



Trajectories of cardiovascular risk predict pregnancy outcomes: The Bogalusa Heart Study and the Cardiovascular Risk in Young Finns Study

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Abstract

Background: Life course patterns of change in risk—trajectories—affect health.

Objectives: To examine how trajectories of cardiovascular risk factors are associated with pregnancy and birth outcomes.

Methods: Data from two cohort studies participating in the International Childhood Cardiovascular Consortium—The Bogalusa Heart Study (BHS; started in 1973, $N=903$ for this analysis) and the Cardiovascular Risk in Young Finns Study (YFS; started in 1980, $N=499$) were used. Both followed children into adulthood and measured cardiovascular risk factors, including body mass index (BMI), systolic and diastolic blood pressure (SBP/DBP), total, lipoprotein (LDL)- and high density lipoprotein (HDL)-cholesterol and serum triglycerides. Discrete mixture modelling was used to divide each cohort into distinct trajectories according to these risk factors from childhood to early adulthood, and these groups were then used to predict pregnancy outcomes including small for gestational age (SGA; <10th study-specific percentile of gestational age by sex), preterm birth (PTB; <37 weeks' gestation), hypertensive disorders of pregnancy (HDP) and gestational diabetes mellitus (GDM), with control for age at baseline and at first birth, parity, socioeconomic status, BMI and smoking.

Results: The models created more trajectories for BMI, SBP and HDL-cholesterol in the YFS than in BHS, for which three classes generally seemed to be sufficient to represent the groups in the population across risk factors. In BHS, the association between the higher and flatter DBP trajectory and PTB was aRR 1.77, 95% confidence interval [CI] 1.06, 2.96. In BHS the association between consistent total cholesterol

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and PTB was aRR 2.16, 95% CI 1.22, 3.85 and in YFS the association between elevated high trajectory and PTB was aRR 3.35, 95% CI 1.28, 8.79. Elevated-increasing SBP was associated with a higher risk of GH in BHS and increasing or persistent-obese BMI trajectories were associated with GDM in both cohorts (BHS: aRR 3.51, 95% CI 1.95, 6.30; YFS: aRR 2.61, 95% CI 0.96, 7.08).

Conclusions: Trajectories of cardiovascular risk, particularly those that represent a consistent or more rapid worsening of cardiovascular health, are associated with a higher risk of pregnancy complications.

KEYWORDS

birthweight, blood pressure, life course, lipids, pregnancy complications, trajectory

1 | BACKGROUND

Increasing interest focuses on life course predictors of health. While a single time point in early life is sometimes critical, there is also interest in how risk changes across time, and how the patterns of change in risk—trajectories—affect health. For instance, the International Cardiovascular Cohort Consortium (i3C) found that childhood risk factors predict adulthood cardiovascular outcomes¹ and that individuals with persistently elevated blood pressure from childhood to adulthood had increased risk of atherosclerosis, but risk was reduced if the elevated blood pressure during childhood resolved by adulthood. One analytic method is to examine a priori hypothesized changes over time, for instance, examining people with consistently increasing or decreasing levels of some factor. In some cases, however, groups with common experiences are extracted from the data. In the Dunedin Multidisciplinary Health and Development Study, latent trajectories of systolic blood pressure were identified,² and blood pressure trajectories leading to prehypertension or hypertension were associated with other cardiovascular risk indicators. The South African Birth to 20 study found three distinct trajectories of BMI in boys and four in girls. Children in the early onset obesity or overweight BMI trajectories were more likely to have high blood pressure in late adolescence.³ The Bogalusa Heart Study (BHS) found five trajectories of life course cardiovascular risk. Those who started with relatively high cardiovascular risk but had lower Framingham risk scores as adults had lower risks of diabetes and lower BMIs, better carotid intima-media thickness and pulse wave velocity than those who were in the high-risk group in both time periods. Children who improved their relative cardiovascular risk over the life course achieved better midlife atherosclerotic health despite maintaining relatively poor metabolic health through adulthood.⁴

These methods can also be applied to understanding the relationship between early life and pregnancy health.⁵ Preconception cardiovascular and metabolic health predict complications of pregnancy and adverse birth outcomes.^{6–9} While most previous studies address the short-term preconception period, lifetime experience also determines health status on entering pregnancy, and may

Synopsis

Study question

How does pre-pregnancy trajectory of cardiovascular health predict pregnancy complications and birth outcomes?

What's already known

Single pre-pregnancy measures of cardiovascular health have been associated with pregnancy outcomes.

