The final version of this paper was published in *Heart, Lung and Circulation 2015; 24: 696-704.*

DELIVERY OF A SMALL-FOR-GESTATIONAL- AGE INFANT AND RISK OF MATERNAL CARDIOVASCULAR DISEASE – A POPULATION-BASED RECORD LINKAGE STUDY

Running head: **SGA INFANT AND MATERNAL CVD**

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Abstract

Background. Delivery of small for gestational age (SGA) infants has been associated with increased risk of future maternal cardiovascular disease (CVD). However, whether the risk increases progressively with the greater severity of SGA and number of SGA infants has not been explored.

Methods. A population-based record linkage study was conducted among 812,732 women delivering live born, singleton infants at term between 1994 and 2011 in New South Wales, Australia. Birth records were linked to the mothers' subsequent hospitalization or death records to identify CVD events (coronary heart disease, cerebrovascular events, and chronic heart failure) after a median of 7.4 years. Cox proportional hazard regression was used to estimate adjusted hazard ratios (AHR) [95% confidence interval (CI)] for the associations between the severity (moderate or extreme) of SGA and number of SGA infants and subsequent risk of maternal CVD, accounting for maternal age at last birth, socioeconomic status, parity, smoking, (pre-gestational and gestational) diabetes, and (chronic and pregnancy) hypertension.

Results. Compared to mothers of non-SGA infants, AHRs [95%CI] of CVD among mothers of moderately and extremely SGA infants were 1.36 [1.23-1.49], and 1.66 [1.47-1.87], respectively, while AHRs among mothers with 1, 2, and ≥3 SGA infants were 1.42 [1.30-1.54], 1.65 [1.34-2.03], and 2.42 [1.52-3.85], respectively, indicating a dose-response relationship. AHRs of specific CVD categories showed a similar pattern.

Conclusions. Delivery of an SGA infant was associated with a dose-dependent increase in the risk of maternal CVD according to both the severity of SGA and number of previous SGA infants.

Key words: *cardiovascular disease; small for gestational age; record linkage; hospitalization; international classification of disease*

Introduction

Cardiovascular disease (CVD) continues to be a leading cause of mortality and morbidity, and accounts for a significant burden of disease worldwide [1]. A range of socioeconomic, behavioural, and biological risk factors shape the distribution and development of CVD. In addition to established risk factors shared by both men and women (e.g., smoking, hypercholesterolaemia, hypertension), complications during pregnancy (including preeclampsia [2], miscarriage [3], preterm birth [4] and low birth weight or fetal growth restriction [5]) have been identified as gender-specific risk factors that may help identify women who are susceptible to premature CVD. This evidence is emerging in parallel with the increased appreciation of the burden of CVD in women [6], including in women aged 18-44 years, in whom CVD is the third leading cause of death [7].

Fetal growth restriction is a pathological condition in which the fetus is unable to achieve genetically determined growth potential [8]. Low birth weight (small) for gestational age (SGA) is used as a proxy measure of fetal growth restriction. SGA is different from unstandardised "low birth weight", which includes both premature and growth restricted infants. Prematurity has a different pathological pathway to growth restriction where chronic placental dysfunction is considered to play a primary role. Indeed, it has been postulated that fetal growth restriction is a marker of chronic processes involving metabolic abnormalities, such as dyslipideamia, and vascular dysfunction, characterized by subclinical inflammation, endothelial activation, and disruption of both endothelial and endothelial-dependent vascular response [9]. Some of these processes may be a result of identifiable risk factors in the mother, such as cigarette smoking, or hypertension, but they may also reflect, as yet, unidentified drivers of cardiovascular disease in these women.

A number of previous studies have demonstrated that women with a history of low birth weight or SGA newborns are at increased risk of CVD morbidity or death later in life [10-16]. However, in general,

available studies have treated SGA as a bimodal variable with inconsistencies in "cut-offs" and standardization approaches. Only one study pointed to the possibility that the increased risk of maternal CVD was restricted to women who gave birth to extremely SGA newborns (versus moderately SGA) [14]. This study was limited by an inability to account for the potential influences of maternal hypertensive diseases, established risk factors for subsequent maternal CVD [2]. Furthermore, while women with an SGA infant are more likely to deliver another SGA baby in subsequent pregnancies [17], it remains unknown whether SGA recurrence or a higher number of SGA infants exerts stronger effects on the future risk of maternal CVD than a single SGA infant in multiparious women.

