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Is Birthweight Associated with Risk of Rheumatoid Arthritis? Data From a Large Cohort Study

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Abstract

Objectives—The "fetal origins of adult disease" hypothesis suggests the uterine environment can influence a fetus' susceptibility to future disease. We examine whether the fetal environment, as reflected by birthweight, could modulate an individual's future risk of rheumatoid arthritis (RA).

Methods—The relationship between birthweight and the risk of incident RA was studied in 87,077 women followed prospectively in the Nurses' Health Study cohort. New cases of RA diagnosed between 1976 and 2002 were confirmed in 619 women. The association between birthweight and the future development of RA was studied in age-adjusted and Cox proportional hazard models adjusting for age and potential confounders, including history of maternal diabetes, childhood socioeconomic status, prematurity, maternal and paternal smoking, as well as additionally adjusting for risk factors for RA including smoking, age at menarche, use of oral contraceptives, use of post-menopausal hormones, total lifetime breast feeding, and body mass index at age 18.

Results—In an age-adjusted model, birthweight > 4.54 kg vs. birthweight 3.2–3.85 kg was associated with a two-fold increased risk of RA (RR=2.1; 95% CI 1.4–3.3). Further adjusting for potential confounders and risk factors did not change this relationship (RR=2.0; 95% CI 1.3–3.0). Findings were similar when we limited cases to those with rheumatoid factor positive RA, (RR=2.1; 95%CI= 1.2–3.6).

Conclusions—In this large prospective cohort, birthweight > 4.54 kg was associated with a twofold increased risk of adult onset RA, compared with those of average birthweight. Further study of this observation may provide insight into the pathogenesis of RA.

Keywords

rheumatoid arthritis; birthweight; risk factors

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Introduction

The "fetal origins of adult disease" hypothesis posits that an increased risk of adult onset chronic disease can be a function of fetal environment. Animal studies and observational human data suggest that changes in fetal nutrition or gene-environment interactions could be responsible for determining a fetus' susceptibility to disease later in life. [1, 2] Strong associations between an increased risk of type 2 diabetes mellitus, coronary heart disease, hypertension, and low birthweight have been documented in a number of different populations.[3–6] One small case-control study has shown an association between high birthweight and rheumatoid arthritis (RA).[7] High birthweight has also been associated with an increased risk of an associated autoimmune disease, primary Sjogren's Syndrome.[8]

Patients with RA are known to have dysregulation of the hyopthalamic-pituitary-adrenal (HPA) axis,[9, 10] and this axis may be modulated *in utero*.[11] This suggests one pathway through which the risk of RA could be related to fetal environment. We assess the association of birthweight with the risk of adult onset RA in a prospective cohort of U.S. women.

Methods

Study Population

We studied the relationship between birthweight and the risk of incident RA in the Nurses' Health Study, a prospective cohort of 121,700 married women between the ages of 30 and 55 years when they completed the baseline questionnaire in 1976. Information was collected from the participants via biennial questionnaires regarding health status, lifestyle, family medical history, and health practices. Overall, we have maintained greater than 90% follow-up of the original cohort.[12] All women who reported cancer (other than non-melanoma skin cancer) at baseline or follow-up, or reported any connective tissue disease (CTD) at baseline were excluded from this analysis. In addition, women who reported RA or other CTD during follow-up, but in whom the diagnosis could not be confirmed by medical record review were also excluded. The study population included only women who answered the 1992 questionnaire which asked about birthweight. After exclusions, 87,077 women were included in this analysis. The Partners HealthCare System Institutional Review Board approved this study.

Identification of Rheumatoid Arthritis

We contacted 11,966 women reporting RA and 1673 reporting any other CTD on any of the biennial questionnaires from 1976–2002 for permission to review their medical records; 10,455 (77%) responded to the mailings. New cases of RA in 683 women were identified using a validated connective tissue screening questionnaire[13] followed by medical record review for American College of Rheumatology diagnostic criteria by two rheumatologists trained in chart abstraction.[14] Subjects with at least four of the seven diagnostic criteria documented in the medical record were considered to have definite RA. Disagreements were resolved by consensus. Sixty-four of these women had not answered the 1992 questionnaire and thus had no information on birthweight, leaving 619 women with confirmed incident RA for this analysis.