What this study adds

In two cohorts with diverse populations, the steepest increase of blood pressure and cholesterol were also associated with preterm birth. Steeper increases in BMI were also associated with gestational diabetes.

directly indicate or affect health during pregnancy. A few studies have examined this lifetime experience with respect to pregnancy, particularly as relates to hypertensive disorders of pregnancy (HDP). An analysis of the trajectories in the 5 years prior to pregnancy among Chicago women found those in the overweight/prehypertensive groups were more likely to develop HDP.¹⁰ Increase in weight over time was associated with increased risk of HDP in Australian women.¹¹ A Canadian study found that women who developed gestational diabetes mellitus (GDM) during pregnancy had a previously higher annual rate of change in HbA1c, glucose and triglycerides, and a greater decrease in high-density lipoprotein (HDL).¹² We are not aware of studies that have associated preconception trajectories of cardiometabolic health with birth outcomes. In the BHS, an overall measure of childhood blood pressure was associated with higher risk of preterm birth,¹³ but trajectory was not assessed.

In this study, we examine how life-long trajectories of cardiovascular risk factors predict pregnancy outcomes in two independent cohorts. We hypothesized that a steeper worsening of cardiovascular risk factors would be associated with an increased risk of adverse pregnancy and birth outcomes.

2 | METHODS

Data from two cohort studies participating in the i3C¹⁴ were used. The BHS began in 1973, examining cardiovascular risk factors in children.¹⁵ Cross-sectional and longitudinal studies have been conducted regularly since then; more recent studies have addressed the midlife cardiovascular, cognitive and physical function. The Bogalusa Babies study interviewed women ($n=1803$) and linked them to vital statistics and medical records where available.¹⁶ The Cardiovascular Risk in Young Finns study (YFS) began in 1980 with children aged 3–18.¹⁷ They have been followed at regular intervals since then, with the most recent follow-up in 2018–2020. Similar to BHS, the primary focus of the YFS has been on cardiovascular risk factors and outcomes since childhood, while new topics such as cognitive function and fatty liver have been introduced in the latest follow-ups.

2.1 | Exposure

Trajectories and change in BMI, systolic blood pressure (SBP), diastolic blood pressure (DBP), serum total cholesterol, serum HDL- and low-density lipoprotein (LDL)-cholesterol and triglycerides were examined as predictors.

2.1.1 | BMI

At each BHS visit (up to 23 total visits), replicate measures of height and weight, using a stadiometer and balance beam metric scale, were obtained. At each YFS visit, unclothed weight was measured to the nearest 0.1 kg using digital scales, and standing height was measured to the nearest 0.1 cm using a wall-mounted stadiometer. BMI (kg/m^2) was calculated using mean values.

2.1.2 | Systolic and diastolic blood pressure (SBP/DBP)

In BHS, blood pressure levels were measured on the right arm of subjects in a relaxed, sitting position by two trained observers (three replicates each). The SBP and DBP were recorded using a mercury sphygmomanometer. In YFS, blood pressure was measured in a sitting position after 5 min rest, using a random zero sphygmomanometer (Hawksley & Sons Ltd). The fifth Korotkoff phase was used as the sign of diastolic blood pressure. Readings were performed at least three times on each subject, and the mean used for analysis.

2.1.3 | Lipids

In BHS, fasting blood samples were drawn for lipids analysis. Prior to 1987, serum total cholesterol levels were determined by a Technicon AutoAnalyzer II (Technicon Instrument). From 1987 to 1996, cholesterol levels were determined by enzymatic procedures on the Abbott VP instrument (Abbott Laboratories) and on the Hitachi 902 Automatic Analyser (Roche Diagnostics, Indianapolis, IN) after 1996. Both chemical and enzymatic procedures met the performance requirements of the Lipid Standardisation Programme of the Centers for Disease Control and Prevention, which has routinely monitored the precision and accuracy of cholesterol and triglyceride measurements since 1973. At each YFS visit, a fasting blood draw was conducted. Cholesterol and other lipids were measured at each visit by the enzymatic cholesterol esterase-cholesterol oxidase method (Cholesterol reagent). As changes in determination methods occurred, the values were standardised to be comparable between the study years.^{18,19}

2.2 | Outcomes

2.2.1 | BHS

1803 women were interviewed about their reproductive history, which formed the baseline group for this analysis. Of these women, 381 also had medical records data, and 1026 were matched to vital records data on their births (the sample included both multiparae and nulliparous women). Outcomes assessed were: small for gestational age (SGA; <10th sex-specific percentile of birthweight by gestational week for all births in the study), preterm birth (PTB; <37 weeks' gestation), gestational hypertension (GH) and gestational diabetes mellitus (GDM), all at any pregnancy. Maternal report of birthweight in babies compared with vital statistics was excellent; mean and median differences were statistically indistinguishable from 0 and kappa for categorised birthweight was >0.9; mean difference for gestational age was 0.01 week.²⁰ Therefore, self-report data of these outcomes was used. As HDP and GDM are under-reported in vital statistics,²¹ these complications were compared only to medical records for the women who had them available ($n=381$). For GH, kappa was 0.65 and 0.73 when clustering was accounted for, depending on how incomplete medical records were treated. For GDM, kappa for agreement was between 0.73 and 0.80 (depending on how incomplete medical records were treated) when clustering was not accounted for, and 0.84–0.92 when clustered kappas²² were calculated. This level or higher quality of recall has been shown for GDM in other studies as well (specificity = 98%, sensitivity = 92%).²³ For pregnancy complications, if more than one data source was available, medical records were used unless information was available from BHS that contradicted them (i.e. if BHS exam records indicated pre-pregnancy hypertension or diabetes, participants were not considered at risk for GH or GDM). The number of self-reported pre-eclampsia cases was implausible, so this outcome was not examined.