The aim of the present study was therefore to investigate whether delivery of an SGA infant is associated with increased risk of subsequent maternal CVD, utilising a large Australian population-based linked dataset. Specifically, using this approach, we sought to provide a more comprehensive assessment of the relationship of severity and number of SGA with a woman's risk of CVD, whilst adjusting for socio-demographic and CVD risk factors both before and during pregnancy.

Methods

Study population and data sources

The study was based on a cohort of 923,098 women giving birth to 1596803 infants between January 1994 and December 2011 in New South Wales (NSW), Australia. With a resident population of nearly 7 million people, NSW is the most populous state of Australia. Approximately one-third of all Australian births occur in NSW. Analysis included the 816,137 women (88%) who delivered live born, singleton infants at term (≥37 and < 44 weeks of gestation). We restricted the study to term births as preterm birth is a recognised risk factor for subsequent maternal CVD [14], and the underlying pathophysiology is likely to be distinct.

Data were obtained from linking 4 computerised datasets: Perinatal Data Collection (PDC) (birth data), Admitted Patient Data Collection (APDC) (hospital data), Registrar of Births, Deaths and Marriages (RBDM) (death data), and Australian Bureau of Statistics (ABS) cause of death data. The PDC is a population-based surveillance system that records all births ≥20 weeks of gestation or ≥ 400 g birth weight in NSW. The PDC contains information on maternal characteristics, pregnancy, labour, delivery and infant outcomes. APDC is a census of inpatients, covering all inpatients admissions or discharges from all public, private hospitals, as well as public multi-purpose services, private day procedure centres and public nursing homes in NSW. It includes information on patient diagnoses and procedures documented in medical records, and coded according to the Tenth revision of the International Classification of Disease (ICD10). The RBDM records all deaths in NSW, while the ABS provides cause of death coded according to the ICD9 (before 2000) and ICD10 (from 2000).

Records were linked cross-sectionally (e.g., birth to hospital records), and longitudinally to create obstetric and medical histories. All linkage was undertaken by the NSW Centre for Health Record Linkage [18]. Probabilistic linkage methods [19] were used to match women's records based on personal information such as name, date of birth, residential address and hospital. For this study, the NSW Centre for Health Record Linkage reported that the quality of the probabilistic record linkage was extremely high with 3 per 1000 false positive and <5 per 1,000 missed links [18]. Approval for the study was provided by NSW Population and Health Services Research Ethics Committee.

Assessment of exposure

Information about birth weight and gestational age (expressed as completed weeks of gestation) was ascertained from birth data. Gestational age was based on the best clinical estimate using ultrasound examination and/or last menstruation period. Birth weight for gestational age was based on Australian national birth weight percentiles for gestational age by infant sex [20]. SGA was defined as <10th

percentiles and stratified to moderately SGA (3rd - <10th percentiles) and extremely SGA (<3rd percentiles).

A woman was classified as "exposed" if she ever had an SGA baby during the study period (i.e., from January 1994 to December 2011). The exposed women were further stratified according to the total number of SGA infants they had (1, 2, >=3). For women with more than 1 SGA infant, the smallest infant was used to determine the severity of SGA (i.e., moderately SGA or extremely SGA). For both exposed and unexposed women, last birth was used as the index birth.

Follow up and outcomes

Because hospital data (APDC) were not available for record linkage before July, 2000, the follow-up was restricted to the period from 1 July, 2000 to 30 June, 2012. Follow up started at 42 days after birth to minimize the immediate effect of pregnancy on maternal CVD, and was censored at the date of first hospitalisation for CVD, date of death, or the end of the study period. CVD examined in the present analysis included coronary heart disease (CHD) (ICD10 codes: I20-I25 or revascularisation procedure), the CHD subgroup - myocardial infarction (MI) (ICD10 codes: I21, I22, I25.2), cerebrovascular events (ICD10 codes: I60-I66 ; I67.0-I67.2 ; I67.4-I67.9; I68.1,I68.2,I68.8,I69,G46; G45.0-G45.2, G45.4, G45.8, G45.9), and congestive heart failure (ICD 10 codes: I50). The study outcome was the first event defined as hospitalisation (after 6 weeks of delivery) or death from any CVD and the CVD subgroups. CVD hospitalisations were identified, using 20 diagnostic fields in hospital records, while death from CVD as the underlying cause was identified from the ABS cause of death data. Validation studies show that CVD outcomes are accurately and reliably obtained from hospital data with positive predictive values > 90% (e.g., MI: 96%; cerebrovascular events: 93%) [21, 22]. Death data were limited as ABS cause of death data were only available from 2000-2007. We subsequently excluded 743 women with a first CVD event occurring before index birth or within 42 days after index birth.

