Longitudinal study of birth weight and adult body mass index in predicting risk of coronary heart disease and stroke in women

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Papers

Longitudinal study of birth weight and adult body mass index in predicting risk of coronary heart disease and stroke in women

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Abstract

Objectives To determine whether birth weight and adult body size interact to predict coronary heart disease in women, as has been observed for men. To determine whether birth weight and adult body size interact to predict risk of stroke.

Design Longitudinal cohort study.

Setting and participants 66 111 female nurses followed since 1976 who were born of singleton, term pregnancies and reported their birth weight in 1992.

Main outcome measures 1504 events of coronary heart disease (myocardial infarction or sudden cardiac death) and 1164 strokes.

Results For each kilogram of higher birth weight, age adjusted hazard ratios from prospective analysis were 0.77 (95% confidence interval 0.69 to 0.87) for coronary heart disease and 0.89 (0.78 to 1.01) for total stroke. In combined prospective and retrospective analysis, hazard ratios were 0.84 (0.76 to 0.93) for total stroke, 0.83 (0.71 to 0.96) for ischaemic stroke, and 0.86 (0.66 to 1.11) for haemorrhagic stroke. Exclusion of macrosomic infants (>4536 g) yielded stronger estimates. Risk of coronary heart disease was especially high for women who crossed from a low centile of weight at birth to a high centile of body mass index in adulthood. The association of lower birth weight with increased risk of stroke was apparent across categories of body mass index in adults and was not especially strong among heavier women.

Conclusions Higher body mass index in adulthood is an especially strong risk factor for coronary heart disease among women who were small at birth. In this large cohort of women, size at birth and adiposity in adulthood interacted to predict events of coronary heart disease but not stroke events.

Introduction

New data continue to fuel the debate surrounding the "fetal origins hypothesis" that prenatal environment affects the risk of adult cardiovascular disease. Fifteen out of 16 published studies have reported inverse associations between birth weight and cardiovascular events.[1–4] Taken as a group, these epidemiological cohort studies have found a roughly 20% lower risk of cardiovascular disease for every kilogram of higher birth weight.[1] The debate has now shifted to the interpretation and importance of the inverse association of birth weight with cardiovascular disease, especially as it relates to postnatal growth and adult body mass index (BMI, kg/m^2), a measure of adiposity.

The inverse associations observed between birth weight and coronary heart disease are not markedly changed by adjustment for adult BMI[1] (in contrast to associations of birth weight with hypertension, which are nearly doubled by adjustment for adult BMI).[5] Although adjustment for BMI has little impact, stratification by BMI has indicated that birth weight and BMI may interact to predict risk of coronary heart disease. Several[6–8] but not all[9] studies among men have reported an especially high risk of coronary heart disease among men who were small at birth and grew large in childhood or adulthood. To our knowledge, three studies have published data regarding a potential interaction of birth weight and adult BMI in predicting risk of coronary heart disease among women, and these have had conflicting results.[2–4 10] We examine whether birth weight and adult BMI interact to predict risk of coronary heart disease in a larger cohort of women. We also examine whether low birth weight and high adult BMI predict risk of stroke, which to our knowledge has not yet been reported for men or women.

Methods

The nurses' health study was established in 1976, when 121 700 American female registered nurses aged 30-55 years responded to mailed questionnaires. The baseline and biennial follow-up questionnaires request information about various past and current risk factors for and occurrence of myocardial infarction and stroke. In 1992, participants indicated their birth weight in categories of pounds (Not sure, <5 lb, 5.0-5.5 lb, 5.6-7.0 lb, 7.1-8.5 lb, 8.6-10.0 lb, and >10 lb, which are equivalent to the categories of <2268 g, 2268-2495 g, >2495-3175 g, >3175-3856 g, >3856-4536 g, and >4536 g presented in this paper).

From the 1976 baseline cohort, we excluded 573 women who reported that they had had cardiovascular events before baseline. We excluded women who died before or who did not respond to the 1992 questionnaire that included the birthweight question (n=42 202) or who did not know their birth weight (n=18 176). We excluded 1249 women who were from multiple births and 3390 women who indicated they were born two or more weeks early. This analysis includes 66 111 singleton, full term participants for whom we had data on birth weight.