The Bogalusa Heart Study (n = 903)		The Young Finns Study (n = 499)	
	N (%)		N (%)
BMI		BMI group	
Slow increase	563 (62.4)	Stable slim	208 (41.7)
Moderate increase	255 (28.2)	Stable normal	207 (41.5)
Steepest increase	85 (9.4)	Progressively overweight	66 (13.2)
		Persistent increasing obese	18 (3.6)
Systolic blood pressure group		Systolic blood pressure group	
Slow increase	304 (33.7)	Low-stable	203 (43.4)
Moderate increase	476 (52.7)	Moderate-increasing	241 (51.5)
Steepest increase	123 (13.6)	Elevated-increasing	24 (5.1)
Diastolic blood pressure group		Diastolic blood pressure group	
Rising	232 (25.7)	Low-stable	241 (51.8)
Starts higher, rising	564 (62.5)	Normal-stable	224 (48.2)
Higher and flatter	107 (11.9)		
Cholesterol		Cholesterol group	
Consistently low	436 (48.3)	Low-stable	106 (21.8)
Middle	419 (46.4)	Elevated-stable	233 (47.8)
Consistently high	48 (5.3)	High-stable	120 (24.6)
		Elevated-high	28 (5.8)
LDL cholesterol		LDL cholesterol group	
Consistently low	389 (43.1)	Low-stable	78 (16.2)
Higher but flat	429 (47.5)	Normal-stable	212 (43.9)
Increasing	85 (9.4)	Elevated-stable	149 (30.9)
		High-stable	44 (9.1)
HDL cholesterol		HDL cholesterol group	
Consistently low	138 (15.3)	Low-stable	150 (30.7)
Medium/flat	629 (69.7)	Normal-stable	272 (55.6)
Declining	136 (15.1)	Elevated-stable	67 (13.7)
Triglycerides		Triglycerides group	
Consistently low	173 (19.2)	Low-stable	441 (90.4)
Moderate and flat	705 (78.1)	Normal-increasing	47 (9.6)
Steep rise	25 (2.8)		

TABLE 1 Trajectories of pre-pregnancy risk factors.

2.2.2 | YFS

Data from the cardiovascular study cohort were merged with the Finnish national birth registry. The birth registry contains information on every birth in Finland since 1987, including data on the pregnancy. Of the 1832 women originally enrolled in the Cardiovascular Risk in YFS, 1323 had a pregnancy in the birth registry; 1316 had at least one singleton in the registry. The birth registry data include direct reports of some medical information, as well as up to 10 spaces to record diagnoses using ICD-9 and ICD-10 codes.

Outcomes analysed were: SGA, PTB, HDP and GDM. SGA was defined as <10th sex-specific percentile of birthweight by gestational week for all births in the study; preterm birth was defined as

birth at <37 weeks' gestation. Overall HDP were defined as any hypertensive disorder specified as having begun during pregnancy or an eclamptic disorder (ICD-9 codes 6423–6427, ICD-10 codes O12–O15). Gestational diabetes was defined as failing a glucose tolerance test, ICD-9 code 6488 or ICD-10 code O24.

2.3 | Statistical analysis

2.3.1 | BHS

The exposures (BMI, SBP, DBP, cholesterol, LDL-cholesterol, HDL-cholesterol and triglycerides) were first used to build a discrete

mixture model to separate the population into subpopulations. Each participant was then identified by their respective class. We selected a class structure and number that minimised the Bayesian information criterion (BIC) and the Likelihood test statistic and ensured that each class comprised at least 5% of the sample. We applied group-based trajectory modelling (using SAS PROC TRAJ [13]) to estimate distinct trajectories of individual risk factors from childhood to adulthood. We tested models using 3–5 distinct groups and selected the model with the lowest absolute BIC value. This analysis was performed limited to visits before the pregnancy. The classes were modelled as predictors, with reproductive outcomes as the dependent variable. The number of trajectories that was optimal varied by risk factor and study (Table 1, Table S1, Figures S1 and S2).

2.3.2 | Cardiovascular Risk in Young Finns Study

A detailed description of the creation of the cardiovascular risk factor trajectories has been reported elsewhere.²⁴ Heterogeneity in the longitudinal development of cardiovascular risk factors was

investigated using group-based trajectory modelling performed with SAS PROC TRAJ procedure⁹ to identify subgroups of YFS participants who shared similar underlying trajectories between ages 9 and 49 years. Participants who used antihypertensive ($N=145$ women) or dyslipidemia medication ($N=32$ women) were excluded from the cardiovascular risk factor-specific trajectory modelling analyses. All other participants were included in trajectory analyses but, for reliability, a minimum of three measurements was required with at least one being from childhood and adolescence (ages 9–18 years) and at least one from adulthood (ages 21–49 years). BICs were checked and the mean posterior probability for each group was >0.70 . Frequency of $>5\%$ was preferred for the size of trajectory groups. Both overall and sex-specific models were applied; as this analysis is limited to women, the sex-specific models are used. This analysis was performed limited to visits before the pregnancy.