Covariates

Information on CVD risk factors was obtained from birth data (before July, 2000) or both birth and hospital data (from July, 2000) to maximize ascertainment. Risk factors (dichotomised as ever versus never) included chronic and pregnancy hypertension (gestational hypertension, preeclampsia, and eclampsia), pregestational and gestational diabetes, and maternal smoking during pregnancy. Key socio-demogaphic characteristics consisted of maternal age at the index birth (categorised as <20; 20-35; and >35), parity (having 1, 2, and ≥ 3 births), country of birth (Australia or New Zealand, Europe or North America, Asia, and other countries), and socioeconomic status. Socioeconomic status was determined using the Socioeconomic Indexes for Areas (SEIFA) Relative Disadvantage developed by the Australian Bureau of Statistics and categorized into quintiles. After excluding 3,022 women (0.4%) with missing covariate information, 812,372 women remained for the analysis. The perinatal exposures and covariates are reliably reported with high levels of agreement when compared with medical records [23-25].

Statistical Analysis

Data analysis was undertaken in 2 sequential steps. First, descriptive statistics were used to provide frequency distribution of women's characteristics as categorical variables stratified according to women's exposure status. Group differences were evaluated using chi-square statistics. Incidence rates of first CVD event were also computed and compared across exposed groups.

Second, Cox proportional hazard regression models were employed to evaluate the relationships between the severity of SGA and number of SGA infants and first occurrence of maternal CVD. These models provided crude and adjusted hazard ratios (AHRs), controlling for maternal age at index birth, parity, country of birth, socioeconomic status, chronic and pregnancy hypertension, pregestational and

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gestational diabetes, maternal smoking during pregnancy. Analyses were performed with the overall maternal CVD and the CVD specific categories (i.e., CHD, MI, cerebrovascular events, congestive heart failure). Two-tailed 95% confidence interval (CI) and p values were ascertained, with $p<0.05$ regarded as significant. The proportionality of hazards was assessed by comparing log minus log plots of survival and by performing tests based on Schoenfeld residuals. Assumptions were satisfied for the exposure variables and all covariates.

Sensitivity analysis

We undertook a sub-group analysis in which we restricted the study population to index births occurring from 2000, the period when follow up was complete for all women. Furthermore, to examine the potential confounding effect by parity on the relationship of the number of SGA infants and CVD outcomes, we performed a sub-group analysis in which only women with 3 births were included. The SAS 9.3 statistical package (SAS Institute Inc., Cary, NC) was used for all analyses

RESULTS

Of 812,372 women who delivered live born, singleton infants at term during the study period, 9.9% and 4.6% (totalling a 14.5%) ever had a moderately or extremely SGA infant, while 12.8%, 1.7%, and 0.3% had 1, 2 , and 3 or more SGA infants, respectively. The characteristics of the study population, stratified according to the severity of SGA, are presented in Table 1. The median age of women at the index birth was 32 (range: 12-56). Overall, women with an SGA infant were less likely to be of Australian/New Zealand origin, while they were more likely to be from areas of socioeconomic disadvantage. They were also more likely to smoke during pregnancy, and more likely to have chronic or pregnancy hypertension (chi-square test: $p<0.001$).

The median follow-up time was 7.4 years (range: 0.12-18.5 years), encompassing 6,706,527 person-years at risk, after taking into account 3,222 deaths (0.4%). During the follow-up period,

4,137 women developed a first CVD event comprising 4,101 hospitalizations and 36 deaths from CVD (CHD, n = 2,053 with MI, n = 753; cerebrovascular events, n = 1,855; and congestive heart failure, n = 444). The median age at the first CVD event was 42 years (range: 19-67 years). This was similar for each of the subcategories of CVD- CHD: 43 years (range: 19-67); MI: 43 (range: 21-67); cereborovascular event: 41 (range: 19-61); and congestive heart failure 41 (range: 21-60). The overall crude incidence of first CVD events was 63 per 100,000 person years at risk. Initial exploration of the data suggested a positive association between greater severity of SGA as well as the number of SGA infants with a higher CVD incidence rate (*p* for trends <0.001; Figure 1).

