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Original article

The joint effect between fetal growth and health behaviors on the risk of cardiovascular diseases in young adulthood

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ABSTRACT

Purpose: To investigate the individual and the joint effect of impaired fetal growth and adult health behaviors on the risk of cardiovascular diseases (CVDs).
Methods: A total of 15,618 individuals were included from three sub-cohorts of the Stockholm Public Health Cohort. Data on participants' birthweight and gestational age were retrieved from the Medical Birth Register. Data on the diagnoses of CVDs were extracted from the Swedish National Patient Register and the Cause of Death Register. Data on health behaviors were identified from self-reported questionnaires, and health behavioral profile was defined based on the recommendations of the American Health Association. The associations of fetal growth and health behaviors with the risk of CVDs were analyzed using Cox proportional hazard model.
Results: Individuals born small for gestational age (SGA) had a higher risk of CVDs than those born appropriate for gestational age (AGA), and the adjusted hazard ratio (HR) and 95% confidence interval (CI) was 1.88 (1.44, 2.47). Participants born SGA and having poor health behavioral profile in adulthood had a higher risk of CVDs than those born AGA and having ideal health behaviors with adjusted HR (95% CI) being 3.58 (1.95, 6.56).
Conclusions: Impaired fetal growth was associated with an increased risk of CVDs in adulthood, and the risk was highest in individuals with both impaired fetal growth and poor health behaviors in adulthood.

Introduction

Cardiovascular diseases (CVDs) are the leading causes of mortality globally and major contributors to reduced quality of life [1,2]. Expert panels on cardiovascular epidemiology emphasize the importance of monitoring and maintaining cardiovascular health across the life course [3,4]. It has been widely acknowledged that the early-life environment in which the embryo, the fetus and the young child grow influences the risk of developing chronic diseases (including CVDs) later in life [5–7]. Impaired fetal growth and maternal exposure to adverse factors during pregnancy may increase the risk of future CVDs [8,9]. Later in life, healthy lifestyles–such as refraining from smoking, being physically active, eating a healthy diet and maintaining an optimal body mass index (BMI)–are recommended to maintain or improve cardiovascular health [10]. It is plausible that favorable health behaviors may compensate for the negative consequences of impaired fetal growth on the risk of CVDs by slowing adverse processes related to cardiovascular remodeling later in life (e.g., blood pressure elevation, arterial stiffening, or atherosclerotic plaque deposition) [11].

Nevertheless, only a few studies have investigated this possible interaction. Two investigations based on the Nurses' Health Study II reported that a healthy lifestyle may attenuate the associations between low birthweight and the risk of type II diabetes and hypertension later in life [12,13]. A study from Helsinki showed that regular exercise modified the association between a small birth size (defined as having a birth weight ≤3000 g and/or a pon-

Abbreviations: CVDs, cardiovascular diseases; SPHC, stockholm public health cohort; SGA, small for gestational age; LGA, large for gestational age; AGA, appropriate for gestational age; LISA, Integrated Database for Labor Market Research; ICD, International Classification of Diseases; BMI, body mass index; HR, hazard ratio; CI, confidence interval.

The authors have no conflicts of interest to disclose.