Once the trajectories were calculated for the two cohorts, similar analytic strategies were followed. Demographic and health characteristics of the final trajectory groupings were tabulated and compared using Pearson's chi-square tests (categorical variables) or analysis of variance (ANOVA) (continuous variables). Next, multivariable

TABLE 2 Description of the analytic cohorts (women with pregnancies).

	Bogalusa Heart Study		Young Finns Study	
	Mean (SD)	Min, max	Mean (SD)	Min, max
Age at first visit	8.5 (2.9)	3.4, 15.6	12.0 (5.1)	3.0, 18.0
Age at last included visit	30.4 (11.5)	7.7, 51.0	39.0 (5.1)	30.0, 45.0
Age at last visit prior to first pregnancy	19.2 (5.3)	7.7, 39.0	27.2 (4.4)	15.0, 39.0
BMI at visit closest to age 18	22.2 (4.6)	12.3, 44.7	21.1 (2.3)	14.8, 29.3
BMI at last included visit	23.0 (5.2)	12.6, 53.9	23.2 (3.8)	17.1, 41.3
SBP at visit closest to age 18	109.0 (8.8)	81.7, 145.3	116.6 (10.7)	90.0, 155.3
SBP at last included visit	108.2 (8.7)	81.7, 145.3	113.8 (12.5)	84.7, 199.3
Total cholesterol at visit closest to age 18	4.2 (0.8)	2.2, 9.0	5.1 (1.0)	3.0, 10.4
Total cholesterol at last included visit	4.4 (0.9)	2.5, 8.4	5.0 (0.8)	3.0, 8.0
	Median (IQR)	Min, max	Median	Min, max
Total number of visits	6 (4, 9)	3, 14	5 (4, 5)	2, 7
Total number of visits <18 years	4 (3, 4)	1, 8	3 (1, 4)	1, 5
Education	N (%)		N (%)	
<High school	58 (6.4)		97 (21.3)	
High school	250 (27.7)		150 (33.0)	
Associates or some college	295 (32.7)		57 (12.5)	
College+	299 (33.2)		151 (33.2)	
Race			a	
Black	327 (36.2)			
White	576 (63.8)			
Pregnancy outcomes (at any pregnancy)				
Small-for-gestational-age	155 (17.2)		82 (16.3)	
Preterm birth	154 (17.1)		50 (9.9)	
Gestational hypertension	81 (9.9)		20 (4.0)	
Gestational diabetes	96 (10.6)		63 (12.5)	

^aNot collected in YFS.

TABLE 3 Trajectories of risk factors and birth outcomes, women in the Bogalusa Heart Study (n = 903).

	Small for gestational age		Preterm birth	
	Adjusted for age at baseline	Adjusted for age at baseline, BMI, parity, SES, smoking, age at first birth	Adjusted for age at baseline	Adjusted for age at baseline, BMI, parity, SES, smoking, age at first birth
	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)
BMI^a				
Slow increase	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Moderate increase	0.77 (0.54, 1.08)	0.72 (0.49, 1.05)	0.97 (0.69, 1.35)	0.96 (0.67, 1.38)
Steepest increase	0.81 (0.48, 1.38)	0.72 (0.40, 1.30)	1.21 (0.77, 1.91)	1.23 (0.74, 2.05)
Systolic blood pressure group				
Slow increase	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Moderate increase	1.00 (0.73, 1.38)	1.16 (0.81, 1.66)	1.00 (0.72, 1.39)	1.05 (0.72, 1.52)
Steepest increase	1.15 (0.74, 1.79)	1.47 (0.88, 2.44)	1.45 (0.96, 2.18)	1.58 (0.98, 2.57)
Diastolic blood pressure group				
Rising	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Starts higher, rising	0.82 (0.59, 1.12)	0.96 (0.67, 1.38)	0.98 (0.70, 1.39)	1.04 (0.71, 1.53)
Higher and flatter	0.86 (0.52, 1.41)	1.18 (0.67, 2.08)	1.61 (1.04, 2.50)	1.77 (1.06, 2.96)
Cholesterol				
Consistently low	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Middle	0.92 (0.69, 1.25)	1.00 (0.72, 1.40)	1.28 (0.94, 1.73)	1.32 (0.94, 1.85)
Consistently high	1.30 (0.74, 2.27)	1.46 (0.77, 2.76)	2.15 (1.33, 3.47)	2.16 (1.22, 3.85)
LDL cholesterol				
Consistently low	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Higher but flat	0.88 (0.65, 1.20)	0.99 (0.70, 1.39)	1.20 (0.88, 1.65)	1.24 (0.88, 1.76)
Increasing	1.17 (0.74, 1.87)	1.34 (0.79, 2.27)	1.55 (0.98, 2.44)	1.59 (0.95, 2.67)
HDL cholesterol				
Consistently low	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Medium/flat	1.05 (0.70, 1.58)	0.97 (0.61, 1.53)	0.87 (0.59, 1.27)	0.81 (0.52, 1.25)
Declining	0.98 (0.57, 1.69)	0.94 (0.51, 1.71)	0.87 (0.52, 1.46)	0.85 (0.48, 1.52)
Triglycerides				
Consistently low	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Moderate and flat	1.05 (0.72, 1.53)	1.00 (0.65, 1.52)	0.66 (0.48, 0.91)	0.61 (0.42, 0.89)
Steep rise	1.46 (0.67, 3.17)	1.62 (0.66, 3.94)	0.86 (0.38, 1.97)	0.89 (0.35, 2.27)