Cox proportional hazard regression analyses showed that, compared with mothers who never had an SGA infant, mothers of SGA infants had a 36% and 66% increased risk of developing CVD according to whether their newborn was moderately SGA or extremely SGA. A dose-dependent pattern remained when specific sub-groups of CVD were examined in association with the severity of SGA, although the associations were not always statistically significant (Figure 2 and Supplementary Table 1),

A dose-dependent pattern was also demonstrated when examining the relationship of CVD risk with the number of SGA infants delivered. Having 1, 2, and ≥3 SGA infants corresponded to a 42%, 65%, and 142% increase in the risk of maternal CVD (AHR [95%CI] = 1.42 [1.30 - 1.54], 1.65 [1.34 – 2.03], and 2.42 [1.52 - 3.85], respectively). A similar pattern of increased risk was also observed for each specific CVD (point estimate of AHRs increased with the number of SGA infants), although the associations did not always achieve statistical significance (95%CI of AHR included unity) (Figure 3 and Supplementary Table 2).

In the sub-group analysis restricted to index births occurring since 2000 (n=227,527 - 72% of the study population), 1,646 CVD events (40% of the total CVD events) were identified. The estimated HRs were

similar, although 95% CIs were wider consistent with the smaller sample size and fewer CVD events. For example, relative to women without an SGA infant, AHRs [95%CI] of CVD among mothers of a moderately SGA and extremely SGA infant were 1.21 [1.04-1.40], and 1.44 [1.05-1.60], while AHRs among mothers having 1, 2, and ≥ 3 SGA infants were 1.25 [1.10-1.42], 1.36 [1.03-1.79], and 2.23 [1.37-3.61], respectively (data not presented). Furthermore, the analysis restricted to women having 3 births (n = 244,008) also provided a similar pattern of HRs in relation to the number of SGA infants. For example, AHRs [95%CI] of CVD among mothers having 1, 2, and 3 SGA infants were 1.50 [1.33-1.69], 2.04 [1.59-2.63], and 2.56 [1.61-4.08], respectively (data not presented).

Discussion

This large, population-based record linkage study provides strong evidence for the relationships of delivery of an SGA infant and the risk of maternal CVD in later life. Consistent with previous studies [14-16], the results indicate that delivery of an SGA infant is an independent risk factor for maternal CVD, when examined after a median of 7.4 years of follow up. This study is the first to show that the risk of CVD rises along with increasing severity of SGA as well as the number of SGA infants, in a dose-dependent manner, even after accounting for sociodemographic and other CVD risk factors (i.e., smoking, hypertension, and diabetes). In particular, the dose-dependent association according to the number of SGA infants was persistent in the subgroup analysis restricted to women with only 3 births where the potential confounding effect by parity was excluded.

Our study confirms and expands findings of previous studies that have identified a relationship between delivery of an SGA infant and greater maternal CVD morbidity and mortality in later life. These include a population-based record linkage study (n= 923,686) that examined interaction of preterm birth and birthweight adjusted for gestational age in predicting maternal CVD. From this study, a dose-response for the severity of SGA and maternal CVD risk can be observed for term infants [14]. Another study

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(n=47,612) showed that delivery of a SGA infant was associated with an over 2-fold increase in maternal

CVD morbidity (HR=2.3 [1.3-4.4]) and 3-fold increase in maternal CVD mortality (HR=3.4 [1.5-7.6]

[15]. However, this study used a single definition of SGA (i.e., defined as birthweight below 10th

percentiles by gestational age and baby sex) to identify SGA infants at first birth, which precluded an

examination of the dose response relationship. Furthermore, the analysis was unable to control for CVD

risk factors before (e.g., preexisting hypertension, diabetes) or during pregnancy (e.g., pregnancy

hypertension, gestational diabetes).

The observed dose-response relationship between the number of previous SGA infants and maternal CVD

risk in our study is novel, with women suffering a recurring SGA infant delivery being at much greater

risk for CVD compared to those who give birth to only one SGA newborn. These findings support the

plausibility of direct biological mechanisms being involved, and are well-aligned with previous studies

demonstrating that the magnitude of the risk of maternal CVD increases with the number and/or

recurrence of other pregnancy complications, including hypertensive pregnancies [26], preterm birth [27],

and miscarriage [3]. The most compelling study is a meta-analysis that showed the association of

recurrent miscarriage with future maternal CVD was stronger than the association of single miscarriage

(pooled odds ratios = 1.99 versus 1.45) [3].

Several aetiological pathways have been proposed to explain the relationships between delivery of an

SGA infant and subsequent maternal CVD morbidity or death. The most commonly cited pathway is the

shared common risk factors and pathophysiologic processes responsible for both fetal growth restriction

and CVD in affected mothers. Chronic maternal hypertension, cigarette smoking, excessive alcohol

consumption are traditional CVD risk factors, which are also associated with fetal growth restriction [28].

