

opposed to trusted and known general practitioners and counsellors) as part of what was perceived as a traumatic hospital admission. These results also indicate the imperative for finding solutions outside the emergency department, in primary care or education systems.

Secondly, it is important that several participants identified abstaining from alcohol as key to the resolution of deliberate self harm. Given the correlation between alcohol dependence and the risk of suicidal behaviours, as well as the potential for brief interventions in emergency departments,⁹ this may be an area for further research, particularly as some participants considered deliberate self harm as a way of accessing services.

Finally, the recognition and treatment of depression, especially in men, in primary care remains important in the prevention of suicidal behaviour, as is the greater challenge of public education campaigns to improve public (and professional) understanding of mental illness and the effective treatments available.

Contributors: See bmj.com

Funding: This study was funded as part of the MRC Training Fellowship held by JS.

Competing interests: None declared.

Ethics approval: Oxford Psychiatric Research ethics committee and the London School of Hygiene and Tropical Medicine ethics committee.

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(Accepted 22 March 2005)

doi 10.1136/bmj.38441.503333.8F

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. Taken as a group, the published cohort studies have found a roughly 20% lower risk of cardiovascular disease for every kilogram of higher birth weight.¹

Stratification by adult body mass index (BMI, kg/m²) has indicated that birth weight and BMI may interact to predict risk of coronary heart disease. Several,²⁻⁴ but not all,⁵ studies among men have reported an especially high risk of coronary heart disease among men who

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BMJ 2005;330:1115-8



This is the abridged version of an article that was posted on bmj.com on 27 April 2005: <http://bmj.com/cgi/doi/10.1136/bmj.38434.629630.E0>

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were small at birth and grew large in childhood or adulthood. To our knowledge three published studies regarding a potential interaction among women have had conflicting results.⁶⁻⁹ 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.

After exclusions from the 1976 baseline cohort (see bmj.com) we included in this analysis 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.

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 reviewed 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. 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.

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,¹⁰ 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. To assess trend across categories, we assigned each birthweight category a representative value based on the reported range. See bmj.com for details of analysis of interaction of birth weight and postnatal BMI.

Results

From 1976 to 2000, we documented 1504 coronary events (myocardial infarction or sudden death) and 1164 strokes. 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 (table 1). 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. 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).

Overall, from 1976 to 2000, each kilogram of birth weight was associated with a 16% decreased risk of stroke (table 2). 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 birthweight 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 (see bmj.com for tables).

We found 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. We found no evidence of elevated risk of coronary heart disease among lower birthweight infants who remained relatively lean into adulthood.

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.

In contrast to the pattern for coronary heart disease, however, the association of adult BMI with stroke was of similar magnitude across birthweight categories. Similarly, the hazard ratios per kilogram birth weight 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

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)						Per kg, across all categories
	<2268	2268-2495	>2495-3175	>3175-3856	>3856-4536	>4536	
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.

*Updated adult body mass index (kg/m²).

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. 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, we found no trend towards lower hazard ratios for birth weight as adult BMI increased, as had been seen for coronary heart disease.

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 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

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. 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.^{6 11}

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); 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.^{12 13} Our ambiguous current findings 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

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

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)						Per kg, across all categories
	<2268	2268-2495	>2495-3175	>3175-3856	>3856-4536	>4536	
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)

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

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 gain as the “true” risk factor for cardiovascular disease, as suggested by the “growth acceleration” hypothesis.¹⁴ 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.^{3 11 15}

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 argu-

ment of a thrifty genotype or thrifty phenotype suggests targeting interventions to prevent obesity at people who were born small.

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.

Contributors: See bmj.com

Funding: National Cancer Institute and the National Heart, Lung, and Blood Institute of the National Institutes of Health.

Competing interests: None declared.

Ethical approval: Partners Human Research Committee as protocol #2004-(000638/1; BWH on 2 March 2004).

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(Accepted 22 March 2005)

doi 10.1136/bmj.38434.629630.E0

Endpiece

Ignorance is bliss

People will sleep better not knowing how their sausages and politics are made.

Attributed to Otto von Bismark (1815-98), German chancellor

Fred Charatan, retired geriatric physician, Florida