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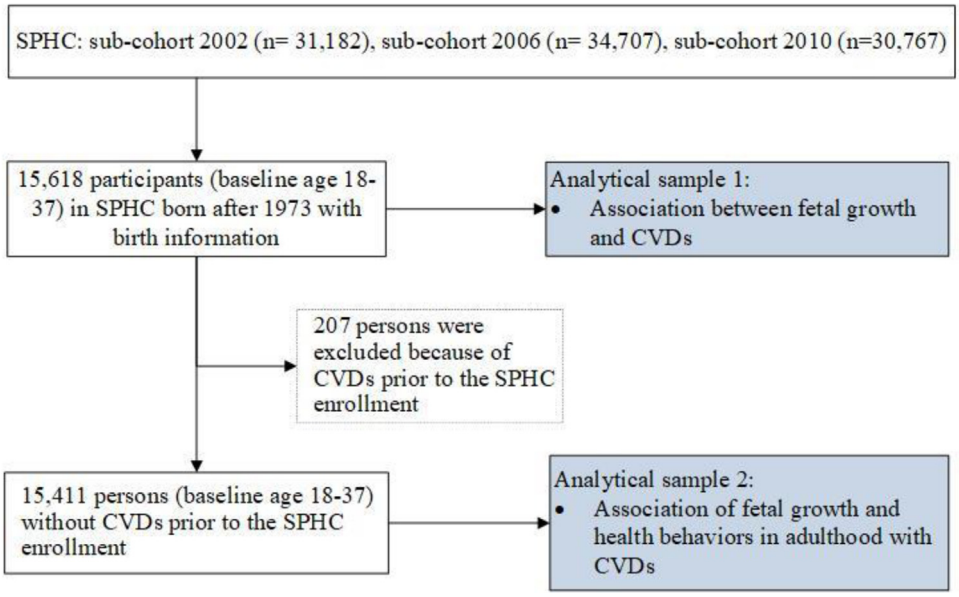

Fig. 1. Flowchart of the study participants.
SPHC, Stockholm Public Health Cohort; CVDs, cardiovascular diseases.

deral index ≤26 kg/m^3) and the risk of developing glucose intolerance [14], while a recent Swedish twin study found that a cumulative health behavior metric moderated the link between low birthweight and a composite endpoint of cardio metabolic diseases [15]. A large US study, including data from several cohorts, reported an interaction between low birthweight and a healthy lifestyle on the risk of CVDs [16]. All these previous studies investigated birthweight without considering gestational age. Furthermore, several of the previous studies investigated only one health behavioral factor and did not take into consideration a wider health behavioral profile (i.e., the combination of several health behaviors). In addition, most of these investigations studied diabetes, hypertension or preclinical CVDs as outcomes, and only one focused on severe CVDs.

The aim of the present study was to investigate the individual and the joint effect of fetal growth and adult health behaviors on the risk of CVDs up to young adulthood (age range 18–45 years).

Methods

Study design and participants

The study was based on the Stockholm Public Health Cohort (SPHC), which is an ongoing population-based cohort study in Stockholm, Sweden. The study design and the purpose of the SPHC have been described in details elsewhere [17]. Briefly, the cohort was established within the framework of the Stockholm County Council's public health surveys, which are undertaken every fourth year with the aim of health and risk factor surveillance, as well as to inform policy. The baseline surveys of three cohorts were conducted in 2002, 2006 and 2010, and the corresponding response rate was 62%, 61% and 56%, respectively [17]. Follow-up was through individual-level linkage to several registers, up to December 31, 2018. Thus, three sub-cohorts were identified for this study: sub-cohort 2002–2018 (n = 31,182), sub-cohort 2006–2018 (n = 34,707), and sub-cohort 2010–2018 (n = 30,767).

Figure 1 shows a flowchart of the study participants. After linkage to the Medical Birth Register (since1973), 15,618 persons from the SPHC with information on birth (born in 1973 and later years) were eligible for this study. These participants constituted the study population for the association between fetal growth and CVDs (Analytical Sample 1 in Fig. 1). We excluded 207 persons who had a diagnosis of CVDs prior to the enrollment in the SPHC. The remaining persons constituted the analytical sample 2 for the association of fetal growth and health behaviors with CVDs (Analytical Sample 2 in Fig. 1, n = 15,411).

The study was approved by the Stockholm Regional Ethical Review Board (Dnr 2019–04767). All participants provided informed consent for both questionnaire and register linkage.

Data sources and variables

The data on health behaviors were collected using the questionnaires distributed as part of the Stockholm County Council's public health surveys. In addition, data on variables of interests and covariates were collected from several population-based registers: (a) the Medical Birth Register (since 1973) including birth markers, maternal medical conditions, and medications during pregnancy; (b) the National Patient Register (since 1960) including diagnoses, admission and discharge dates; (c) the Cause of Death Register (since 1952) including death date and causes of death; (d) the Integrated Database for Labor Market Research (LISA, since 1990) including sociodemographic factors such as sex, age, and education.