^aBMI group not adjusted for BMI in multivariable models.

generalised linear modelling were performed (log-binomial or robust log-Poisson models).²⁵ Trajectory assignment probabilities served as the independent variables in this model, while pregnancy outcomes were used as the dependent variables. The covariates controlled for were slightly different due to differences in data collected across studies. For BHS, models controlled for age at first pregnancy, age at last pregnancy, total births, education, smoking and lifetime BMI (for non-BMI exposures), estimated with area under the curve.²⁶ For YFS, models controlled for age at baseline, age at first birth, total births, socioeconomic status, smoking in 2001 and BMI in 2001. These covariates were chosen as likely to be associated with the outcome and exposure, and not on the causal pathway. Interactions with parity were examined to determine whether the associations with exposure trajectories differed in those who had more births.

2.3.3 | Missing data

Multiple imputation was used to address missing covariate data (321 observations from BHS and 127 observations in YFS with missing data on at least one covariate; 50 imputations with Markov chain Monte Carlo methods; more details in the Appendix S1 and Figure S1). The adjusted models use the multiply imputed data.

2.4 | Ethics approval

The Bogalusa Heart Study and Bogalusa Babies studies were approved by the Tulane University Institutional Review Board. The Young Finns study was approved by the local ethical committees (1st Ethical

Committee of the Hospital District of Southwest Finland, the Regional Ethics Committee of the Expert Responsibility area of Tampere University Hospital, Helsinki University Hospital Ethical Committee of Medicine, The Research Ethics Committee of the Northern Savo Hospital District and Ethics Committee of the Northern Ostrobothnia Hospital District) of the participating sites (ETMK: 88/180/2010).

3 | RESULTS

The analysis was limited to women with pregnancies and descriptions of samples for the two cohorts are provided in Table 2. The

age at the last included visit was higher for YFS participants (mean 37.7) than BHS (mean 31.2), and the age range was narrower in YFS than in BHS. The models created more trajectories for BMI, SBP and HDL-cholesterol in the YFS (and fewer for triglycerides) than in BHS, for which three classes generally seemed to be sufficient to represent the groups in the population across risk factors. For BHS, three classes generally seemed to be sufficient across risk factors. In both cohorts, BMI and SBP were likely to increase substantially, at least in some groups, while cholesterol was more stable (Table 1, Figures S1 and S2).

Higher and more strongly worsening risk factors were associated with birth outcomes (Tables 3 and 4). The elevated-increasing

TABLE 4 Trajectories of risk factors and birth outcomes, women in the Young Finns Study (n = 499).

