

Population—A total of 25 021 Singaporean Chinese women aged 45–74 years from the Singapore Chinese Health Study who were free of cancer, heart disease, stroke, and diabetes at baseline (1993–1998).

Methods—Women were followed through 2004 for incident diabetes. Hazard ratios for type-II diabetes were computed across parity (of live births) categories and adjusted for baseline age,

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Details of ethics approval Ethical approval was obtained by the institutional review boards at the National University of Singapore and the University of Minnesota. Below are the approval details from the National University of Singapore and University of Minnesota going back over the last 2 years. The Institutional Review Board Human Subjects Committee renewed its approval of study number 0811M53641 (principal investigator, Mark Pereira; expiration date 30 October 2013; approval date, 31 October 2012) and study number 0811M53641 (principal investigator, Mark Pereira; expiration date, 14 November 2012; approval date, 16 November 2011).

interview year, dialect, education, smoking, dietary pattern, physical activity, age at menarche, oral contraceptive use, menopausal status, hormone therapy use, and body mass index (BMI).

Main outcome measure—Self-reported diabetes, as diagnosed by a doctor.

Results—Over an average of 5.7 person-years of follow-up, 1294 women were diagnosed with diabetes. Before and after multivariable adjustment there was a positive graded association between parity and type-II diabetes risk ($P < 0.001$). In the fully adjusted model, which included adult BMI, the risk of type-II diabetes increased by 31% (from –2 to 76%), 62% (from 22 to 116%), and 74% (from 29 to 133%) for women with one or two, three or four, and five or more live births, respectively, compared with women with no live births. Moreover, in a supplementary multivariate analysis in non-diabetic women we found a positive monotonic association between parity and glycated haemoglobin (HbA1c) ($P = 0.01$).

Conclusions—Increased parity may be a risk factor for type-II diabetes in Chinese women. More research is needed on lifestyle and physiologic factors that may explain this association.

Keywords

Cohort studies; Epidemiology; pregnancy; prevention of type-II diabetes

Introduction

Pregnancy involves marked alterations in metabolic parameters, including reduced insulin sensitivity in peripheral tissues, increased production of insulin from the pancreas, and accumulation and redistribution of body fat.^{1,2} During this time, women tend to increase their energy intake, alter the composition of their diet, and maintain or reduce physical activity: changes that may increase their risk for developing cardiometabolic diseases.³ It is still unknown if pregnancy, or repeated pregnancies, may have long-term implications for metabolic disease because of these physiologic and lifestyle changes.

In 1956, Pyke conducted one of the first investigations on parity and type-II diabetes, finding a positive graded association between number of live births and incidence of diabetes in female patients.⁴ Since this groundbreaking research, various cohort studies have corroborated the finding of a positive association between parity, particularly five or more births (grandmultiparity), and type-II diabetes.^{5–11} However, others have suggested no increased diabetes risk among multiparous women,^{12–14} or even an increased risk in nulliparous women.^{15–17} The discordance of findings on this topic has led some researchers to suspect that the association between parity and type-II diabetes may not be causal, but instead reflect residual confounding from demographic or lifestyle factors, or mediation by adiposity.¹⁸

No studies on this topic have been conducted in women from Southeast Asian populations, where the development of type-II diabetes is common at low body mass index (BMI).¹⁹ In the present study, we examined the association between number of live births, referred to as ‘parity’ in this paper, and type-II diabetes in a cohort of Chinese women living in Singapore. The purpose of our investigation was to determine whether higher parity is associated with type-II diabetes after adjusting for demographics, lifestyle, reproductive health factors, and

BMI. Our hypothesis was that women with higher parity are at increased risk of type-II diabetes compared with nulliparous women.

Methods

Study participants

The Singapore Chinese Health Study (SCHS) is a prospective cohort assessing diet and health among men and women. The study design of the SCHS has been described previously.²⁰ The cohort included permanent residents of government-built housing estates (86% of citizens lived in these properties at the time), who belonged to one of the two major dialect groups of Chinese in Singapore: Hokkien and Cantonese.²⁰ Recruitment was initiated with a letter informing potential participants of the study and inviting them to take part. After 5–7 days, the study staff went door-to-door to invite subjects to participate. Approximately 85% of the eligible subjects invited agreed to participate. This study was carried out in accordance with the principles of the Declaration of Helsinki, as revised in 2000, approved by the institutional review boards at the National University of Singapore and the University of Minnesota, and all participants provided written informed consent.