Assessment of fetal growth

Information on birth weight and gestational age was extracted from the Medical Birth Register. Analytical Sample 1 was considered as the reference population for the calculation of percentiles of birthweight according to gender-specific gestational age. Children with a birthweight below the 10th percentile for the gender-specific gestational age were classified as being small for gestational age (SGA); children with birthweight above the 90th percentile for the gender-specific gestational age were classified as being large for gestational age (LGA); appropriate for gestational age (AGA) was defined as having a birthweight between the 10th and the 90th percentiles for the gender-specific gestational age [18]. Being SGA was regarded a proxy for impaired fetal growth.

Assessment of health behaviors

Information on health behaviors (smoking, alcohol consumption, physical activity, and diet), weight (in kilograms), and height (in meters) was obtained from the SPHC questionnaire. Based on the American Heart Association's recommendations [19], behavioral health metrics (i.e., health behavioral profile) were defined based on four components: smoking, physical activity, dietary factors, and BMI. The data on these measures were retrieved from the baseline questionnaire; in case of missing at baseline, we used data from the subsequent wave. Each health behavioral component was categorized as poor (score = 0), intermediate (score = 1), or ideal (score = 2). Ideal smoking status was defined as never smoking or having quitted smoking for more than a year. Ideal physical activity was defined as walking/cycling >20 min/d or exercising >2 h/wk. Ideal diet was defined as eating fruits every day. Ideal BMI was defined as a BMI <25 kg/m^2 (Supplementary Table 1). The health behavioral profile was defined and calculated as the total score of these four components and was categorized into poor (total score ≤4), intermediate (total score=5–6) and ideal (total score ≥7) levels.

Assessment of cardiovascular diseases

Information on CVDs was extracted from the Swedish National Patient Register and from the Cause of Death Register. Both registers used International Classification of Diseases (ICD) codes to code medical conditions or causes of death, respectively. Participants were considered to have CVDs if they had any diagnosis of CVDs during the study period based on the ICD-9 codes 390–459 or ICD-10 codes I00-I99. The three most common diagnoses of CVDs were other forms of heart disease (ICD-10 code: I30-I52), diseases of veins, lymphatic vessels and lymph nodes, not elsewhere classified (ICD-10 code: I80-I89), and diseases of arteries, arterioles and capillaries (ICD-10 code: I70-I79).

Assessment of covariates

Sociodemographic factors (sex, age, and education) were identified from LISA. The level of baseline education in the SPHC was categorized into compulsory school (≤9 years), upper secondary school (9–11 years), and university and above (≥12 years). Alcohol consumption was assessed by the following questionnaire item: "During the last 12 months how often have you, on the same occasion, consumed alcoholic beverages equivalent to at least: one bottle of wine, or five glasses of spirits, or four cans of strong beer, or six cans of medium-strength beer." Alcohol consumption was categorized as never, 1–6 times/year, and at least once per month. Maternal CVDs were identified from the Medical Birth Register using the above ICD codes (ICD-9 codes 390–459 or ICD-10 codes I00-I99).

Statistical analysis

Characteristics of study participants born SGA, AGA and LGA were compared using ANOVA in case of continuous variables and chi-square tests in case of categorical variables.

Cox regression was performed to estimate the independent and the joint effects between fetal growth and health behaviors on the risk of CVDs. The Cox proportional hazard assumption was tested by including in the model an interaction term between our exposures and time, and there was no evidence for non-proportionality. The end of follow-up was defined as the time for first diagnosis of CVDs, death, or end of follow-up, whichever occurred first. Attained age was considered as the underlying time scale.