Self reported anthropometric exposures

We calculated participants' BMI from self reported height in 1976 and weight self reported on biennial questionnaires. BMI at age 18 years was based on weight at age 18 recalled in 1980. Previous studies have established the validity of self reported birth weight, height, and weight in this and similar cohorts.[11 12]

Documentation of end points

We considered incident coronary heart disease (non-fatal myocardial infarction or fatal coronary heart disease) and stroke

that occurred between the return of the baseline 1976 questionnaire and 1 June 2000. We sought permission to review the medical records from the participants who reported a diagnosis of non-fatal coronary heart disease or non-fatal stroke on follow-up questionnaires. Doctors blinded to the questionnaire information of the participants reviewed the records; the criteria for determining cardiovascular events has been described previously.[13] We identified deaths from state death records and the national death index, or the subject's family or postal authorities reported them. We determined cause of death from hospital records or autopsy, as described elsewhere.[13] When a participant had more than one cardiovascular event (for example, coronary heart disease and stroke) we counted only the first event.

We examined the main effects of birth weight and cardiovascular disease prospectively from 1992 to 2000. As the results of this prospective analysis were generally similar to the previously published retrospective (1976-1992) analysis,[13]we exploited the statistical power of the entire period of follow-up—1976 to 2000—to examine subtypes of stroke and the interaction between birth weight and adult BMI.

Statistical analysis

We assigned incident cases of cardiovascular disease to the birthweight categories, with the follow-up period dating from the return of the baseline questionnaire (1976 or 1992) to the date of occurrence of disease or 1 June 2000, whichever came first. We used a Cox proportional hazards model to estimate hazard ratios adjusted for age in months and for changing cardiovascular risk factors in adulthood.[14] We used the hazards ratio to compare the risk of disease for women in a given birthweight category with that of women who weighed 3221-3856 g (7.1-8.5 lb) at birth. To assess trend across categories, we assigned each birthweight category a representative value based on the reported range (2.16 kg, 2.39 kg, 2.84 kg, 3.52 kg, 4.20 kg, and 4.66 kg). Two sided P values and 95% confidence intervals are presented.

One way to investigate the interaction of birth weight and postnatal BMI is to examine "centile crossing" in body size from birth to adulthood. We collapsed the extreme birthweight categories and calculated the centiles included in the four resulting birthweight categories (for example, the 11% of the cohort that weighed 2495 g or less at birth were considered to be below the 11th centile of birth weight). We then converted adult BMI into four BMI centile categories corresponding to the four birthweight centile categories (for example, we classified an adult BMI below the 11th centile for the distribution of BMI in this cohort into the $<11\%$ adult BMI category.) This generated 16 categories representing the interaction of birth weight and adult BMI. We used likelihood ratio tests to assess whether the set of categories representing this interaction differed from a more parsimonious model including only birthweight and BMI centile groups. We repeated a similar process for BMI at age 18.

We adjusted all analyses for age in months as a continuous variable; multivariate relative risks were derived from proportional hazards models including terms as specified in the tables and text. As in previous analyses,[9 13 15] adjustment for adult cigarette smoking, parental occupation, and whether or not the nurse had been breast fed, as well as updated hypertension, hypercholesterolaemia and diabetes mellitus made no material difference to the estimates associated with birth weight reported here. Therefore, we report primarily estimates that are adjusted for age and adult BMI. Although cigarette smoking did not confound the associations between birth weight and cardiovascular disease, it confounded associations of adult BMI with cardiovascular disease. We therefore included cigarette smoking in models of interactions between birth weight and adult BMI.

Results

From 1976 to 2000, we documented 1504 coronary events (myocardial infarction or sudden death) and 1164 strokes. Table 1 shows the results of the prospective analysis (1992-2000) of birth weight and risk of fatal and non-fatal cardiovascular events. The risk of coronary heart disease generally declined as birth weight increased, with the exception of the macrosomic (>4536 g) infants, whose risk of coronary heart disease was similar to that of the median (reference) birthweight category. Risk of stroke also dropped as birth weight increased, again with the exception of macrosomic infants, who seemed to be at the highest risk of stroke. Over all birthweight categories, the risk of coronary heart disease fell by 23% and of stroke by 11% per kilogram increase in birth weight. As previous studies had observed an upturn in cardiovascular risk among macrosomic infants,[16–18] we also calculated the linear trend per kilogram of birth weight after excluding the macrosomic infants. This showed a 25% (15% to 34%) decrease in risk of coronary heart disease and an 18% (5% to 29%) decrease in risk of stroke per kilogram of birth weight. Adjustment for adult BMI did not materially change the association of birth weight with coronary heart disease (table 1).