Exposure assessment

Between April 1993 and December 1998, 35 303 women aged 45–74 years (mean age 56.5 years) completed an in-person interview, including questions on demographics, education, height, weight, use of tobacco and alcohol, usual physical activity, menstrual and reproductive history, medical history, family history of cancer, and dietary intake.

The number of live births was self-reported at baseline in the following categories: no live births; one or two live births; three or four live births; and five or more live births.

Information on age at menarche, age at menopause, and use of oral contraceptives and hormone therapy (estrogen or progesterone) was also derived from baseline questionnaire data. Education was categorised into: no formal education; primary school; and secondary school or above.

Information on the age at which women started smoking and the number of cigarettes they smoked per day was used to categorise smoking status. We characterised the level of physical activity of the participants through self-reported number of hours per week spent doing strenuous sports (e.g. jogging, cycling in the hills, tennis, swimming, or aerobics), vigorous work (e.g. moving heavy furniture, loading/unloading heavy trucks, shovelling), and moderate activities (e.g. brisk walking, bowling, cycling on level ground, tai chi, and chi kung). Self-reported height and weight were collected at baseline interview and used to calculate BMI (kg/m^2).

At baseline, participants completed a semi-quantitative food-frequency questionnaire (FFQ) of 165 food items commonly consumed in Singapore. The FFQ has been validated against a series of 24-hour dietary recalls and selected biomarkers.^{21,22} Dietary patterns were derived for this study by principal component analysis of all 165 foods and beverages.²³ As a covariate we included a vegetable-, fruit-, and soy-rich diet, characterized by a high intake of these respective foods and a lower intake of Western fast food, meats, dim sum, and soft

drinks. The frequency of alcohol consumption was determined by summing the intake of beer, rice wine, other wine, and hard liquor.

Ascertainment of diabetes

Self-reported diabetes, as diagnosed by a doctor, was evaluated at baseline and follow-up by the question: 'Have you been told by a doctor that you have diabetes (high blood sugar)?' If yes, 'Please also tell me the age at which you were first diagnosed?' Participants with diagnosed diabetes reported at baseline were excluded from the main analysis. We excluded participants with prevalent diabetes at baseline to: (1) rule out diabetes cases that occurred before or during pregnancy; (2) avoid the influence of differential duration of diabetes; and (3) reduce bias that may result from diabetes diagnosis-related change (or at least reported change) in lifestyle risk factors (e.g. diet and physical activity) used for covariate adjustment in our analyses. We also performed a separate analysis of parity and prevalent diabetes, and the results were similar. We classified participants as having incident type-II diabetes if they reported a diabetes diagnosis between baseline and the first follow-up telephone interview that occurred between July 1999 and October 2004. The validation of incident diabetes cases used two different methods: (1) a hospital-based discharge summary database; and (2) a telephone-administered supplementary questionnaire regarding symptoms, diagnostic tests, and hypoglycaemic therapy. This biphasic validation effort, which is reported in detail by Odegaard and colleagues²⁴ yielded a positive predictive value of 99% for incident diabetes cases. Furthermore, 2966 randomly selected participants who answered 'no' to the question of diabetes diagnosis at baseline and at the first follow-up had their first follow-up blood samples analysed for glycated haemoglobin (HbA1c) %. Of these participants, 94% had HbA1c below the diabetes diagnosis threshold (<6.5% HbA1c).

Statistical analysis

Women who had reported baseline diabetes ($n = 3679$), cancer ($n = 1275$), heart disease ($n = 833$), or stroke ($n = 242$), had died before the follow-up interview ($n = 3818$), reported extreme energy intakes (<600 or >5000 kcal; $n = 391$), had missing information on covariates ($n = 5$), or women from the initial cohort that migrated out of Singapore ($n = 28$) were not included in these analyses (Figure 1). These exclusions, along with the further exclusion of 11 women whose diabetes status was not clear after the validation effort, left 25 021 participants in the present analysis.