The hazard ratios (HR) and 95% confidence intervals (CI) were estimated from an unadjusted and two adjusted models. When studying the association of fetal growth separately or jointly with health behaviors with CVDs, we adjusted for birth year, sex, education, drinking, maternal CVDs, and if appropriate, for BMI, smoking, fruit intake and physical activity. When studying the association between each individual health behavior and CVDs, we adjusted for age at baseline, sex, education, drinking, maternal CVDs as well as the other three health behavioral components. When studying the association between health behavioral profile and CVDs, we adjusted for age at baseline, sex, education, drinking, and maternal CVDs.

SAS 9.4 (SAS Institute, 2013, Cary, North Carolina, United States of America) was used for the analysis.

Results

Characteristics of study participants

The characteristics of participants born with SGA, AGA and LGA according to the study variables are shown in Table 1. The gestational age ranged between 26 and 45 weeks. Compared with those born AGA, persons born SGA had lower birthweight ($P < .001$) and older age at the baseline SPHC assessment ($P = .006$), were more likely to be women, never drinkers, and to have an ideal BMI (all $P < .001$). There were no significant differences among the three groups in gestational age, maternal CVDs, baseline education, smoking, physical activity, fruit consumption, and behavioral health metrics.

Fetal growth and risk of CVDs

A total of 429 participants were diagnosed with CVDs, and the mean age at the first CVDs diagnosis was 27.6 years. Compared to individuals born AGA, individuals born SGA had a higher risk of CVDs, with the adjusted HR (95% CI) being 1.88 (1.44, 2.47). Participants born LGA did not have an increased risk of CVDs, and adjusted HR (95% CI) was 0.76 (0.55, 1.06) (Table 2).

Health behaviors and the risk of CVDs

Individuals with a poor BMI had a higher risk of CVDs than those with an ideal BMI, and the adjusted HR (95% CI) was 3.28 (2.26, 4.76). There were no significant associations between the other three health behavioral components and the risk of CVDs (Table 3). Compared to individuals with ideal health behavioral profile, those with poor health behaviors had a higher risk of CVDs with adjusted HR (95% CI) being 1.42 (1.00, 2.03), whereas those with intermediate health behaviors did not have an increased risk of CVDs (Table 3).

Joint effect between fetal growth and health behaviors on the risk of CVDs

Compared to participants born AGA and having ideal health behaviors before midlife, those born SGA and having poor health behaviors had an increased risk of CVDs, and the adjusted HR (95%CI) was 3.58 (1.95, 6.56) (Table 4). The association with CVDs was not significant among those born SGA and having intermediate [HR (95% CI): 1.45 (0.77, 2.74)] or ideal health behaviors [HR (95% CI): 1.61 (0.76, 3.41)]. The interactive effect between fetal growth and health behaviors on the risk of CVDs was not statistically significant either ($P = .11$).

Table 1
Characteristics of study participants from the Stockholm Public Health Cohort (2002–2018) by birthweight for gestational age (n = 15,618).