During pregnancy, the cardiovascular system undergoes dramatic hemodynamic changes to accommodate

placental circulation in order to meet fetal demand for oxygen and nutrient supply. Women with

preexisting CVD risk factors may have an impaired ability to respond to these changes and be at higher risk of placental dysfunction, the most common cause of intrauterine growth restriction [29]. Furthermore, mothers of growth-restricted babies often exhibit metabolic abnormalities (e.g., dyslipidaemia) and chronic vascular and endothelium dysfunction, leading to early onset of CVD later in life. It has been suggested that delivery of a SGA neonate is the initial clinical manifestation of long-term abnormalities in vascular function in women who have pre-determined higher vascular risk [9].

The relationship between delivery of an SGA infant and risk of CVD is consistent with the Barker hypothesis [30]. According to this well-known hypothesis, cardiovascular perinatal programming operates across generations, and women born small for gestational age themselves are not only at higher risk for CVD later in life but are also more likely to give birth to an SGA infant. This intergenerational relationship may reflect a common genetic disposition that underlies both vascular and metabolic maladaptation to pregnancy and aging [31], culminating in SGA pregnancies and subsequent CVD in affected mothers.

Additionally, the complex interplay between maternal, placental, and fetal hormones that maintain fetal growth has been implicated to contribute to the elevated risk of maternal CVD associated with delivery of SGA infant. Notably, low levels of insulin-like growth factor that result in impaired glucose and lipid metabolism [32] (an important biological antecedent of CVD) are also found in pregnancies complicated by intrauterine growth restriction.[33] Furthermore, lower concentrations of placental growth factor in the circulation of women who give birth to SGA infant have been shown to increase risk of subsequent CHD. This factor stimulates long-term angiogenesis in ischaemic heart,[34] and deficiency in maternal circulation ultimately decreases angiogenesis and repair of the coronary circulation, resulting in CHD later in life.

The study has important strengths. It is a large, recent population-based study, using well-validated, longitudinally-linked data from women of diverse cultural backgrounds. The ability to control for potential confounders including conventional CVD risk factors preceding and during pregnancy adds further strengths. Further, the large study population provided sufficient statistical power to perform separate analyses on specific CVD categories, and to examine the variation in CVD risks according to both the severity of SGA and the number of SGA babies.

The study also has limitations. The ascertainment of CVD death was only possible up until 2007 due to an incomplete data regarding cause of death. However, given that only 36 deaths from CVD without prior hospital admission for CVD were identified in the first 8 years (2000 – 2007), we estimated the number of missing deaths from CVD is minimal. A potential weakness relates to the delayed commencement of follow up in women who gave birth before 2000. In these women, acute cardiovascular events may have been missed, leading to an underestimate of the incidence of these events and the strength of the association with SGA delivery. However, these shortcomings are not without precedent in population-based studies relying on record linkage data. In one study, for example, the follow-up only started 4-14 years after the index (first) pregnancy [11]. The subgroup analysis restricted to women with complete follow up provided essentially the same results. Such consistent findings give confidence that the statistically significant relationships observed in the present study were reliable despite follow-up was incomplete for many women. Another limitation is the potential for residual confounding by other CVD risk factors before (e.g., miscarriage, maternal obesity) and after (e.g., maternal hypertension, hyperlipideamia) delivery, because information on these risk factors was not available in the datasets used for the present study.

An important finding in our study is that, despite the young age of the women, the incidence of first CVD events is not small (63 per 100000 person-years at risk), and occurs at a median of 42 years old. This is

consistent with data demonstrating that CVD is the 3rd most common cause of death in women aged 18-44 years old [7], but may surprise many clinicians and contradict their impression of health issues in women of this age. An additional factor pointing to the clinical relevance of our findings, is the knowledge in the field that, although traditional risk factors such as smoking, diabetes, hypertension and/or hypercholesterolemia serve well as a proxy for atherosclerotic burden and increased risk of clinical CVD in older individuals, the situation appears to be different in younger adults [35]. The Framingham Heart Study cohort comprised primarily of middle-aged Caucasian men, making the inference of the Framingham-derived models to women particularly tenuous [36]. Also, because age is the most heavily weighted variable in 10-year risk models derived from populations that span the adult age spectrum, in younger adults (including women <65 years of age), modest elevations in traditional risk factors have little effect on the predicted 10 year risk [37]. This is not completely resolved by more recent efforts aiming at deriving a more comprehensive risk predictive model specific for women, with Reynolds Risk Score being the most accepted model. This model is based on women >44 years old from the Women's Health Study (median age of 52 years) [38]. A lack of reliable event predictive models in younger women makes it difficult to discriminate risk effectively, and to target medical and lifestyle changes to individuals at highest risk at an early time point. Thus, future clinical models should consider alternative strategies to estimate and communicate risk in these populations, and adverse pregnancy outcomes including delivery of an SGA infant may play a key role.