Person-years for each participant were calculated from the year of recruitment to the year of reported type-II diabetes diagnosis, or year of follow-up telephone interview for those who did not report a diagnosis of diabetes. Cox regression was applied to calculate hazard ratios (HRs) and 95% confidence intervals (95% CIs) across parity categories. Women with zero live births were the reference category. There was no evidence that proportional hazards assumptions were violated by the lack of significant interaction between parity and survival time in the models. The selection of potential confounding factors was based on prior consideration of their association with both parity, in this population, and type-II diabetes. Model 1 included age (continuous), interview year (1993–1995 versus 1996–1998), dialect (Hokkien versus Cantonese), and education (no formal education, primary school, high school, and secondary education or higher). Model 2 included the variables in model 1 plus

age at menarche (12 years, 13–14 years, 15–16 years, and 17 years), cigarette smoking [never smoked; light smoker (started smoking at 15 years of age or <15 years of age and smoked 13 cigarettes per day); and heavy smoker (started smoking at <15 years of age and smoked >13 cigarettes per day)], physical activity (2 hours/week moderate or any strenuous activity versus lower levels of activity), alcohol use (none, monthly, weekly, or daily), vegetable-, fruit-, and soy-rich diet (quin-tiles), total energy intake (continuous), menopausal status/ age (pre- versus postmenopausal), oral contraceptive use (never versus ever), and hormone (estrogen or progesterone) replacement therapy use (never versus ever). Lastly, model 3 included the covariates in model 2 plus BMI [$<18.5 \text{ kg/m}^2$, $18.5\text{--}21.49 \text{ kg/m}^2$ (reference), $21.5\text{--}24.49 \text{ kg/m}^2$, $24.5\text{--}27.49 \text{ kg/m}^2$, and $\geq 27.5 \text{ kg/m}^2$).

We evaluated whether the association between parity and type-II diabetes risk was modified by dialect (Hokkien versus Cantonese), baseline age (<55 years versus ≥ 55 years), education (none versus any), smoking status (ever versus never), physical activity (any versus no moderate or strenuous activity), menopausal status (pre- versus post-menopausal), or BMI ($<27.5 \text{ kg/m}^2$ versus $\geq 27.5 \text{ kg/m}^2$) using analyses stratified by these variables and by modelling interaction terms. The log-likelihood ratio test was used to evaluate interaction terms.

We conducted a supplementary analysis of parity in relation to HbA1c, an objective measure of glycaemic control, to shed mechanistic light on the parity–diabetes relationship. We performed multivariate linear regression, regressing HbA1c on parity in women ($n = 3138$) who provided a blood sample and reported ‘no’ to diabetes at baseline and at the first follow-up interview. The linear regression model was adjusted for the variables in model 3 of the Cox regression analysis.

All analyses were performed using SAS 9.2 (SAS Institute, Inc., Cary, NC, USA), and tests of statistical significance were based on a two-sided probability set at $P < 0.05$.

Results

The baseline characteristics of the study participants according to category of parity are presented in Table 1. Women with five or more live births, compared with women with fewer or no live births, tended to be older, with the Hokkien-dialect, have lower educational achievement, less physical activity, and a higher BMI. These women were also more likely to have later menarche age, use oral contraceptives, and be postmenopausal. Yet, fewer women with five or more live births reported using hormone therapy.

Over a mean of 5.7 years of follow-up per woman there were 1294 incident cases of type-II diabetes in our sample of women. Unadjusted and multivariate adjusted HRs and 95% CIs for type-II diabetes across categories of parity are presented in Table 2. Before and after multivariable adjustment, including adjustment for baseline BMI, there was a positive, graded association between parity and type-II diabetes risk (all $P < 0.0001$). In the fully adjusted model, which included adjustment for BMI, the risk of type-II diabetes increased by 31% (from -2 to 76%), 62% (from 22 to 116%), and 74% (from 29 to 133%) for women

with one or two, three or four, and five or more live births, respectively, compared with women with no live births (Table 2).