Characteristics	Total (N = 15,618)	Exposure group			P[†]
		SGA (n = 1361)	AGA (n = 12,158)	LGA (n = 2099)	
Age at entry (years), mean (SD)	26.5 (5.4)	27.0 (5.4)	26.5 (5.4)	26.5 (5.4)	.006
Female, n (%)	12,158 (77.9)	938 (68.9)	7125 (58.6)	924 (44.0)	<.001
Early life characteristics					
Gestational age, mean (SD)	39.6 (1.8)	39.5 (2.0)	39.6 (1.8)	39.6 (1.9)	.12
Birthweight (kg), mean (SD)	3.5 (0.5)	2.6 (0.4)	3.4 (0.4)	4.2 (0.4)	<.001
Maternal CVDs, n (%)	197 (1.3)	16 (1.2)	159 (1.3)	22 (1.1)	.59
Adulthood characteristics					
Baseline education, n (%)					.06
Compulsory school	2243 (14.4)	206 (15.1)	1726 (14.2)	311 (14.8)	
Upper secondary school	5840 (37.4)	508 (37.3)	4546 (37.4)	786 (37.5)	
University and above	5499 (35.2)	437 (32.1)	4319 (35.5)	743 (35.4)	
Missing[*]	2036 (13.0)	210 (15.4)	1567 (12.9)	259 (12.3)	
Drinking, n (%)					<.001
At least once a month	10,601 (68.0)	809 (59.4)	8265 (68.0)	1527 (72.8)	
1–6 times per year	3730 (23.9)	416 (30.6)	2904 (23.9)	410 (19.5)	
Never	1287 (8.2)	136 (10.0)	989 (8.1)	162 (7.7)	
Body mass index, n (%)					<.001
Poor	890 (5.7)	79 (5.8)	669 (5.5)	142 (6.8)	
Intermediate	3092 (19.8)	247 (18.2)	2354 (19.4)	491 (23.4)	
Ideal	11,636 (74.5)	1035 (76.1)	9135 (75.1)	1466 (69.8)	
Smoking, n (%)					.05
Poor	1792 (11.5)	182 (13.4)	1396 (11.5)	214 (10.2)	
Intermediate	1154 (7.44)	107 (7.9)	896 (7.4)	151 (7.2)	
Ideal	12,672 (81.1)	1072 (78.8)	9866 (81.2)	1734 (82.6)	
Physical activity, n (%)					.07
Poor	4274 (27.4)	403 (29.6)	3283 (27.0)	588 (28.0)	
Intermediate	6202 (39.7)	547 (40.2)	4855 (39.9)	800 (38.1)	
Ideal	5142 (32.9)	411 (30.2)	4020 (33.1)	711 (33.9)	
Fruits consumption, n (%)					.67
Poor	1741 (11.2)	152 (11.2)	1355 (11.1)	234 (11.2)	
Intermediate	7798 (49.9)	654 (48.1)	6094 (50.1)	1050 (50.0)	
Ideal	6079 (38.9)	555 (40.8)	4709 (38.7)	815 (38.8)	
Behavioral health metric score, mean (SD)	5.7 (1.5)	5.7 (1.6)	5.7 (1.5)	5.7 (1.6)	.18
Behavioral health metrics, n (%)					.06
Poor (≤4)	3086 (19.8)	282 (20.7)	2356 (19.4)	448 (21.3)	
Intermediate (5–6)	7198 (46.1)	648 (47.6)	5619 (46.2)	931 (44.4)	
Ideal (≥7)	5334 (34.2)	431 (31.7)	4183 (34.4)	720 (34.3)	

Abbreviations: AGA, appropriate for gestational age; CVD, cardiovascular disease; LGA, large for gestational age; SGA, small for gestational age.

[*] Those with missing data on education were considered as a separate group in the subsequent multivariate analysis.

[†] The P-values were from ANOVA analysis in case of continuous variables and from chi-square tests in case of categorical variables.

Table 2
Hazard ratios and 95% confidence intervals for cardiovascular diseases according to fetal growth (n = 15,618).

Fetal growth	Number of participants	Number of CVD cases	Hazard ratio (95% confidence interval)	
			Unadjusted	Adjusted[*]
AGA	12,158	319	Reference	Reference
SGA	1361	66	1.80 (1.38, 2.34)	1.88 (1.44, 2.47)
LGA	2099	44	0.87 (0.64, 1.20)	0.76 (0.55, 1.06)

Abbreviations: AGA, appropriate for gestational age; CVD, cardiovascular disease; LGA, large for gestational age; SGA, small for gestational age.

[*] The model was adjusted for birth year, sex, education, drinking, body-mass index, smoking, fruit intake, physical activity and maternal cardiovascular diseases.

Discussion

In this cohort study, we found that impaired fetal growth was associated with an increased risk of CVDs in young adulthood. In addition, compared to study participants born with normal fetal growth and having ideal health behaviors, those born SGA and having poor health behaviors in adulthood had an increased risk of CVDs.