Self-Reported Birthweight

In 1992, the nurses were asked their own birthweight in categories: <2.26 kg, 2.3–2.49 kg, 2.5–3.175 kg, 3.2–3.85 kg, 3.9–4.54 kg, >4.54 kg and not sure. (These cut-offs were converted from the original categories of < 5 lbs, 5–5.5 lbs, 5.6–7.0 lbs, 7.1–8.5 lbs, 8.6–10.0 lbs, >10 lbs).

Birthweight was assessed in a similar manner in the related Nurses' Health Study II cohort. In a validation study in that cohort, birthweight was obtained from state birth certificates for 220 randomly chosen female nurses from the Nurses' Health Study II, and divided into five categories. Actual birthweight was then compared with self-reported birthweight. Seventy percent of nurses reported the same birthweight category as documented on their birth certificate (Spearman correlation coefficient = 0.74).[15] Since these nurses in the Nurses' Health Study II cohort are younger than those in the present study (aged 20–35 in 1989 at start of the Nurses' Health Study II cohort), they might be expected to remember their birthweight more accurately than older nurses. However, nurses in the Nurses' Health Study II were equally accurate in the recall of their birthweight over a wide range of ages (27–44 years), suggesting recall of birthweight remains stable over time.

Risk Factors and Potential Confounders

The original 1976 NHS questionnaire asked for information on health status, age, smoking history, weight, height, father's occupation when the nurse was sixteen years old, and reproductive history. Follow-up surveys were mailed every 2 years, which allows information on variables to be updated to ensure a more accurate calculation of actual person years of exposure. BMI at age 18 was calculated based on reported weight at age 18 and height at cohort entry. Data on age, cigarette smoking, oral contraceptive use, (collected through 1982, after which the cohort was aged 36–61 years and use of contraception was rare), postmenopausal hormone use and personal history of diabetes were updated to reflect each patient's changing exposure status over time. Data on age at menarche and father's occupation at age 16, (manager or professional vs. other occupations) were collected in the 1976 questionnaire report. We considered father's occupation when the nurse was 16 as proxy for socioeconomic status at time of birth. We also considered a history of parents' smoking as a proxy for fetal second hand smoke exposure.[16] Some risk factors or possible confounders were asked for the first time subsequent to the 1976 baseline survey. In 1982 nurses were asked if their mother had diabetes mellitus. The American state where the nurse was born was asked in 1992 and categorized into five regions: West, Mid-West, Atlantic, New England, and Southeast. This was included as a possible confounder given analyses in this cohort that birth location may be associated with the development of RA[17]. In 1986, parous nurses were asked the total number of months they had spent breastfeeding their children. In 1988 nurses were also asked to choose a pictogram depicting their mother's body shape at age 50. This was used as a proxy for maternal size at the time of the nurse's birth, and included as a covariate because birthweight is strongly associated with maternal size.[18, 19] In 1992 the nurses were asked their birthweight and if they were born two or more weeks premature.

Statistical analysis—Age-adjusted incidence rate ratios were calculated for the relative risk (RR) of RA for women in each birthweight category, compared with the referent category of 3.2–3.85 kg. Three Cox proportional hazards models were then used to study the association between RA and birthweight. The first model adjusted for age (Table 2). The second adjusted for age, maternal history of diabetes, father's occupation at age 16, (a proxy for socioeconomic status at time of birth), prematurity, maternal and paternal smoking, region of the United States the nurse lived in at birth, and maternal body shape at age 50 (i.e. potential perinatal confounders.) The third model adjusted both for the above confounders and for other potential risk factors for RA (including pack years smoked, age at menarche, use of oral contraceptives, use of post-menopausal hormones, total lifetime breast feeding of their own children, and BMI at age 18), that could be intermediate variables in the pathway between perinatal exposure and RA. This model also controlled for the nurses' history of diabetes mellitus, which is known to be associated with low birthweight.[3, 6] Each study participant contributed person-time from the time of the baseline questionnaire to the end of the follow-up period, the date of diagnosis of RA, death, exclusion, or loss-to-follow-up (whichever occurred first). In a subgroup

analysis, we repeated all analyses including only women who had rheumatoid factor positive disease.

We performed two sets of analyses. The primary analysis considered 1976 as baseline, and included all incident cases of RA (N=619) diagnosed from 1976–2002. In this analysis, the data on birthweight were collected after the diagnosis of RA for any prevalent cases in 1992. Similarly, covariates collected for the first time after 1976 were reported after the diagnosis of RA in some women. A secondary sensitivity analysis considered 1992 as baseline, when data on birthweight were collected, and only included incident cases of RA after that date. This is a true prospective analysis, with all covariates, including birthweight, being reported before the diagnosis of RA; however, this analysis included a much smaller number of RA cases (N=219). The relationship between birthweight and RA was similar in both analyses; therefore, we present more detailed analyses using data from 1976–2002.