Table 2 examines stroke more closely, including follow-up from 1976 to 2000, which combined retrospective and prospective analysis. Overall, from 1976 to 2000, each kilogram of birth weight was associated with a 16% decreased risk of stroke. The association of birth weight with ischaemic stroke was similar to the association of birth weight with coronary heart disease: risk dropped as birth weight increased, with the exception of macrosomic infants. Overall, the risk of ischaemic stroke fell by 17% per kilogram increase in birth weight and increased to 22% (8% to 34%) when macrosomic infants were excluded. We observed 189 haemorrhagic strokes, with few strokes in the extreme birth weight categories. No consistent pattern emerged between birth weight and risk of haemorrhagic stroke.

We then examined interactions of birth weight with BMI at age 18 years and as updated throughout adulthood. Tables 3, 4, 5, and 6 show hazard ratios adjusted for age and smoking for each combination of birth weight and BMI centile, compared with a reference group of women who were at the median ($\geq$42nd centile and $<$87th centile for birth weight and BMI). The tables also provide estimates in the margins of the change in coronary heart disease and stroke risk per kilogram increase in birth weight within each adult BMI category, as well as change in disease risk per unit of BMI change in each birth weight category.

Table 3 shows an interaction of birth weight and adult BMI in predicting coronary heart disease ($P=0.05$, comparing the model with interaction terms with the model without). The risk of coronary heart disease associated with increasing adult BMI was most consistent and striking among women born with low birth weight. As birth weight increased, risk of coronary heart disease generally decreased, except in the group with the lowest BMI in adulthood. The inverse association of birth weight with coronary heart disease was sizeable and reached significance only among adults who were (roughly) at or above the median adult BMI (42nd BMI centile and above). In short, risk of coronary heart disease was highest among women who were smaller infants at birth and grew to be heavier adults. We found no evidence of elevated risk of coronary heart disease among lower birthweight infants who remained relatively lean into adulthood.

Table 1 Hazard ratios with 95% confidence intervals for the association of birth weight with coronary heart disease, stroke, and total cardiovascular disease, nurses' health study, 1992-2000

	Birth weight (g)						
	<2268	2268-2495	>2495-3175	>3175-3856	>3856-4536	>4536	Per kg, across all categories
Coronary heart disease							
Events	21	59	329	392	91	26	918
Person years	8493	25 174	158 727	237 378	58 718	12 518	501 008
Adjusted hazard ratio:							
For age	1.31 (0.84 to 2.04)	1.48 (1.12 to 1.95)	1.26 (1.09 to 1.46)	1.00	0.86 (0.68 to 1.08)	0.98 (0.66 to 1.46)	0.77 (0.69 to 0.87)
For age and BMI	1.31 (0.84 to 2.03)	1.50 (1.14 to 1.98)	1.30 (1.12 to 1.51)	1.00	0.84 (0.67 to 1.06)	0.93 (0.63 to 1.39)	0.75 (0.67 to 0.84)
Stroke							
Events	18	36	259	349	75	32	769
Adjusted hazard ratio:							
For age	1.23 (0.76 to 1.98)	1.04 (0.74 to 1.46)	1.13 (0.96 to 1.33)	1.00	0.78 (0.60 to 1.00)	1.32 (0.92 to 1.91)	0.89 (0.78 to 1.01)
For age and BMI*	1.23 (0.76 to 1.98)	1.05 (0.74 to 1.48)	1.16 (0.98 to 1.36)	1.00	0.77 (0.60 to 0.99)	1.28 (0.89 to 1.85)	0.87 (0.76 to 0.99)
Total cardiovascular disease							
Events	39	95	588	741	166	58	1687
Adjusted hazard ratio:							
For age	1.27 (0.92 to 1.76)	1.27 (1.03 to 1.58)	1.20 (1.08 to 1.34)	1.00	0.82 (0.69 to 0.97)	1.14 (0.87 to 1.50)	0.82 (0.75 to 0.90)
For age and BMI*	1.27 (0.92 to 1.76)	1.29 (1.04 to 1.60)	1.23 (1.10 to 1.37)	1.00	0.81 (0.68 to 0.95)	1.10 (0.84 to 1.43)	0.80 (0.74 to 0.88)

BMI=body mass index.