Our findings that impaired fetal growth was associated with an increased risk of CVDs in young adulthood are consistent with results of several previous studies [8,9,20]. A meta-analysis of 135 studies showed that birthweight was associated with CVD risk in a J-shaped manner [21]. In contrast, a population-based birth cohort study in Sweden found that birthweight was not associated with CVDs neither before nor after adjusting for gestational age [22]. Most of the earlier studies regarding the link between fetal growth

Table 3
Hazard ratios and 95% confidence intervals for cardiovascular diseases by individual and composite behavioral health metrics (n = 15,411).

Behavioral health metrics	Number of participants	Number of CVD cases	Hazard ratio (95% confidence interval)	
			Unadjusted	Adjusted*
Body mass index				
Poor	878	37	2.91 (2.02, 4.19)	3.28 (2.26, 4.76)
Intermediate	3034	43	0.98 (0.70, 1.39)	1.11 (0.78, 1.57)
Ideal	11,499	142	Reference	Reference
Smoking				
Poor	1771	32	1.43 (0.98, 2.11)	1.18 (0.79, 1.75)
Intermediate	1142	14	0.89 (0.51, 1.53)	0.71 (0.41, 1.23)
Ideal	12,498	176	Reference	Reference
Physical activity				
Poor	4213	67	1.01 (0.71, 1.45)	1.01 (0.70, 1.45)
Intermediate	6117	95	1.04 (0.75, 1.44)	1.12 (0.81, 1.56)
Ideal	5081	60	Reference	Reference
Fruits consumption				
Poor	1722	23	0.89 (0.56, 1.43)	0.73 (0.45, 1.17)
Intermediate	7686	113	1.02 (0.77, 1.35)	0.95 (0.71, 1.27)
Ideal	6003	86	Reference	Reference
Behavioral health metrics				
Poor	3043	65	1.66 (1.18, 2.35)	1.42 (1.00, 2.03)
Intermediate	7100	94	0.98 (0.72, 1.36)	0.95 (0.69, 1.31)
Ideal	5268	63	Reference	Reference

Abbreviations: CVD, cardiovascular disease.
* The model was adjusted for age at baseline, sex, education, drinking and maternal cardiovascular diseases.

Table 4
Hazard ratios and 95% confidence intervals for cardiovascular diseases according to fetal growth and health behaviors (n = 15,411).

Combinations of fetal growth and health behaviors	Number of participants	Number of CVD cases	Hazard ratio (95% confidence interval)	
			Unadjusted	Adjusted*
AGA and poor health behavior	2325	45	1.61 (1.07, 2.42)	1.40 (0.92, 2.14)
AGA and intermediate health behavior	5545	72	1.02 (0.71, 1.48)	1.03 (0.71, 1.49)
AGA and ideal health behavior	4133	47	Reference	Reference
SGA and poor health behavior	274	14	3.98 (2.19, 7.23)	3.58 (1.95, 6.56)
SGA and intermediate health behavior	635	12	1.42 (0.75, 2.68)	1.45 (0.77, 2.74)
SGA and ideal health behavior	420	8	1.60 (0.75, 3.38)	1.61 (0.76, 3.41)
LGA and poor health behavior	444	6	1.07 (0.46, 2.50)	0.80 (0.32, 2.04)
LGA and intermediate health behavior	920	10	0.87 (0.44, 1.71)	0.86 (0.43, 1.71)
LGA and ideal health behavior	715	8	1.04 (0.49, 2.19)	1.03 (0.49, 2.18)

Abbreviations: AGA, appropriate for gestational age; CVD, cardiovascular disease; LGA, large for gestational age; SGA, small for gestational age.
* The model was adjusted for birth year, sex, education, drinking and maternal cardiovascular diseases.

and CVDs used birthweight but not SGA as we did in this study. Although some of the previous studies adjusted for gestational age, the results may be still different from those of our study. The differences in covariates included in the analysis (such as physical exercise level, socioeconomic status, and diet) may also contribute to discrepancies in findings across studies.