Stratified analyses were also performed to determine whether maternal history of diabetes was an effect modifier of the birthweight – RA association.

Results

From 1976 to 2002, there were 619 confirmed cases of RA in this cohort. Table 1 shows the age-adjusted distribution of birthweight and other pertinent characteristics of this cohort.

As might be expected, the proportion of participants whose mothers had diabetes increased with self-reported birthweight categories. In accordance with other studies, women who themselves were diabetic were more likely to have been in the lowest birthweight category.[3, 6] The proportion of nurses whose father's occupation was managerial or professional when the participant was 16 years of age decreased with increasing birthweight

In an age-adjusted model using data from 1976–2002 (N=619), women with the highest birthweight (> 4.54 kg) had an increased risk of RA compared with women with average birthweight (3.2–3.85 kg) (RR=2.1; 95% CI 1.4–3.3 Table 2). A history of maternal diabetes was not associated with an increased risk of RA in either an age-adjusted analysis (RR=1.2; 95% CI=0.9–1.5), or an analysis adjusted for both perinatal confounders and risk factors for RA (RR=1.2; 95% CI=0.9–1.5). There was no relationship between risk of RA and father's occupation when the nurse was 16 in either the age-adjusted or the full multivariable model, (RR= 1.1; 95% CI 0.9–1.3 for both models).

In multivariable Cox proportional hazards models, adjusting for age and potential confounders, there was a statistically significant two-fold increased risk of RA among those with a birthweight > 4.54 kg, compared to those with average birthweight (RR=2.0; 95% CI 1.3–3.0) (Table 2**).** Further adjusting for risk factors for RA, (including pack years smoked, age at menarche, use of oral contraceptives, use of post-menopausal hormones, total lifetime breast feeding, BMI at age 18 and a history of diabetes mellitus), did not change the relative risk estimate (Table 2). In age-adjusted analyses, the association between high birthweight and RA was not appreciably different across strata of maternal history of diabetes (RR among those with high birthweight and history of maternal diabetes = 2.0; 95% CI 0.8–5.4; RR among those with high birthweight and no history of maternal diabetes = 2.1; 95% CI 1.4–3.3). There was no evidence of interaction between these two factors (p for multiplicative interaction=0.23). The association between high birthweight and RA was similar when we limited the analyses to the 378 (61.1%) cases of incident rheumatoid factor positive RA (RR= 2.1; 95% CI 1.2–3.6; See Table 3).

As a sensitivity analysis, we limited the analysis to RA cases diagnosed after the birthweight exposure assessment in 1992 (n=219). In the multivariable model, women with the highest

birthweight had a modest increased risk of RA compared with women with average birthweight (RR=1.3; 95% CI 0.5–3.3).

Discussion

Pregnancy is a vulnerable period in human development during which medication or environmental exposures can lead to discrete, identifiable defects post-partum. For example, administration of thalidomide during pregnancy leads to severe limb defects,[20] and exposure to alcohol can lead to a constellation of signs and symptoms known as the fetal alcohol syndrome.[21, 22] Recent data suggest that the gestational period may also be critical in more subtly "pre-programming" a newborn's future susceptibility to chronic disease. According to the "fetal origins of adult disease" hypothesis, the fetus responds appropriately when faced with an abnormal fetal environment; however, this response may result in permanent physiologic changes that could be maladaptive in later life.[3] This hypothesis is supported by a number of epidemiologic studies in non-rheumatic diseases: non-insulin dependant diabetes mellitus, hypertension and coronary heart disease (CHD) are all associated with low birthweight in a variety of populations.[4, 5, 23–25] High birthweight has been associated with breast cancer[26, 27] and acute lymphocytic leukemia.[28]

In this prospective cohort study of 87,077 women, including 619 women with confirmed incident RA, we found a statistically significant association between high birthweight and risk of RA. This is a similar association as reported in a small case-control from Sweden.[7] The two studies looked at patients born at different times: Nurses' Health Study participants were born between 1921 and 1946, and the Swedish cohort participants between 1940 and 1960, suggesting there is no birth cohort effect through 1960. In addition, the Swedish group found an association between low paternal socioeconomic status and risk of RA, which we did not. However, our analysis was limited by a single assessment of socioeconomic status at age 16, and we used dichotomous categories. A similar relationship between birthweight and incident adult disease has also been reported in both primary Sjogren's Syndrome[8] and systemic lupus erythematosus, although not consistently in the latter.[29, 30]