Table 4 shows the hazard ratios for coronary heart disease by categories of birth weight and BMI at age 18 years. In general, stratification by age 18 BMI showed patterns similar to stratification by updated adult BMI, although the global test of interaction was not significant (P = 0.22). Risk of coronary heart disease was highest among women who were born small and had grown relatively large by young adulthood.

Table 5 shows the cross classification of birth weight and adult BMI in relation to risk of stroke. In contrast to the pattern for coronary heart disease, however, the association of adult BMI with stroke was of similar magnitude across birthweight categories (far right margin of table 5). Similarly, the hazard ratios per kilogram birth weight (bottom margin of table 5) were nearly identical for all but the largest adult BMI group. The smallest infants were consistently at highest risk of stroke. In sum, the trends of BMI within birthweight groups were similar, as were trends of birth weight within BMI groups (as reflected in the P value for test of interaction of 0.57).

We found no apparent interaction (P = 0.39) between birth weight and BMI at age 18 in predicting stroke risk, as shown in table 6. Stroke risk generally rose with BMI and dropped with higher birth weight. Although the hazard ratios of stroke per kilogram birth weight varied across the four age 18 BMI categories (bottom row), we found no trend towards lower hazard ratios for birth weight as adult BMI increased, as had been seen for coronary heart disease.

Table 2 Age adjusted hazard ratios with 95% confidence intervals for the association of birth weight with stroke, nurses' health study, 1976-2000

	Birth weight (g)						
	<2268	2268-2495	>2495-3175	>3175-3856	>3856-4536	>4536	Per kg, across all categories
Total stroke							
Events	37	59	393	514	120	41	1,164
Person years	26 605	78 162	491 999	733 963	181 780	38,854	1,551,362
Hazard ratio	1.74 (1.24 to 2.44)	1.14 (0.87 to 1.50)	1.16 (1.02 to 1.33)	1.00	0.86 (0.70 to 1.05)	1.19 (0.86 to 1.64)	0.84 (0.76 to 0.93)
Ischaemic stroke							
Events	17	35	190	252	61	21	576
Hazard ratio	1.56 (0.95 to 2.56)	1.43 (1.00 to 2.04)	1.14 (0.95 to 1.38)	1.00	0.86 (0.65 to 1.14)	1.18 (0.76 to 1.85)	0.83 (0.71 to 0.96)
Haemorrhagic stroke							
Events	6	8	70	78	20	7	189
Hazard ratio	1.85 (0.80 to 4.28)	0.96 (0.47 to 2.00)	1.34 (0.97 to 1.86)	1.00	1.00 (0.61 to 1.64)	1.48 (0.68 to 3.23)	0.86 (0.66 to 1.11)

Table 3 Hazard ratios (with 95% confidence intervals) and numbers of cases for coronary heart disease by category of birth weight and updated adult body mass index, adjusted for age and updated smoking status, nurses' health study, 1976-2000

	Adult BMI centile				
Birth weight in kg (centile)	**<11th**	**11th-42nd**	**43rd-87th**	**≥87th**	**Hazard ratio per unit BMI**
<2.50 (<11th)	0.54 (6)	0.88 (22)	1.17 (49)	3.62 (45)	1.12 (1.08 to 1.15)
2.50≤3.18 (11th≤42nd)	0.89 (45)	0.79 (101)	1.29 (255)	1.81 (89)	1.05 (1.04 to 1.07)
3.19≤3.86 (43rd≤87th)	0.74 (46)	0.72 (125)	1.00* (315)	1.67 (156)	1.06 (1.04 to 1.07)
≥3.87 (≥87th)	0.77 (15)	0.70 (39)	0.79 (87)	1.62 (60)	1.06 (1.04 to 1.09)
Hazard ratio per kg birth weight	1.04 (0.73 to 1.48)	0.89 (0.72 to 1.11)	0.77 (0.67 to 0.88)	0.70 (0.58 to 0.85)	—

Birthweight percentiles were determined by the categorical birthweight question boundaries. Adult BMI percentile groups were created to correspond to the birthweight percentile groups.
BMI=body mass index.
*Reference value.