Conclusions

The current study strengthens the evidence linking delivery of SGA infants and increased risk of maternal CVD in later life by showing that the risk increased incrementally with the severity and number of SGA infants in a dose-dependent fashion, and independently of established risk factors. While mechanistic pathways underlying this relationship remain to be established, careful recording of a woman's reproductive history including baby weight and gestational age, as well as communication of this to

primary care physicians will likely be of benefit in our efforts to identify those at high risk of CVD, and

more effectively target screening, education and preventative therapies.

Acknowledgements

Conflict of interest

Authors declare that they have no conflict of interests.

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Table 1 Characteristics of the study population (n=812,372)

Characteristics	Women with		
	non-SGA infants (n=692,378) n (%)	moderately SGA infants (n=817,12) n (%)	extremely SGA infants (n=38,282) n (%)
Age group*			
<20	17,668 (2.6)	2,242 (2.7)	1,090 (2.9)
20-34	489,956 (70.8)	58,678 (71.8)	27,531 (71.9)
≥35	184,754 (26.7)	20,792 (25.5)	9,661 (25.2)
Country of birth*			
Other	49917 (7.2)	6794 (8.3)	3,277 (8.6)
Asia	94,304 (13.6)	15,889 (19.5)	7,200 (18.8)
Australia/New Zealand	494,833 (71.5)	53952 (66.0)	25,678 (67.1)
Europe/North America	53,324 (7.7)	5,077 (6.2)	2,127 (5.6)
SEIFA index*			
1st quintile (most advantaged)	137,022 (19.8)	13,213 (16.2)	5,302 (13.9)
2nd quintile	130,444 (18.8)	17,021 (17.3)	6,194 (16.1)
3rd quintile	145,746 (21.0)	17,021 (20.9)	8,055 (21.0)
4th quintile	138,822 (20.1)	17,421 (21.3)	8,571 (22.3)
5th quintile (most disadvantaged)	140,341 (20.3)	19,962 (24.3)	10,156 (26.6)
Number of births*			
1	209,435 (30.3)	23,296 (28.5)	10,574 (27.6)
2	275,640 (39.8)	32,236 (39.5)	14,562 (38.1)
≥ 3	207,303 (29.9)	26,180 (32.0)	13,146 (34.3)
Smoking*			
Never	564450 (81.5)	64,722 (79.2)	29,915 (78.1)
Ever	127,928 (18.5)	16,990 (20.8)	8,367 (21.9)
Chronic hypertension*			
No	67,7087 (97.8)	79,710 (97.5)	37,215 (7.2)
Yes	15,291 (2.2)	2,002 (2.5)	1,067 (2.8)
Pregestational diabetes*			
No	688,289 (99.4)	81,370 (99.6)	38,073 (99.5)
Yes	4,089 (0.6)	342 (0.4)	209 (0.6)
Pregnancy hypertension*			
Never	621,992 (89.8)	72,215 (88.3)	33,535 (87.6)
Ever	70,386 (10.2)	9,497 (11.7)	4,747 (12.4)
Gestational diabetes			
Never	653,314 (94.4)	76,940 (94.2)	36,118 (94.4)
Ever	39,064 (5.6)	4,772 (5.8)	2,164 (5.6)