Although the biologic mechanism behind the association between RA and high birthweight is unknown, there are observational studies that provide intriguing corroborative physiologic data. Adults with RA have dysregulation of the HPA axis,[9, 10] and there are observational data linking birthweight and adult HPA function. In a cohort of men born in 1934, mean fasting plasma cortisol concentrations were measured at age 64, and found to be inversely related to birthweight in a step-wise, dose-dependent fashion. Those heaviest at birth had fasting plasma cortisol levels 32% lower than those with the lightest birthweights, independent of adult BMI.[31] Similarly, RA patients are known to have abnormally low levels of cortisol.[32, 33] In adult humans, low birthweight has been linked to increased cortisol responsiveness to synthetic adrenocorticotrophic hormone in men and women.[34–36] The opposite is true of RA patients: they are unable to increase cortisol production in the face of chronic inflammation or stress.[37–40] Although indirect, these data are consistent with our findings, and support an association between high birthweight and the type of HPA dysregulation that is seen in RA.

Limitations of this study include our use of self-reported birthweight, although as noted above this has been validated in a similar cohort, and any misclassification of self-reported birthweight would likely attenuate our findings. A large number of women had missing or unknown birthweight data. However, the relative risk estimates for this group were very similar to those in the lower birthweight groups, and demographic information was similar to the rest of the cohort, suggesting no systematic bias in reporting this birthweight category. The Nurses' Health Study is a homogenous population, composed almost entirely of Caucasian women, and these findings may not be generalizable to other groups. We do not have data on birth

length or early childhood weight, and cannot evaluate their effect on RA incidence; these alternate measures of fetal and childhood growth may also be important.[41] In addition, although we know whether the nurse was born ≥ 2 weeks premature, a more precise measure of gestational age would be important in future studies. Depending on the date of diagnosis, some data were collected after the ascertainment of RA, including birthweight, prematurity, maternal history of diabetes, father's occupation, and lifetime history of breast feeding. However, the results of our primary analysis (N=619) compared with the truly prospective sensitivity analysis (N=219) were similar, suggesting little recall bias. The latter showed a less precise risk estimate, which is not surprising as this analysis had many fewer cases of RA. In addition, adult reports of maternal diabetes were imprecise, as we could not determine the date of the mother's diabetes, the type of diabetes, and whether it preceded the nurse's birth.

We did not perform genetic testing on our participants, and cannot exclude confounding by genotype. However, although the association of cardiovascular disease and diabetes with birthweight may be mediated through genetic variation of the insulin-like growth factor 1,[42] it is unlikely that the association between birthweight and risk of adult onset disease is exclusively genetic. Fetal growth, of which birthweight is a cumulative measure, is profoundly influenced by fetal nutrition and fetal environment, independent of genetics.[43] In pregnancies using ovum donation, small women have small babies even if the donated ovum comes from a large woman.[18] Embryo transplant experiments also show that birth size is dependent on the maternal uterine environment, with minimal contribution from parental genotypes.[19]

Our data suggest a birthweight threshold above which risk of RA increases. The biology underlying this association is speculative, and the relative importance of fetal nutrition versus genotype is unknown. However, if fetal nutrition has an impact on future risk of RA, this could be a potentially modifiable risk factor. Further study of our observation that high birthweight is associated with an increased risk of RA could provide insight into the pathogenesis of RA. These data also provide further evidence for the importance of fetal environment as a crucible for future adult diseases.

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Table 1

Age-adjusted characteristics of this Nurses' Health Study cohort in 1992, stratified by own birthweight

Variable	< 2.5 kg	2.5–3.175 kg	3.2–3.85 kg	3.9–4.54 kg	>4.54 kg	Not sure/missing
Women (n)	7614	21499	31036	7614	1618	17,696
Mean age (years)	58.7	58.7	58.7	58.7	58.8	58.8
Born more than 2 weeks premature† (%)	35.9	2.8	0.7	0.3	0.3	1.3
History of diabetes (%)	6.3	3.7	3.7	4.0	4.4	3.7
Maternal history of diabetes (%)††	8.9	8.4	9.2	11.8	17.4	10.0
Oral contraceptive use (%)	48.9	48.2	47.7	47.2	46.9	45.1
Current post-menopausal hormone use (%)¶	35.0	35.1	35.4	34.1	31.8	32.4
Mean age at first birth (years)	22.8	22.8	22.9	22.8	22.7	23.0
History of breast feeding own children (%)	32.7	30.6	29.2	30.4	30.7	33.0
Ever Smoked (%)	54.1	55.1	56.0	58.6	60.5	56.6
BMI at age 18 (kg/m^2)	21.2	21.1	21.5	21.9	22.5	21.2
High socioeconomic status at Age 16 (%)‡	26.1	27.5	26.9	24.6	19.6	21.8