	Small for gestational age		Preterm birth	
	Adjusted for age at baseline	Adjusted for age at baseline, BMI, parity, SES, smoking, age at first birth	Adjusted for age at baseline	Adjusted for age at baseline, BMI, parity, SES, smoking, age at first birth
	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)
BMI group				
Stable slim	1.15 (0.75, 1.77)	1.15 (0.72, 1.85)	1.24 (0.72, 2.13)	1.20 (0.67, 2.13)
Stable normal	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Progressively overweight	0.98 (0.51, 1.88)	0.93 (0.46, 1.90)	0.15 (0.02, 1.09)	0.14 (0.02, 1.02)
Persistent increasing obese	0.71 (0.18, 2.80)	0.73 (0.17, 3.08)	1.04 (0.27, 4.10)	1.16 (0.27, 5.02)
Systolic blood pressure group				
Low-stable	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Moderate-increasing	1.03 (0.67, 1.59)	1.02 (0.63, 1.66)	1.39 (0.76, 2.57)	1.52 (0.79, 2.91)
Elevated-increasing	1.90 (0.95, 3.80)	2.12 (0.90, 5.00)	1.73 (0.54, 5.57)	2.45 (0.68, 8.85)
Diastolic blood pressure group				
Low-stable	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Normal-stable	0.80 (0.53, 1.21)	0.82 (0.51, 1.32)	1.02 (0.58, 1.81)	1.15 (0.62, 2.13)
Cholesterol group				
Low-stable	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Elevated-stable	0.88 (0.52, 1.49)	0.87 (0.49, 1.56)	1.13 (0.54, 2.40)	1.12 (0.51, 2.45)
High-stable	0.93 (0.51, 1.70)	0.93 (0.48, 1.78)	0.90 (0.37, 2.22)	0.88 (0.35, 2.23)
Elevated-high	1.89 (0.96, 3.75)	1.79 (0.80, 4.02)	3.39 (1.44, 8.00)	3.35 (1.28, 8.79)
LDL cholesterol group				
Low-stable	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Normal-stable	0.58 (0.34, 1.01)	0.56 (0.30, 1.04)	1.63 (0.64, 4.17)	1.51 (0.57, 4.02)
Elevated-stable	0.77 (0.44, 1.34)	0.76 (0.41, 1.42)	1.29 (0.47, 3.55)	1.23 (0.43, 3.53)
High-stable	1.04 (0.53, 2.07)	1.00 (0.45, 2.19)	3.24 (1.16, 9.12)	3.13 (1.04, 9.39)
HDL cholesterol group				
Low-stable	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Normal-stable	1.40 (0.85, 2.30)	1.33 (0.78, 2.29)	0.97 (0.54, 1.74)	0.81 (0.43, 1.51)
Elevated-stable	1.55 (0.80, 3.01)	1.48 (0.71, 3.06)	0.57 (0.20, 1.63)	0.47 (0.15, 1.45)
Triglycerides group				
Low-stable	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Normal-increasing	1.20 (0.63, 2.27)	1.30 (0.63, 2.66)	0.83 (0.31, 2.22)	1.00 (0.35, 2.86)

TABLE 5 Trajectories of risk factors and pregnancy complications, women in the Bogalusa Heart Study (n = 903).

	Any gestational hypertension		Any gestational diabetes	
	Adjusted for age at baseline	Adjusted for age at baseline, BMI, parity, SES, smoking, age at first birth ^a	Adjusted for age at baseline	Adjusted for age at baseline, BMI, parity, SES, smoking, age at first birth ^a
	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)
BMI				
Slow increase	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Moderate increase	1.68 (1.05, 2.70)	1.37 (0.88, 2.14)	1.35 (0.89, 2.06)	1.72 (1.04, 2.84)
Steepest increase	3.40 (2.03, 5.70)	3.51 (1.95, 6.30)	1.61 (0.91, 2.85)	1.70 (0.91, 3.17)
Systolic blood pressure group				
Slow increase	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Moderate increase	2.11 (1.21, 3.70)	1.80 (0.99, 3.26)	1.47 (0.94, 2.30)	1.35 (0.83, 2.18)
Steepest increase	3.68 (1.95, 6.93)	2.69 (1.31, 5.56)	1.40 (0.75, 2.60)	1.21 (0.61, 2.40)
Diastolic blood pressure group				
Rising	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Starts higher, rising	1.91 (1.07, 3.42)	1.62 (0.87, 2.99)	1.34 (0.83, 2.16)	1.22 (0.73, 2.05)
Higher and flatter	2.62 (1.23, 5.57)	1.91 (0.82, 4.45)	1.49 (0.77, 2.90)	1.25 (0.61, 2.59)
Cholesterol				
Consistently low	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Middle	0.71 (0.46, 1.10)	0.76 (0.48, 1.22)	1.04 (0.71, 1.54)	1.06 (0.70, 1.61)
Consistently high	1.49 (0.72, 3.07)	1.24 (0.55, 2.79)	0.96 (0.40, 2.30)	0.94 (0.37, 2.40)
LDL cholesterol				
Consistently low	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Higher but flat	0.77 (0.50, 1.20)	0.83 (0.52, 1.32)	0.96 (0.64, 1.44)	0.96 (0.62, 1.48)
Increasing	1.07 (0.56, 2.06)	1.04 (0.51, 2.11)	1.28 (0.70, 2.35)	1.30 (0.67, 2.49)
HDL cholesterol				
Consistently low	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Medium/flat	0.86 (0.51, 1.44)	1.07 (0.61, 1.91)	1.25 (0.71, 2.19)	1.35 (0.74, 2.47)
Declining	0.46 (0.18, 1.13)	0.58 (0.22, 1.51)	0.83 (0.37, 1.84)	0.91 (0.39, 2.11)
Triglycerides				
Consistently low	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Moderate and flat	0.87 (0.52, 1.44)	1.08 (0.61, 1.89)	0.73 (0.47, 1.14)	0.78 (0.48, 1.27)
Steep rise	1.84 (0.69, 4.90)	1.72 (0.58, 5.15)	1.20 (0.45, 3.18)	1.20 (0.41, 3.54)

^aBMI group not adjusted for BMI in multivariable models.