Measures of association were not materially different when we examined parity in relation to baseline prevalent cases of diabetes that were excluded for incident analyses. We also completed sensitivity analyses among women, with one or two live births as the reference, adjusted for age at first live birth, and the results were not markedly altered. There was no statistical evidence that the associations were modified by dialect, age, education, smoking status, physical activity, menopausal status, or BMI. Finally, in a supplementary analysis HbA1c (%) was 5.73, 5.75, 5.79, and 5.85 across the respective categories of live births (0, 1–2, 3–4, and ≥5), after full multivariate adjustment ($P = 0.01$).

Discussion

Main findings

In a large, prospective cohort of Singaporean Chinese women, we found a strong and graded positive association between parity and type-II diabetes, after adjusting for various demographic, lifestyle, reproductive health factors, and BMI. These findings are largely consistent with the results of previous studies on this topic.^{4–11} Yet, unlike other prospective studies, which after adjustment for sociodemographic factors and body fat only observed a greater risk among grand multiparous women (i.e. with five or more births),^{8,9} we found an increased risk of type-II diabetes in women with one or two, three or four, and five or more live births, compared with no live births.

Demographic, lifestyle, and reproductive health factors were highly variable across parity levels. Hokkien women were more likely to have five or more live births compared with Cantonese women, which may be a result of education (48% of Hokkien women, compared with 32% of Cantonese women, had no formal education). Other differences across parity, including level of education, cigarette smoking, physical activity, and the use of oral contraceptives and hormone replacement therapy, are consistent with prior studies.^{8,9} However, unlike other studies,²⁵ the differences in demographic, lifestyle, and reproductive health factors in our study did not explain the positive association between parity and risk of diabetes. The divergent findings may arise from contextual differences across populations. China's 'One Child Policy', which was implemented in 1979, does not apply to our sample of Chinese women living in Singapore.²⁶ The Singaporean Chinese women in our sample tend to have more children than Western populations, and the sociodemographic nature of the women in higher parity levels may differ in important, immeasurable ways.

An increasing body of evidence suggests that pregnancy-induced hormonal, metabolic, and lifestyle changes play a larger role than other socio-economic factors in the association between parity and type-II diabetes.¹⁹ Childbearing is associated with weight gain during, and weight redistribution and retention after, pregnancy.² In our study, women with higher parity tended to have a higher BMI. Yet, adjustment for BMI did not explain the observed association between parity and type-II diabetes. This aligns with a recent study of Filipino American women that found grand multiparous women had a three-fold increased risk of type-II diabetes after adjusting for visceral fat and adiponectin.⁹

In addition to the accretion and redistribution of adipose tissue, pregnancy is marked by insulin resistance in peripheral tissues, a compensatory increase in insulin secretion, lipolysis, elevated leptin, and reduced adiponectin.²⁷ Whether repeated exposure to these metabolic alterations have pathologic perturbations many years after parturition is still unclear. In supplemental analysis, we found parity was positively associated with HbA1c levels in women reporting no history of diabetes diagnosis. This suggests that even in non-diabetic women multiparity may alter long-term glucose homeostasis.

Childbearing also impacts a women's lifestyle through dietary habits and physical activity.¹ Type-II diabetes is highly preventable through diet, exercise, and weight gain prevention.²⁸ Pregnancy can be a trigger for lifestyle-related weight gain that may not be resolved in the postpartum period.² Additionally, women tend to be less active, continue to gain weight, and may change their dietary patterns in the postpartum period.^{2,3} Several randomised controlled trials have shown that lifestyle modification during pregnancy can reduce excessive gestational weight gain.^{29,30} A healthy lifestyle during gestation and in the postpartum period may be key to reducing a women's risk of type-II diabetes after parturition.^{2,3}

Strengths and limitations

This study has several strengths, including its large population-based sample, prospective design, systematic data collection, validation of type-II diabetes cases, and high follow-up retention rates. The results from our analysis with HbA1c as an outcome adds further support for the validity of the main findings, and suggests that diagnostic bias does not explain the observed results; however, we cannot rule out the potential for other biases.