*Chi-square statistics for group difference: $p<0.05$

Figure 1 Crude incidence of first CVD events according to the severity of SGA and number of SGA infants
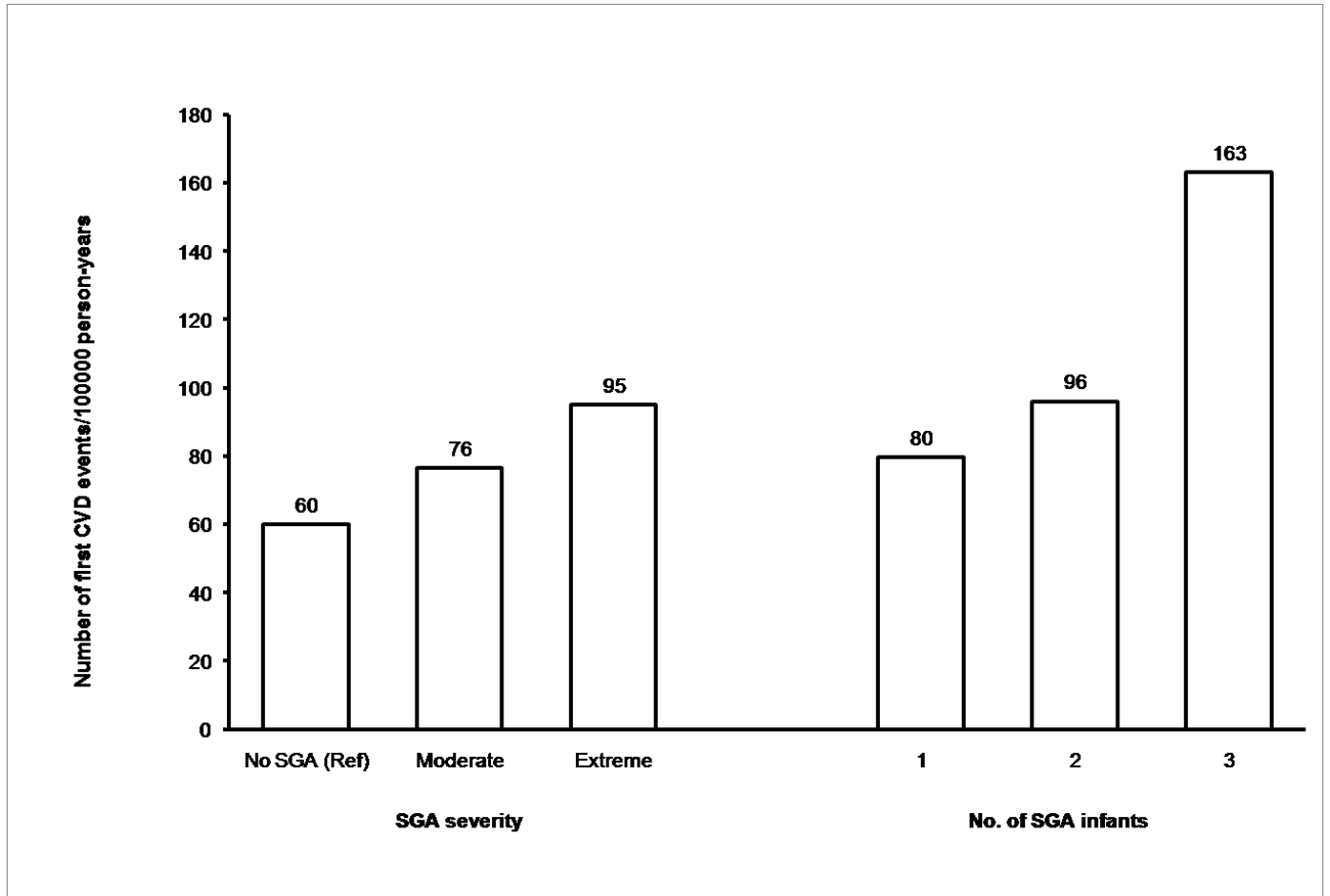
Figure 2 Associations between the severity of SGA and maternal CVD