Studies investigating the joint effect of fetal growth and health behaviors on the risk of CVDs later in life are sparse. Three previous studies documented an additive effect of low birthweight and unhealthy lifestyle on the risk of type II diabetes [12], hypertension [13] or a composite endpoint of cardio metabolic diseases [15]. We are aware of only one previous study that investigated the synergy between low birthweight and poor lifestyles in adulthood to on the risk of coronary heart disease [16]. Its findings that the risk of CVDs was highest in those born with impaired fetal growth and having poor health behaviors in adulthood are in line with our results.

There are several potential mechanisms by which fetal growth may increase the risk of CVDs. Studies showed high levels of oxidative stress [23] and inflammation [24] in these neonates. Alterations in fetal epigenomics [25], lipid profile [26], and gut microbiota [28] in these infants may further contribute to an increased risk of CVDs later in life. Furthermore, birthweight-for-gestational age was associated with DNA methylation at birth and in childhood [27]. The biological mechanisms underlying the association of behavioral health metrics and CVDs are not entirely clear. Recent data suggested that the harmful effects of health behaviors on CVDs may be mediated by its adverse effects on subclinical disease [28,29], cardiovascular structure [30,31] and the adverse changes in metabolic, inflammatory, hemostatic or other cardiovascular biomarkers [10]. A healthy lifestyle may compensate for the adverse effect of impaired fetal growth on CVDs through cardiovascular remodeling [11,32] or lowering the concentrations of certain cardiovascular biomarkers [10]. As the possible mechanisms underlying these findings are not known, further studies that take into account the cardiometabolic biomarkers as well as lifestyle factors from a life-course perspective are needed.

Early-life growth has not yet been considered in the clinical management or prevention of CVDs. In contrast, health behavioral risk factors later in life have received substantial attention in cardiovascular prevention. Our findings showed that those with impaired fetal growth, and especially if combined with poor health behaviors in adulthood, had significantly higher risk of CVDs. These findings imply the importance of an early and life-course preven-

tion of CVDs and that counseling regarding health behaviors may be considered for those with impaired fetal growth for reducing their future risk of CVDs.

Strengths and limitations

The main strength of the study is the population-based longitudinal database with linkage to Swedish registers. In addition, the study questionnaire was consistent across waves making the data reliable and comparable across sub-cohorts. However, there might be some limitations. The first limitation is related to the single time-point of adult health behaviors without considering the changes of health behaviors during follow-up period. Future studies should take into consideration the variations of health behaviors within the long time-interval periods. Secondly, the health behaviors were self-reported, which might lead to an underestimation of the unhealthy lifestyles and subsequently an underestimation of the studied association. Thirdly, since our analyses are secondary analyses of a pre-existing data source, we could only use a modified definition of behavioral health metrics. For example, our dietary data is not comprehensive, which may underestimate the actual effect of a healthy diet with CVDs. Fourthly, CVDs diagnoses were identified from a patient register and a death register, which generally contain the more severe CVD cases, that is require hospitalization or lead to death. We were not able to include certain milder CVDs or subclinical CVDs. Thus, the associations observed in our study might be underestimated. Fifthly, the statistical power was limited in some subgroups when studying the joint effect between SGA/LGA and health behaviors. Similarly, the statistical power did not allow us to study specific CVDs. Finally, we cannot rule out the possibility of residual confounding. For example, education was used as a proxy for socioeconomic status, but other socioeconomic measures such as occupation and family income might also be confounders in the associations between fetal growth, health behaviors, and CVDs. Other candidates may include familial genetics and environmental and health-related risk factors.

Conclusions

We found that impaired fetal growth was associated with and increased risk of CVDs in adulthood. The risk of CVDs was highest in study participants with impaired fetal growth and poor health behaviors in adulthood. This study emphasizes the importance of life-course prevention of CVDs.

Author contributions

YL designed the study. MM performed statistical analysis and wrote the manuscript. JM, KL, and YL interpreted the results and revised the manuscript. All authors read final manuscript and approved the submission.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.annepidem.2022.12.013.

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