There are also limitations to this study. Parity was defined as the number of live births because data were not available for miscarriages or abortions, or for the births of stillborn babies. There is also concern about residual confounding, as information was also not available for history of gestational diabetes, family history of type-II diabetes, or weight gain after pregnancy. Women with gestational diabetes and impaired glucose tolerance during pregnancy are at an increased risk of developing type-II diabetes later in life.¹⁸ Our ability to shed light on potential mechanisms was limited by the lack of lifestyle and physiologic measures before, during, and after pregnancy. We also cannot rule out the potential for residual confounding by unmeasured socio-economic and lifestyle factors, nor can we exclude the possibility that the results would have been mediated by more specific measures of adiposity or metabolic parameters postpartum. Finally, there was evidence of under-reporting of diabetes in our cohort, generally expected to bias the associations towards the null, and underestimate the strength of the association between parity and diabetes.

Interpretation

Our study infers that parity among women is an independent predictor of future risk of type-II diabetes. Grand multiparous women had 74% increased risk of type-II diabetes compared with nulliparous women. Those with intermediate numbers of births were also at an increased risk, as we observed a dose response with higher parity and type-II diabetes risk. To our knowledge, this was the first study to assess this association in a Southeast Asian population of women. A causal association, according to Sir Bradford Hill's criteria,³¹ is

supported by the strength, temporality, biologic gradient, plausibility, and *coherence* of the observed findings. The causal evidence is also strengthened by *consistency* across most,^{4–11} but not all studies.²⁵

In summary, our findings suggest that parity in women alters long-term glycaemic control and increases diabetes risk. Practitioners should be aware of the potential metabolic consequences of higher parity, particularly grand multiparity. More research on explanatory factors, including glucose homeostasis, adiposity, and hormones before, during, and after pregnancy is needed to shed light on potential mechanisms. If this association is indeed causal, future studies are needed to determine whether the increased risk can be ameliorated through lifestyle modification during and after childbearing.

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Figure 1.

Flow chart of participation exclusions for the analysis of parity and incident diabetes in the Singapore Chinese Health Study.

Table 1

Baseline characteristics of women from the Singapore Chinese Health Study

	0 live births	1–2 live births	3–4 live births	5 live births	<i>P</i>
<i>n</i>	1847	7575	9739	6036	
Age (mean years $\pm$ SD)	53.9 $\pm$ 7.7	52.1 $\pm$ 6.6	53.9 $\pm$ 6.8	61.1 $\pm$ 6.7	<0.001
Cantonese dialect	62	58	48	35	<0.001
High school education or more	42	39	19	4	<0.001
Ever smoker	7	5	6	13	<0.001
Weekly physical activity	26	27	23	20	<0.001
BMI (mean kg/m ² $\pm$ SD)	22.4 $\pm$ 3.4	22.7 $\pm$ 3.2	23.3 $\pm$ 3.3	23.6 $\pm$ 3.3	<0.001
Menarche 12 years or younger	23	22	13	7	<0.001
Ever used oral contraceptives	2	29	37	21	<0.001
Postmenopausal	61	53	65	92	<0.001
Ever used hormone therapy	8	8	7	2	<0.001

Data reported are percentages, unless otherwise indicated.

Table 2

Hazard ratios and 95% confidence intervals for type-II diabetes by parity in women from the Singapore Chinese Health Study

	0 live births (reference)	1–2 live births	3–4 live births	5 live births	P
No. type-II diabetes cases/n	54/1837	286/7532	525/9677	429/5975	
Unadjusted	1.0	1.31 (0.98–1.75)	1.79 (1.36–2.37)	2.25 (1.69–2.98)	<0.001
Model 1	1.0	1.35 (1.01–1.81)	1.76 (1.33–2.33)	1.94 (1.45–2.60)	<0.001
Model 2	1.0	1.36 (1.01–1.82)	1.79 (1.34–2.38)	1.98 (1.47–2.66)	<0.001
Model 3	1.0	1.31 (0.98–1.76)	1.62 (1.22–2.16)	1.74 (1.29–2.33)	<0.001

Model 1 adjusted for: age, interview year, dialect, and education.

Model 2 adjusted for covariates in model 1 plus age at menarche, menopausal status, and hormone therapy, oral contraceptive use, smoking status, alcohol use, physical activity, dietary pattern, and total energy intake.

Model 3 adjusted for covariates in model 2 plus baseline BMI.