Table 4 Hazard ratios (with 95% confidence intervals) and numbers of cases for coronary age and heart disease by category of birth weight and body mass index (BMI) at age 18 years, adjusted for age and updated smoking status, nurses' health study, 1976-2000

	Age 18 BMI centile				
Birth weight in kg (centile)	**<11th**	**11th-42nd**	**43rd-87th**	**≥87th**	**Hazard ratio per unit BMI**
<2.50 (<11th)	1.02 (11)	1.29 (28)	1.27 (38)	3.60 (34)	1.14 (1.08 to 1.21)
2.50≤3.18 (11th≤42nd)	1.37 (61)	1.05 (116)	1.30 (190)	1.84 (72)	1.06 (1.03 to 1.09)
3.19≤3.86 (43rd≤87th)	1.37 (62)	0.95 (146)	1.00* (240)	1.70 (133)	1.05 (1.03 to 1.08)
≥3.87 (≥87th)	1.12 (16)	0.86 (41)	0.95 (74)	1.46 (52)	1.05 (1.01 to 1.09)
Hazard ratio per kg birth weight	1.04 (0.77 to 1.40)	0.83 (0.68 to 1.02)	0.80 (0.68 to 0.94)	0.67 (0.55 to 0.83)	—

BMI=body mass index.
*Reference value.

Discussion

Weight gain increases the risk of cardiovascular disease among all adults, but especially for those born small. This study confirms and quantifies more precisely than previous studies, including our own, the inverse associations between birth weight and risk of cardiovascular disease in adult women. For each kilogram increase in birth weight, we found a decrease of approximately 23% in risk of coronary heart disease and an increase of 11% in risk of stroke. Ischaemic stroke had an inverse association with birth weight that resembled that of coronary heart disease, lending support to an underlying ischaemic mechanism. Stronger associations were observed when macrosomic infants (>4536 g) were excluded.

Limitations

This study was limited by its reliance on self reported birth weight. As discussed previously,[13] missing birthweight data are unlikely to have caused the associations we observed artefactually. A greater limitation is the misclassification of self reported birth weight, weight, or height, which may have caused some bias towards the null. Nevertheless, other studies that have had complete cohort follow-up or documented birth weight have found inverse associations of birth weight with cardiovascular disease of similar magnitude.[2 17 19]

Association of birth weight with haemorrhagic stroke

We had observed a strong inverse association of birth weight with haemorrhagic stroke in our previous analysis (based on 76 cases)[13]; however, this association was weaker and inconsistent with increased follow-up in the current analysis (based on 189 cases). Two other studies have reported striking inverse associations of birth weight with haemorrhagic stroke. Among men in Helsinki, lower birth weight predicted a higher risk of haemorrhagic stroke.[20] In a cohort of women and men from Uppsala, each kilogram increase in birth weight was associated with a 41% (17% to 57%) decreased risk of haemorrhagic stroke.[21] Our ambiguous current findings therefore stand in contrast to the still small literature on birth weight and haemorrhagic stroke, and an inverse relation cannot be excluded.

Association of birth weight and coronary heart disease

Although adjustment for adult BMI did not alter the association of birth weight with cardiovascular disease, stratification by adult BMI found interactions between birth weight and adult body size for coronary heart disease. In particular, low birthweight infants who grew to be heavy adults were at high risk of coronary heart disease. In contrast, low birthweight infants who remained lean were not at heightened risk of coronary heart disease. For stroke, we found little evidence for a multiplicative interaction between birth weight and adult BMI, which perhaps reflects the lesser importance of adult BMI as a risk factor for stroke than for coronary heart disease.