SBP group was associated with an increased likelihood of SGA (aRR 2.12, 95% CI 0.90, 5.00) in YFS, while the steepest increase in SBP (aRR 1.58, 95% CI 0.98, 2.57) and DBP (aRR 1.77, 95% CI 1.06, 2.96) were associated with PTB in BHS. The elevated high total cholesterol group was also associated with PTB in YFS (aRR 3.38, 95% CI 1.28, 8.79), while the high-stable LDL group (aRR, 3.13, 95% CI 1.04, 9.39) in YFS and the LDL group with the highest increase in BHS had higher risks of PTB (aRR 1.59, 95% CI 0.95, 2.67).

For pregnancy complications (Tables 5 and 6), trajectories of blood pressure and BMI had the strongest associations. The group with the steepest increase in SBP had the highest risk of GH for BHS (aRR 2.69, 95% CI 1.31, 5.56); in YFS, the point estimate for the groups with increasing trajectories were similar but very imprecise. For both BHS and YFS, groups with higher and increasing BMI were

at higher risk for GDM (BHS: aRR 3.51, 95% CI 1.95, 6.30; YFS: aRR 2.61, 95% CI 0.96, 7.08).

No interactions were found with parity.

4 | COMMENT

4.1 | Principal findings

This analysis of two cohorts of different populations found both similarities and differences for the classes. The shapes of the trajectories were similar enough, however, that some comparisons can be drawn. Trajectories of cardiovascular risk factors were associated with some pregnancy and birth outcomes. In both cohorts, the

TABLE 6 Trajectories of risk factors and pregnancy complications, women in the Young Finns Study (n = 499).

	Any hypertensive disorders		Any gestational diabetes	
	Adjusted for age at baseline	Adjusted for age at baseline, BMI, parity, SES, smoking, age at first birth	Adjusted for age at baseline	Adjusted for age at baseline, BMI, parity, SES, smoking, age at first birth
	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)
BMI group				
Stable slim	0.51 (0.18, 1.48)	0.51 (0.17, 1.51)	1.13 (0.68, 1.91)	1.01 (0.57, 1.79)
Stable normal	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Progressively overweight	1.26 (0.41, 3.89)	1.27 (0.39, 4.19)	1.39 (0.70, 2.77)	1.17 (0.53, 2.54)
Persistent increasing obese	0.89 (0.11, 7.58)	1.10 (0.13, 8.93)	1.82 (0.85, 3.87)	2.61 (0.96, 7.08)
Systolic blood pressure group				
Low-stable	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Moderate-increasing	2.40 (0.90, 6.43)	2.39 (0.80, 7.12)	1.34 (0.82, 2.19)	1.31 (0.76, 2.26)
Elevated-increasing	2.43 (0.30, 19.58)	1.77 (0.18, 17.15)	0.97 (0.25, 3.80)	0.66 (0.15, 2.95)
Diastolic blood pressure group				
Low-stable	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Normal-stable	1.86 (0.74, 4.66)	1.60 (0.59, 4.36)	1.13 (0.71, 1.81)	1.10 (0.65, 1.89)
Cholesterol group				
Low-stable	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Elevated-stable	0.86 (0.29, 2.58)	0.97 (0.30, 3.08)	0.81 (0.47, 1.41)	0.85 (0.46, 1.59)
High-stable	0.87 (0.24, 3.17)	0.78 (0.21, 2.97)	0.95 (0.50, 1.80)	0.84 (0.42, 1.68)
Elevated-high	1.59 (0.32, 7.82)	1.42 (0.27, 7.53)	0.44 (0.11, 1.78)	0.42 (0.10, 1.84)
LDL cholesterol group				
Low-stable	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Normal-stable	0.87 (0.28, 2.70)	0.90 (0.27, 3.01)	0.91 (0.49, 1.66)	0.95 (0.48, 1.91)
Elevated-stable	0.31 (0.06, 1.65)	0.32 (0.06, 1.81)	0.96 (0.50, 1.87)	1.12 (0.53, 2.36)
High-stable	1.98 (0.53, 7.41)	1.86 (0.45, 7.59)	0.51 (0.15, 1.67)	0.42 (0.12, 1.51)
HDL cholesterol group				
Low-stable	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Normal-stable	0.74 (0.30, 1.83)	0.91 (0.34, 2.43)	0.77 (0.48, 1.23)	0.82 (0.48, 1.42)
Elevated-stable	0.35 (0.04, 2.89)	0.45 (0.06, 3.66)	0.47 (0.17, 1.29)	0.59 (0.20, 1.73)
Triglycerides group				
Low-stable	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Normal-increasing	0.89 (0.21, 3.77)	0.43 (0.09, 2.12)	2.21 (1.34, 3.66)	1.81 (0.92, 3.57)

steepest trajectories of cholesterol and LDL were associated with PTB. Higher DBP was associated with PTB in BHS, and point estimates were raised for SBP and PTB in both cohorts, though very imprecisely in some cases. Steeper increases in SBP were associated with a higher risk of GH in BHS and increasing or persistent-obese BMI trajectories with associated with GDM.