† Proportion of participants on the 1992 questionnaire who indicated that they were born 2 or more weeks premature.

†† Proportion of participants on the 1982 questionnaire who indicated that their mother had received a diagnosis of diabetes

¶ Current post-menopausal hormone use among post-menopausal women

‡ Father's occupation was manager or professional when the participant was 16 years of age

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Table 2

Association of one's own birthweight and risk of rheumatoid arthritis in the Nurses' Health Study (N=619)

Birthweight	RA cases	Person-years	Age-adjusted RR (95%CI)	Multivariable RR(95% CI) adjusted for Perinatal Confounders†	Multivariable RR (95% CI) adjusted for Perinatal Confounders and RA Risk Factors ††
< 2.5 kg	57	174,759	1.1 (0.8–1.5)	1.1 (0.8–1.5)	1.1(0.8–1.5)
2.5–3.175 kg	156	495,710	1.1 (0.9–1.3)	1.1 (0.9–1.3)	1.1 (0.9–1.3)
3.2–3.85 kg	214	716,671	1.0 (ref)	1.0 (ref)	1.0 (ref)
3.9–4.54 kg	51	174,616	1.0 (0.7–1.3)	1.0 (0.7–1.3)	0.9 (0.6–1.2)
>4.54 kg	24	36,247	**2.1 (1.4–3.3)**	**2.0 (1.3–3.0)**	**2.0 (1.3–3.0)**
Not sure/missing	117	400,559	0.9 (0.7–1.2)	0.9 (0.7–1.2)	0.9 (0.7–1.1)

† Adjusted for potential confounders that occurred during the perinatal period: age, maternal history of diabetes, father's occupation at age 16, (proxy for socioeconomic status at time of birth), prematurity, history of parents' smoking, (a proxy for fetal second hand smoke exposure), mother's body shape at age 50, region of country lived in at birth

†† Adjusted for potential peri-natal confounders above plus risk factors for RA, including pack years smoked, age at menarche, use of oral contraceptives, use of post-menopausal hormones, total lifetime breast feeding, BMI at age 18, and a history of diabetes mellitus.

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Table 3

Association of one's own birthweight and future risk of rheumatoid factor positive rheumatoid arthritis in the Nurses' Health Study (N=378)

Birthweight	RA cases	Person-years	Age-adjusted RR (95%CI)	Multivariable RR(95% CI) adjusted for Perinatal Confounders†	Multivariable RR (95% CI) adjusted for Perinatal Confounders and RA Risk Factors ††
< 2.5 kg	31	174,782	0.9 (0.6–1.4)	0.9 (0.6–1.4)	0.9 (0.6–1.5)
2.5–3.175 kg	91	495,776	1.0 (0.7–1.2)	0.9 (0.7–1.2)	1.0 (0.7–1.3)
3.2–3.85 kg	139	716,737	1.0 (ref)	1.0 (ref)	1.0 (ref)
3.9–4.54 kg	28	174,632	0.8 (0.5–1.2)	0.8 (0.5–1.2)	0.7 (0.4–1.1)
>4.54 kg	16	36,249	**2.2 (1.3–3.7)**	**2.1 (1.2–3.5)**	**2.1 (1.2–3.6)**
Not sure/missing	73	400,594	0.9 (0.7–1.2)	0.9 (0.6–1.3)	0.8 (0.6–1.1)

† Adjusted for potential confounders that occurred during the perinatal period: age, maternal history of diabetes, father's occupation at age 16, (proxy for socioeconomic status at time of birth), prematurity, history of parents' smoking, (a proxy for fetal second hand smoke exposure), mother's body shape at age 50, region of country lived in at birth

†† Adjusted for potential perinatal confounders above plus risk factors for RA, including pack years smoked, age at menarche, use of oral contraceptives, use of post-menopausal hormones, total lifetime breast feeding, BMI at age 18 and a history of diabetes mellitus.