Possible interpretations of statistical interaction

A statistical interaction between body size at birth and postnatal body size can be interpreted in several ways. Firstly, the high risk among small infants grown large may implicate rapid weight

Table 5 Hazard ratios (with 95% confidence intervals) and numbers of cases for stroke by category of birth weight and updated adult body mass index, adjusted for age and updated smoking status, nurses' health study, 1976-2000

	Adult BMI centile				
Birth weight in kg (centile)	**<11th**	**11th-42nd**	**43rd-87th**	**≥87th**	**Hazard ratio per unit BMI**
<2.50 (<11th)	1.35 (11)	1.06 (19)	1.34 (45)	1.96 (19)	1.05 (1.01 to 1.09)
2.50≤3.18 (11th≤42nd)	0.88 (31)	1.07 (101)	1.27 (193)	1.30 (53)	1.03 (1.00 to 1.05)
3.19≤3.86 (43rd≤87th)	0.78 (35)	0.81 (106)	1.00* (243)	1.54 (116)	1.05 (1.04 to 1.07)
≥3.87 (≥87th)	0.98 (14)	0.79 (31)	0.89 (75)	1.30 (38)	1.04 (1.01 to 1.07)
Hazard ratio per kg birth weight	0.83 (0.55 to 1.24)	0.79 (0.62 to 0.99)	0.79 (0.68 to 0.92)	0.99 (0.78 to 1.26)	—

BMI=body mass index.
*Reference value.

Table 6 Hazard ratios (with 95% confidence intervals) and numbers of cases for stroke by category of birth weight and body mass index at age 18 years, adjusted for age and updated smoking status, nurses' health study, 1976-2000

	Age 18 BMI centile				
Birth weight in kg (centile)	**<11th**	**11-42nd**	**43rd-87th**	**≥87th**	**Hazard ratio per unit BMI**
<2.50 (<11th)	1.86 (16)	0.95 (17)	1.48 (38)	2.20 (16)	1.08 (1.01 to 1.17)
2.50≤3.18 (11th≤42nd)	1.28 (47)	1.29 (115)	1.05 (125)	1.50 (47)	1.03 (0.99 to 1.07)
3.19≤3.86 (43rd≤87th)	0.89 (33)	1.14 (143)	1.00 (ref) (196)	1.28 (82)	1.02 (0.99 to 1.05)
≤3.87 (≥87th)	1.06 (13)	0.84 (33)	0.93 (58)	1.29 (36)	1.04 (1.00 to 1.09)
Hazard ratio per kg birth weight	0.69 (0.48 to 1.02)	0.89 (0.72 to 1.10)	0.83 (0.70 to 0.99)	0.86 (0.66 to 1.11)	—

BMI=body mass index.

What is already known on this topic

Birth weight is inversely associated with risk of coronary heart disease and stroke, although associations with stroke type are not established

Studies among men have suggested the inverse association of birth weight with coronary heart disease is apparent only among those who are heavy in adulthood

Studies among women are contradictory whether such an interaction exists between birth weight and adult body size

No study has examined whether birth weight and adult body mass index interact to predict stroke

What this study adds

Birth weight was inversely associated with coronary heart disease, total stroke, and ischaemic stroke in women

The inverse association of birth weight with coronary heart disease was especially strong among heavier women. Alternatively, the heart disease risk associated with each unit of adult body mass index was greater among women who were smaller at birth

The inverse association of birth weight with stroke was similar for women in all categories of adult body mass index, indicating no interaction between size at birth and in adulthood in determining risk of stroke

gain as the "true" risk factor for cardiovascular disease, as suggested by the "growth acceleration" hypothesis of Singhal and Lucas.[22] Interpreted in this way, the observed inverse associations of birth weight with cardiovascular disease are merely statistical artefacts of rapid postnatal growth rather than real associations between prenatal growth and cardiovascular disease. The public health implications of this interpretation are to prevent childhood and adult weight gain. However, observational data from several cohorts indicate that growth faltering in infancy may be a risk factor for later insulin resistance and cardiovascular disease.[7 16 19 23]

Alternatively, small newborns who grow rapidly may be "catching up" to their genetic potential—rapid "centile crossing" after birth could be a marker of growth restriction in the womb. Under this interpretation, the prevention of growth restriction in the womb might be an appropriate goal.

Finally, the statistical interaction may reflect a true biological interaction of early growth and later growth: perhaps those genetically or environmentally determined to be small at birth are especially vulnerable to an adult environment of nutritional excess. This argument of a thrifty genotype or thrifty phenotype suggests targeting interventions to prevent obesity at people who were born small.[24]

Conclusion

Available data indicate that weight gain increases cardiovascular disease risk among all adults, but especially for those born small. Whether this observation implicates prenatal growth, postnatal growth, or their biological interaction remains to be determined. More importantly, the specific genetic and environmental determinants of growth that directly affect the cardiovascular system need to be identified.

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