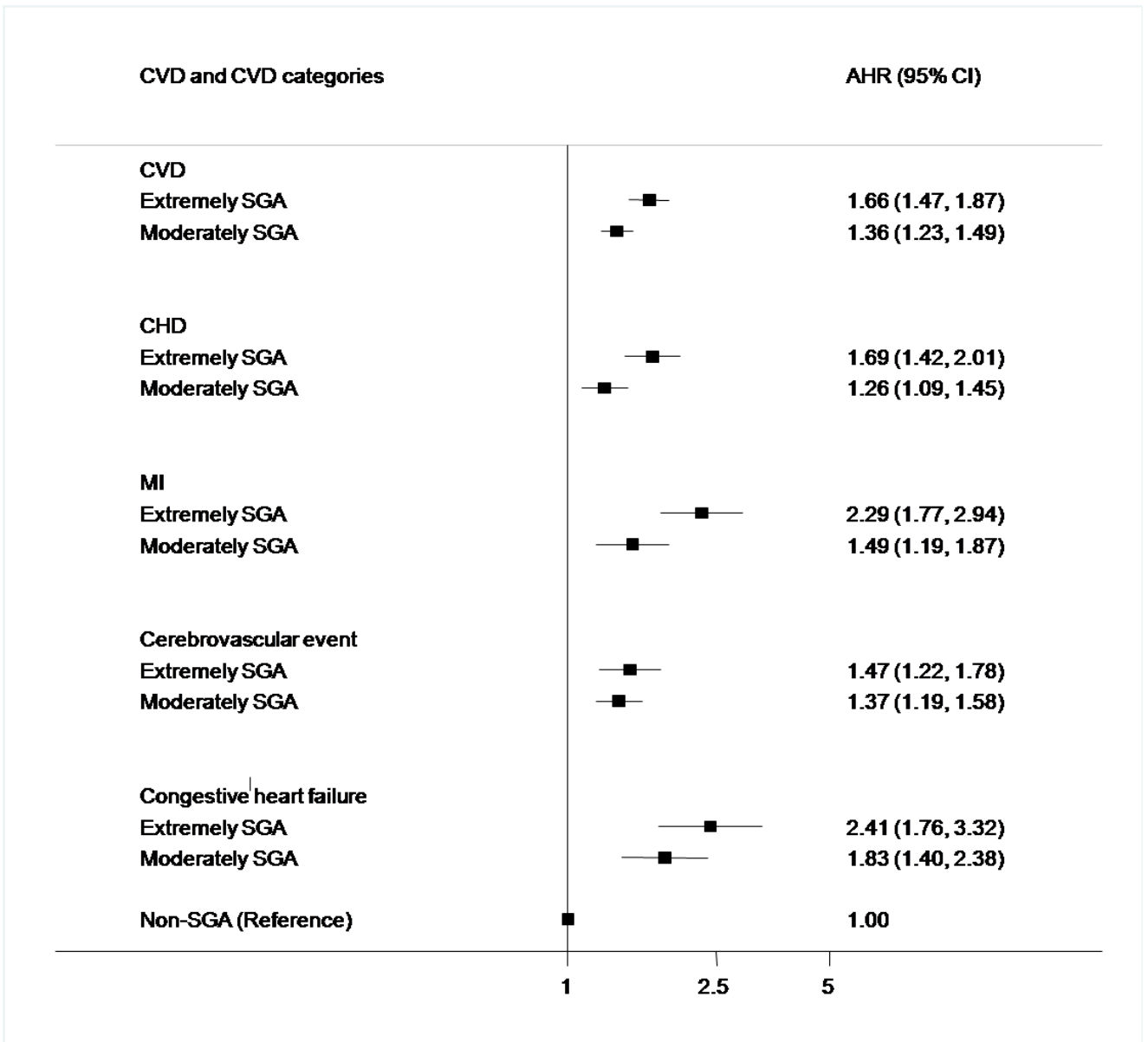| CVD and CVD categories		AHR (95% CI)
CVD		
Extremely SGA		1.66 (1.47, 1.87)
Moderately SGA		1.36 (1.23, 1.49)
CHD		
Extremely SGA		1.69 (1.42, 2.01)
Moderately SGA		1.26 (1.09, 1.45)
MI		
Extremely SGA		2.29 (1.77, 2.94)
Moderately SGA		1.49 (1.19, 1.87)
Cerebrovascular event		
Extremely SGA		1.47 (1.22, 1.78)
Moderately SGA		1.37 (1.19, 1.58)
Congestive heart failure		
Extremely SGA		2.41 (1.76, 3.32)
Moderately SGA		1.83 (1.40, 2.38)
Non-SGA (Reference)		1.00

1   2.5   5

Figure 3 Associations between the number of SGA infants and maternal CVD

CVD and CVD categories	AHR (95% CI)
CVD	
3 SGA infants	2.42 (1.52, 3.85)
2 SGA infants	1.65 (1.34, 2.03)
1 SGA infant	1.42 (1.30, 1.54)
CHD	
3 SGA infants	2.41 (1.25, 4.65)
2 SGA infants	1.45 (1.06, 2.00)
1 SGA infant	1.38 (1.22, 1.56)
MI	
3 SGA infants	4.85 (2.16, 10.88)
2 SGA infants	2.00 (1.25, 3.20)
1 SGA infant	1.68 (1.39, 2.03)
CVA	
3 SGA infants	2.20 (1.04, 4.63)
2 SGA infants	1.80 (1.34, 2.42)
1 SGA infant	1.35 (1.19, 1.53)
CHF	
3 SGA infants	5.20 (1.93, 14.04)
2 SGA infants	1.97 (1.08, 3.60)
1 SGA infant	1.97 (1.57, 2.48)
No SGA infant (Reference)	1.00