4.2 | Strengths of the study

Strengths of this analysis include the two cohorts in diverse populations with detailed and consistent measurements of cardiovascular

risk factors. Because the studies were not limited to tests ordered for clinical reasons, the populations reflect a range of nonclinical and nonsymptomatic values. The trajectories go back to childhood for a fuller understanding of the life course. Some previous studies have been limited to adult measures¹², for pregnancy, which usually occurs in early adulthood, this is a narrow window. Trajectory modelling creates data-driven groupings of participants in longitudinal studies, which may reveal patterns that are not apparent when participants are categorised a priori, and allow for using more than two data points per participant, unlike using an annual rate of change^{12,27} or piecewise linear models,²⁸ which may impose a linear relationship on the data.

4.3 | Limitations of the data

Limitations include the variation in number of visits and the lack of information on cardiovascular risk factors during pregnancy. Particularly the YFS was left with a relatively small sample size when limited by the number of visits necessary in pre-pregnancy. Pregnancy complications were self-reported in some cases (BHS) or limited to what is recorded in the Medical Birth Registry (YFS); while both sources of information are broadly valid,²⁹⁻³⁵ details may be missed, particularly for HDP. The assignment to classes is based on probabilities and may not reflect an underlying biological reality.

4.4 | Interpretation

The two studies had relatively similar designs but different populations. Both included longitudinal follow-up of participants who were children and young adults primarily in the 1980s. The BHS only recruited from a single site, a small town in Louisiana, and includes Black and white participants. YFS recruited from five sites around Finland, centred in urban centres and recruiting from the surrounding area, and includes people of Finnish ethnicity. For the most part, results are consistent in the two cohorts and population differences in baseline measures were not substantial (Table 2; for a comparison of the full cohorts, see¹⁴) In general, the health status of the Finnish population has improved more strongly than that of United States over the last 40 years, although current population mean levels of most cardiovascular risk factors are not far apart.^{36,37}

These results are consistent with some previous analyses, in these cohorts and others, including finding increasing BMI associated with GDM¹¹ and that overweight/prehypertensive groups were more likely to develop HDP.¹⁰ GDM has been associated with a higher annual rate of change in triglycerides and a greater decrease in HDL¹²; the analysis in YFS found neither of these patterns and in BHS was consistent with the HDL result, though imprecise. In BHS, when childhood and pre-pregnancy were considered as a whole, mean and area under the curve pre-pregnancy blood pressure were associated with PTB and term LBW, and pre-pregnancy total cholesterol was negatively associated with gestational age.¹³ While other studies have similarly found higher preconception blood pressure was associated with lower birthweight and higher preterm birth,^{9,38} previous research on lipids is more ambiguous. Our previous analysis of preconception cardiovascular risk factors in the YFS indicated an increased risk of adverse birth outcomes with higher blood pressure and lipids (effect sizes between 1.2 and 1.4 for a 1-SD increase),⁷ and SBP and total cholesterol were somewhat higher at baseline in the YFS compared to BHS. Romundstad et al. found higher preconception levels of cholesterol and triglycerides and lower HDL were associated with higher birthweight,⁹ while Catov et al. found that both low and high total cholesterol was associated with increased preterm birth risk,⁶ but not triglycerides, LDL, or HDL. So, while

our results are broadly consistent with these studies, we found more associations with LDL.

5 | CONCLUSIONS

In summary, life course trajectories of cardiovascular risk are associated with a higher risk of pregnancy complications. This analysis contributes to the greater understanding of pregnancy in the life course; it has become increasingly clear that pregnancy is not an isolated event, but intimately intertwined with health before and after pregnancy, and may require interventions beyond the 9 months of pregnancy to improve population levels of pregnancy-related morbidity. Future studies should continue to examine cardiovascular health across the life course and attempt to determine groups and inflection points for intervention.

AUTHOR CONTRIBUTIONS

EW: conceptualization; formal analysis; methodology; writing of original draft. JH: formal analysis; methodology; visualization. SPR: formal analysis; methodology. KP: investigation; resources. TL: investigation; funding acquisition; resources. OR: investigation; funding acquisition; project administration; supervision. All authors revised the work critically for important intellectual content; gave final approval of the version to be published; agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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CONFLICT OF INTEREST STATEMENT

None of the authors has a conflict of interest.

DATA AVAILABILITY STATEMENT

The datasets generated and/or analysed during the current study are not publicly available. For BHS, data are confidential to protect participant privacy. However, data are available upon request from BHS Steering Committee. Data requests can be submitted by email and are subject to approval. For YF, due to legal restrictions, the Ethics Committee of the Hospital District of Southwest Finland has in 2016 stated that individual level data cannot be stored in public repositories or otherwise made publicly available. However, data are available upon request from YFS Project Application. Data requests can be submitted by email and are subject to approval by the YFS Board.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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